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 (e.g., diagnosis of juvenile idiopathic arthritis) because there is insufficient clinical evidence to support the use of this test in the diagnosis of RA.

Aetna considers the Avise CDT assay, Avsie PG, Avise SLE, and
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.

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-cyclic citrullinated peptide (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.

Autoimmune CTD and SLE differential evaluation (Avise SLE 2.0 / Avise SLE + Connective Tissue 2.0 panels) combines a two-tier, multi-level testing process of cell-bound complement activation products (CB-CAPs) and the proprietary Avise algorithm, in
addition to anti-nuclear antibodies (ANA), double-stranded DNA (dsDNA) and extractable nuclear antigen (ENA) testing. Anti-nuclear antibodies (ANAs) are antibodies that attack cell nuclei which are found in patients whose immune system is predisposed to cause inflammation against their own body tissues. Extractable nuclear antigens (ENAs) are a grouping of antibodies often used to screen for mixed connective tissue disease (MCTD), Sjögren's syndrome and SLE and commonly is composed of four tests: anti-Sm (for SLE), anti-RNP (for MCTD), anti-La (for Sjögren's), anti-Ro (for Sjögren's), anti-Scl70 (for Scleroderma) and anti-Jo (for Dermatomyositis).

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 (s14-3-3e) dose-dependently induced the release of catabolic
factors by chondrocytes, mimicking the effects of cell compression. Addition of a 14-3-3e blocking antibody greatly attenuated the CCM-mediated induction of MMP-3 and MMP-13 expression. Furthermore, in human OA subchondral bone, s14-3-3e was strongly released, and in cultures of human OA chondrocytes, s14-3-3e 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. Rheumatoid arthritis (RA) disease activity multianalyte assay (e.g., Vectra DA) measures concentrations of twelve serum proteins purportedly associated with RA disease activity. These concentrations are then applied in an algorithm to estimate a disease activity score. The panel measures the following proteins: C-reactive protein (CRP), epidermal growth factor (EGF), interleukin 6 (IL-6), leptin, matrix metalloproteinase 1 (MMP-1), matrix metalloproteinase 3 (MMP-3), resistin, serum amyloid (SAA), tumor necrosis factor receptor, type 1 (TNF-R1), vascular cell adhesion molecule 1 (VCAM-1), vascular endothelial growth factor A (VEGF-A) and YKL-40.

Epidermal growth factor (EGF) is a protein that stimulates cells to enter mitosis and cell division. EGF promotes cell growth and differentiation, is essential in embryogenesis and is important in wound healing. Interleukin 6 (IL-6) is a cytokine derived from fibroblasts, macrophages and tumor cells. Leptin is a protein hormone that affects feeding behavior and hunger in humans. Matrix metalloproteinases (MMPs) are zinc dependent endopeptidases that hydrolyze proteins of the extracellular matrix. Endopeptidases are a large group of enzymes that catalyze the hydrolysis of peptide bonds in the interior of a polypeptide (small protein) chain or protein molecule. The extracellular matrix (ECM) refers to any substance produced by
cells and excreted to the extracellular space within the tissues, serving as a scaffolding to hold tissues together and helping to determine their characteristics. Resistin is a cytokine secreted by fat cells into the circulation; a cytokine is a general term for nonantibody proteins released by a specific type of cell as part of the body's immune response. Serum amyloid (SAA) is a protein whose plasma concentrations increase in response to tissue injury or to inflammation. Tumor necrosis factor (TNF) refers to a group of cytokines family that can cause cell death. Vascular cell adhesion molecule 1 (VCAM-1) is a class of membrane proteins located on the surface of endothelial and synovial cells involved with binding of other cells. Vascular endothelial growth factor (VEGF) is a signal protein produced by cells that stimulates the growth of new blood vessels; it is part of the system that restores the oxygen supply to tissues when blood circulation is inadequate. YKL-40 is a type of glycoprotein that may be found in higher than normal amounts in the blood of patients with certain types of cancer and inflammatory diseases; it is also referred to as human cartilage glycoprotein 39.

According to the manufacturer, the Vectra DA 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 RA. 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 RA patient sera. Biomarkers with qualifying assays were prioritized in a series of studies based on their correlations to RA 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 multi-variate 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 versus moderate/high disease activity. The effect of co-morbidities 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 out-performed individual biomarkers at estimating disease activity. Biomarker-based scores were significantly correlated with DAS28-CRP and could discriminate patients with low versus 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 co-morbidities.

Eastman et al (2012) stated that accurate and frequent assessment of RA 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 RA therapies was also assessed. The individual biomarker assays had 3 to 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 less than 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 anti-rheumatic drugs (DMARDs) 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 RA 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 (AUC) 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 multi-variate 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 and colleagues (2012) validated the Vectra DA MBDA test relative to clinical disease activity in RA. 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 sero-positive and sero-negative 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 to 12 weeks after initiation of anti-tumor necrosis factor (TNF) 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 sero-positive (AUROC 0.77, \( p < 0.001 \)) and sero-negative (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 sero-positive and most sero-negative subgroups. These investigators reported that changes in the MBDA score at 6 to 12 weeks could discriminate both American College of Rheumatology (ACR) criteria for 50% improvement responses \( (p = 0.03) \) and DAS28-CRP improvement \( pP = 0.002 \). 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 1 year. The investigators studied 125 patients with RA 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 \( \rho = 0.66, p < 0.0001 \)) 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 \( (\rho = 0.55, p < 0.0001) \). Groups stratified by European League Against Rheumatism disease activity (DAS28-ESR less than or equal to 3.2, 3.2 to 5.1 and greater than 5.1) had significantly different MBDA scores \( (p < 0.0001) \) and MBDA score could discriminate ACR/EULAR Boolean remission with an AUROC of 0.83 \( (p < 0.0001) \).

Markusse et al (2014) reported that the Vectra DA MBDA score predicts radiographic damage progression over 1 year in patients with early RA. For this study, these 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); 12 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 greater than or equal to 5 points) and patients who did not [AUC 0.767, 95% confidence interval [CI]: 0.639 to 0.896] than did DAS (AUC 0.521, 95% CI: 0.358 to 0.684). At 1 year, MBDA score had an AUC of 0.691 (95% CI: 0.453 to 0.929) and DAS had an AUC of 0.649 (95% CI: 0.417 to 0.880). Adjusted for anti-citrullinated 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 to 1.059 for baseline MBDA score; 1.037, 95% CI: 1.009 to 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 RA 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 (ΔSHS) greater than 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 less than 2.32), EULAR/ACR Boolean criteria and MBDA score (less than or equal to 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-progressers between patients in remission and those not in
reminiscence using either DAS28-CRP or EULAR/ACR criteria. The PLR for non-progression over 12 months for MBDA reminiscence was 4.73 (95 % CI: 1.67 to 15.0). Among patients in DAS28-CRP reminiscence, those with a high MBDA score were 2.3 times as likely (95 % CI: 1.1 to 3.7) to have joint damage progression during the next year.

Hambardzumyan et al (2015) 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 3 months were analyzed for 235 patients with early RA 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 5 points over 1 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 RA, 5 had low and 29 moderate MBDA scores at baseline. None of the former and only 1 of the latter group (3.4 %) had radiographic progression during 1 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 (odds ratio [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 RA, 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 RA 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 RA 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, 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 less than 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 RA. Board-certified rheumatologists without prior experience with the MBDA test (n = 81) were randomized into an intervention or control group as part of a longitudinal randomized-control study. All physicians were asked to care for 3 simulated RA 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 RA 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 % (p = 0.02) 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).

Segurado and Sasso (2014) stated that quantitative and regular
assessment of disease activity in RA is needed to achieve
treatment targets such as remission and to optimize clinical
outcomes. To assess inflammation accurately, predict joint
damage and monitor treatment response, a measure of disease
activity in RA should reflect the pathological processes resulting
in irreversible joint damage and functional disability. The Vectra
DA blood test supposedly provides an accurate, reproducible
score on a scale of 1 to 100 based on the concentrations of 12
biomarkers that reflect the pathophysiologic diversity of RA.
The analytical validity, clinical validity, and clinical utility of
Vectra DA have been evaluated for patients with RA in registries
and prospective and retrospective clinical studies. As a
biomarker-based instrument for assessing disease activity in
RA, the Vectra DA test can help monitor therapeutic response
to methotrexate and biologic agents and assess clinically
challenging situations, such as when clinical measures are
confounded by non-inflammatory pain from fibromyalgia.
Vectra DA scores correlate with imaging of joint inflammation
and are predictive for radiographic progression, with high
Vectra DA scores being associated with more frequent and
severe progression and low scores being predictive for
non-progression. The authors concluded that the Vectra DA score has the potential to complement conventional clinical and laboratory measures and optimize clinical decision-making.

Li et al (2016) evaluated the MBDA score as a predictor of radiographic progression and compared it with other risk factors among patients with established RA receiving non-biologic DMARDs. For 163 patients with RA in the Leiden Early Arthritis Cohort, investigators retrospectively assessed 271 visits for MBDA score (scale of 1 to 100), clinical data and subsequent 1-year radiographic progression (change in Sharp–van der Heijde score [SHS]). Scatter plot and non-parametric quantile regression curves evaluated the relationship between the MBDA score and change in SHS. Changes in joint space narrowing and erosions were compared among MBDA categories with Wilcoxon rank-sum tests. The ability of the MBDA score to independently predict progression was determined by multivariate models and cross-classification of MBDA score with other risk factors. Generalized estimating equation methodology was used in model estimations to adjust for same-patient visits, always greater than or equal to 1 year apart.

Patient characteristics included 67% female, 66%/67% RF+/anti-CCP+; mean age of 55 years, MBDA score 43 (moderate = 30 to 44); median disease duration 4.6 years, SHS 23. Radiographic progression was infrequent for low MBDA scores. Relative risk for progression increased continuously as the MBDA score increased, reaching 17.4 for change in SHS greater than 5 with MBDA scores greater than or equal to 60. Joint space narrowing and erosion progression were associated with MBDA score. The investigators found that MBDA score was associated with radiographic progression after adjustments for other risk factors. The investigators stated that MBDA score significantly differentiated risk for progression when swollen joint count, CRP or DAS28-CRP was low, and among sero-positive patients. The investigators concluded that MBDA score enhanced the ability of conventional risk factors to predict radiographic progression in patients with established RA receiving non-biologic DMARDs.
Hirata et al (2015) assessed the ability of a MBDA score to track clinical response in patients with RA treated with different TNF inhibitors. The retrospective observational study included 147 patients who had received adalimumab, etanercept, or infliximab for a year or more, during routine clinical care at the University Hospital of Occupational and Environmental Health, Japan. MBDA scores and clinical measures of disease activity were evaluated at baseline and, after 24 weeks (n = 84) and 52 weeks of treatment. Relationships between the changes (Δ) in MBDA score and changes in clinical measures or EULAR response categories were evaluated. The median disease activity was 5.7 by Disease Activity Score 28-erythrocyte sedimentation rate (DAS28-ESR) and 64 by MBDA score at baseline, and decreased significantly with treatment. ΔMBDA scores over 1 year correlated with ΔDAS28-ESR (r = 0.48) and ΔDAS28-CRP (r = 0.46). Linear relationships between ΔMBDA scores and ΔDAS28-ESR or ΔDAS28-CRP were not significantly different between TNF inhibitors. The MBDA scores declined significantly more in good responders (median change: -29) than moderate (-21), and more in moderate than in non-responders (+2), by the EULAR criteria. The investigators concluded that MBDA scores tracked disease activity and treatment response in patients with RA treated with 3 TNF inhibitors. The relationships between ΔMBDA scores and ΔDAS28-ESR or ΔDAS28-CRP were consistent across the 3 TNF inhibitor groups.

Rech et al (2016) analyzed the role of MBDA score in predicting disease relapses in patients with RA in sustained remission who tapered DMARD therapy in the RETRO study. MBDA scores (scale 1 to 100) were determined based on 12 inflammation markers in baseline serum samples from 94 patients of the RETRO study. MBDA scores were compared between patients relapsing or remaining in remission when tapering DMARDs. Demographic and disease-specific parameters were included in multi-variate logistic regression analysis for defining predictors of relapse. Moderate-to-high MBDA scores were found in 33 % of patients with RA overall. Twice as many patients who relapsed (58 %) had moderate/high MBDA compared with
patients who remained in remission (21%). Baseline MBDA scores were significantly higher in patients with RA who were relapsing than those remaining in stable remission (n = 94; p = 0.0001) and those tapering/stopping (n = 59; p = 0.0001). Multi-variate regression analysis identified MBDA scores as independent predictor for relapses in addition to anticitrullinated protein antibody (ACPA) status. Relapse rates were low (13%) in patients who were MBDA-/ACPA-, moderate in patients who were MBDA+/ACPA- (33.3%) and MBDA-ACPA+ (31.8%) and high in patients who were MBDA+/ACPA+ (76.4%). The investigators concluded that MBDA improved the prediction of relapses in patients with RA in stable remission undergoing DMARD tapering. The investigators commented that, if combined with ACPA testing, MBDA allowed prediction of relapse in more than 80% of the patients.

Reiss et al (2016) evaluated the relationship between DA and MBDA scores and changes in MBDA component biomarkers in tocilizumab (TCZ)-treated patients. Patients from the ACT-RAY study were included in this analysis if they had DA measures and serum collected at pre-specified time-points with sufficient serum for MBDA testing at greater than or equal to 1 visit. Descriptive statistics, associations between outcomes, and percentage agreement between DA categories were calculated. A total of 78 patients were included and were similar to the ACT-RAY population. Correlations between MBDA score and DAS28-CRP were \( \rho = 0.50 \) at baseline and \( \rho = 0.26 \) at week 24. Agreement between low/moderate/high categories of MBDA score and DAS28-CRP was observed for 77.1% of patients at baseline and 23.7% at week 24. Mean changes from baseline to weeks 4, 12, and 24 were proportionately smaller for MBDA score than DAS28-CRP. Unlike some other MBDA biomarkers, interleukin-6 (IL-6) concentrations increased in most patients during TCZ treatment. Correlations and agreement between MBDA and DAS28-CRP or Clinical Disease Activity Index (CDAI) scores were lower at week 24 versus baseline. The proportionately smaller magnitude of response observed for MBDA score versus DAS28-CRP may be due to the influence of the increase in IL-6 concentrations on MBDA score. The
investigators concluded that MBDA scores obtained during TCZ treatment should be interpreted cautiously and in the context of available clinical information.

Safi and colleagues (2015) evaluated the prevalence of anti-MCV antibodies and RF and examined their association in RA patients, both Saudi and non-Saudi. These investigators retrospectively studied 280 RA patients, at King Abdulaziz University Hospital. The antibodies were measured by enzyme linked immunosorbent assay and RF by nephelometry. The 280 patients included 196 Saudis and 84 non-Saudis, 88 % females and 12 % males, and the mean age was 45.3 years (SD = 14.3). Prevalence of RF was 141/280 (50 %) -- 93/196 (47.5 %) Saudis and 48/84 (57 %) non-Saudis -- with no significant differences (p > 0.05). Prevalence of mutated citrullinated vimentin antibodies was 165/280 (58.2 %) -- 121/196 (61.7 %) Saudis and 44/84 (52.4 %) non-Saudis -- with no significant differences (p > 0.05). Among RF-negative patients, considerable numbers were anti-MCV positive, and vice versa. Also, among the anti-MCV negative patients, considerable numbers were RF-positive, and vice versa. In all cohorts and in Saudi and non-Saudi patients, anti-MCV positivity was significantly associated with RF positivity (OR 3.15; 95 % CI: 1.9 to 5.19, p = 0.001); ESR and CRP were high with significant correlation (p < 0.005) with each other, with RF positivity but not with anti-MC positivity. Anti-MC positivity showed no significant correlation with age and gender. The authors concluded that in this cohort of patients, anti-MCV antibodies are a useful diagnostic tool for RA, but its combination with RF is essential; both markers are significantly associated. They stated that larger scale studies are recommended; correlation of anti-MCV with treatment and with disease activity still has to be published.

Lee and colleagues (2015) compared the diagnostic performance of anti-MCV and anti-CCP antibodies in RA. These investigators searched the Medline, Embase, and Cochrane library databases and performed 2 meta-analyses on the diagnostic accuracy of anti-MCV and anti-CCP in patients with RA compared to healthy controls. They identified 12 studies
that included a total of 2,003 RA patients and 831 healthy controls for the meta-analysis. The pooled sensitivity and specificity of anti-MCV were 68.6 % [95 % CI: 66.6 to 79.7] and 94.2 % (95 % CI: 92.4 to 96.7) and those of anti-CCP were 61.7 % (95 % CI: 59.5 to 63.8) and 97.1 % (95 % CI: 96.7 to 98.1), respectively. Anti-MCV PLR, NLR, and DOR were 12.99 (95 % CI: 8.013 to 21.27), 0.297 (95 % CI: 0.238 to 0.369), and 47.78 (95 % CI: 28.59 to 79.84), and those for anti-CCP were 16.71 (95 % CI: 11.42 to 24.47), 0.378 (95 % CI: 0.325 to 0.439), and 54.20 (95 % CI: 31.65 to 92.82), respectively. The AUC of anti-MCV was 0.886, and its Q* index was 0.817, indicating modest accuracy, while the AUC of anti-CCP was 0.946, and its Q* index was 0.885. The sensitivity of anti-MCV was significantly higher than that of anti-CCP in the diagnosis of RA (difference 0.069, 95 % CI: 0.039 to 0.098, p < 0.0001), but the specificity of anti-MCV was lower than that of anti-CCP (difference ‐ 0.029, 95 % CI: ‐ 0.051 to ‐ 0.006, p = 0.012). The Q* index of anti-MCV was significantly lower than that of anti-CCP (difference - 0.068, 95 % CI: - 0.070 to - 0.065, p < 0.0001). The authors concluded that the findings of this meta-analysis demonstrated that anti-MCV is more sensitive but less specific, and has lower diagnostic accuracy than anti-CCP in RA, although anti-MCV and anti-CCP showed comparable high PLRs.

van Tuyl and Lems (2014) stated that recent qualitative research has shown that stiffness is an important symptom for patients with RA to identify remission. However, it is unclear how to measure stiffness in low disease activity. These researchers summarized the existing literature on validity of patient reported outcomes to measure stiffness in RA low disease activity states to aid the choice for a measurement instrument. An extensive PubMed search was undertaken, identifying measurement instruments for patient perceived stiffness used in low disease activity. Eligible studies reported on (i) stiffness as an outcome in relation to other core set measures, (ii) development of a patient reported tool to measure stiffness, or (iii) comparison of 2 different tools to measure aspects of stiffness, all in low disease activity. Of 788 titles, only 2 studies report on validity of stiffness measures within low disease activity.
activity. Morning stiffness (MS) is reported in 44 to 80% of patients in low disease activity. A difference of 40 to 60 minutes in duration until maximum improvement is observed between active and inactive patients. Severity of MS might discriminate better between high and low disease activity compared to measurement of duration of MS. The authors concluded that there is insufficient data on measurement of stiffness in the spectrum of low disease activity or remission.

Halls et al (2015) noted that stiffness is internationally recognized as an important indicator of inflammatory activity in RA but is poorly understood and difficult to measure. These investigators explored the experience of stiffness from the patient perspective. Semi-structured interviews conducted with 16 RA patients were analyzed independently by researchers and patient partners using inductive thematic analysis. Six themes were identified: (i) Part of having RA identified stiffness as a normal consequence of RA, perceived as associated with disease-related aspects such as fluctuating disease activity, other RA symptoms and disease duration, (ii) local and widespread highlighted stiffness occurring not only in joints, but also over the whole body, being more widespread during the morning or flare, (iii) linked to behavior and environment illustrated factors that influence stiffness, including movement, medications and weather, (iv) highly variable captured the fluctuating nature of stiffness within and between patients and in relation to temporality, duration and intensity, (v) impacts on daily life emphasized the effect of stiffness on a range of domains, including physical function, quality of life, psychological well-being, activities of daily living and participation in work and leisure activities, and (vi) requires self-management detailed self-management strategies targeting both the symptom and its consequences. The authors concluded that patients' experiences of stiffness were varied, complex and not exclusive to the morning period. Importantly, stiffness was reported in terms of impact rather than the traditional measurement concepts of severity or duration. They stated that based on these findings, further research is needed to develop a patient-centered measure that adequately reflects...
inflammatory activity.

Hambardzumyan et al (2016) previously showed that the MBDA score (Vectra) in patients with newly diagnosed RA identified patients at risk for radiographic progression (RP). These researchers evaluated the MBDA score at multiple time-points as a predictor of RP during 2 years of follow-up. A subset of patients with RA (n = 220) from the Swedish Farmacotherapy (SWEFOT) trial were analyzed for MBDA score, DAS28, CRP and ESR at baseline (BL), month 3 and year 1, for predicting RP based on modified Sharp/van der Heijde scores at BL, year 1 and year 2. Patients with persistently low MBDA (less than 30) scores or those with a decrease from moderate (30 to 44) to low MBDA scores, did not develop RP during 2 years of follow-up. The highest risk for RP during 2 years of follow-up (42%) was observed among patients with persistently high (greater than 44) MBDA scores. Among methotrexate (MTX) non-responders with a high MBDA score at BL or month 3, significantly more of those who received triple therapy (TT) had RP at year 2 compared with those who received anti-TNF therapy. The authors concluded that a low MBDA score at BL, month 3 and year 1, was predictive for low risk of rapid RP (RRP) over 2 years of follow-up in patients with early RA, and this association was stronger (non-significantly) than associations with low DAS28, CRP or ESR. They stated that the MBDA score may thereby become a useful tool for guiding treatment choices in individual patients. The drawbacks of this study were: (i) it was based on one cohort, which was not a full representation of the RA population, (ii) the MTX responder population lacked MBDA data at year 1, which limited the ability to perform analyses, (iii) due to the lack of information about cut-offs for CRP and ESR categories, these researchers had to use non-validated cut-offs for CRP and tertiles for ESR in order to define low/moderate/high levels of disease activity. This rendered the comparison with MBDA score more limited and the health-economic point of view cannot be evaluated, (iv) changes in the treatment of patients from different arms could affect the radiographic outcome, and (v) in comparison of proportion of RRP within each therapy group, some subgroups
of patients were very small. Considering this and the fact of multiple testing, the results of significant difference of proportions of RRP between TT and anti-TNF therapy groups need to be confirmed.

Fleischmann and colleagues (2016) evaluated the ability of a MBDA test (Vectra DA score) to reflect clinical measures of disease activity in patients enrolled in the AMPLE (abatacept versus adalimumab comparison in biologic-naive RA subjects with background methotrexate) trial (NCT00929864). In the AMPLE trial, patients with active RA who were naïve to biologic agents and had an inadequate response to methotrexate (MTX) were randomized (1:1) to subcutaneous (SC) abatacept (125 mg, weekly) or SC adalimumab (40 mg, every 2 weeks), with background MTX, for 2 years; MBDA score was analyzed in serum samples collected at baseline, month 3, and years 1 and 2. Adjusted mean change from baseline in MBDA score was compared for abatacept and adalimumab treatment groups. Cross-tabulation was used to compare MBDA score and clinical measures of disease activity: CDAI, Simplified Disease Activity Index (SDAI), DAS28-CRP, and Routine Assessment of Patient Index Data (RAPID)-3. A total of 318 patients were randomized to abatacept and 328 to adalimumab; MBDA data were available for 259 and 265 patients, respectively. There was no association between MBDA score and disease activity defined by CDAI, SDAI, DAS28-CRP, or RAPID-3 in the abatacept and adalimumab treatment groups. The authors concluded that MBDA score did not reflect clinical disease activity in patients enrolled in AMPLE and should not be used to guide decision-making in the management of RA, particularly in those patients who receive abatacept or adalimumab as a first biologic therapy.

Antibodies to Mutated Citrullinated Vimentin (MCV) for the Diagnosis of Juvenile Idiopathic Arthritis:

Zhang et al (2015) compared the diagnostic value of antibodies to MCV and some associated autoantibodies in juvenile idiopathic arthritis (JIA) and analyzed the relation between
antibodies and inflammatory markers. Antibodies to CCP and anti-MCV antibodies were detected by enzyme-linked immunosorbent assay (ELISA), anti-perinuclear factor (APF) and anti-keratin antibody (AKA) by indirect immunofluorescent assay, as well as RF by latex agglutination test in serum samples from 113 patients with JIA and 56 children without RA. The positive rate of anti-MCV antibodies, anti-CCP antibodies, and RF was 16.8 %, 14.2 %, and 21.2 % in the JIA. In the other group, the positive rate was 2.2 %, 2.2 %, and 6.5 %. There was a significant difference between the 2 groups ($\chi^2(2) = 8.105, 6.337, 7.036, p < 0.05$). The positive rate of AKA and APF were not significantly different. The area under the ROC curve of anti-MCV antibodies, anti-CCP antibodies, RF, AKA, APF was 0.579, 0.561, 0.578, 0.539, 0.505. The positive rate of anti-MCV antibodies and anti-CCP antibodies were higher than other antibodies. In the RF-positive poly-articular disease patients, they were higher than those in the other subtypes ($p < 0.05$). Antibody levels were not significantly different ($p > 0.05$) from other subtypes. The swollen joint counts and tender joint counts had a low correlation to anti-MCV antibodies, anti-CCP antibodies, RF, AKA and APF. No correlation was found between ESR, CRP and anti-MCV antibodies, anti-CCP antibodies, RF, AKA and APF. The authors concluded that the diagnostic value of anti-MCV antibodies was low for JIA. The positive rate of anti-MCV antibodies was higher than the other antibodies in the classification of JIA. There was a low correlation between anti-MCV antibodies, anti-CCP antibodies, RF, AKA, APF and swollen joint counts, tender joint counts.

Lipinska et al (2016) evaluated the diagnostic and prognostic value of anti-MCV antibodies in JIA comparing to anti-CCP. A total of 30 children with confirmed JIA diagnosis and 20 children as a control group were included into the study. Serum and synovial fluid levels of anti-CCP, anti-MCV, and immunoglobulin M- RF (IgM-RF) antibodies were assessed. Anti-MCV was positive in 11/30 (36.6 %), whereas anti-CCP positivity was found in 12/30 (40 %) children with JIA. Among 11 children with JIA positive for anti-MCV, 5 (45.5 %) were also positive for anti-CCP and among 18 JIA children negative for
anti-CCP, 6 (33.33 %) were also anti-MCV positive; 6 out of 30 JIA children were found to be IgM-RF positive. In general, 2 out of all those 11 anti-MCV-positive patients demonstrated oligo-arthritis and 9/11 had poly-articular type of onset. Anti-MCV serum concentration correlated positively with anti-CCP (p = 0.004). Almost 60 % of children in early stage of JIA were anti-MCV positive. Levels of anti-CCP antibodies correlated positively with the disease activity (p = 0.0014) and radiological outcome (p = 0.00017). In all synovial fluid samples, the concentration of autoantibodies was under the cut-off values.

The authors concluded that the findings of this study indicated that anti-MCV as well as anti-CCP antibodies may be helpful in the diagnosis of JIA, especially in the early course of the disease. They stated that anti-MCV antibodies could identify a group of children with JIA that is negative for anti-CCP antibodies and RF. However, it appeared that in JIA, anti-CCP rather than anti-MCV antibodies have impact on radiographic changes. These preliminary findings from a small study (n = 30) need to be validated by well-designed studies.

Furthermore, UpToDate reviews on “Systemic juvenile idiopathic arthritis: Clinical manifestations and diagnosis” (Kimura, 2016), “Polyarticular juvenile idiopathic arthritis: Clinical manifestations, diagnosis, and complications” (Weiss, 2016a), and “Oligoarticular juvenile idiopathic arthritis” (Weiss, 2016b) do not mention measurement of anti-mutated citrullinated vimentin antibodies as a diagnostic tool.

**CPT Codes / HCPCS Codes / ICD-10 Codes**

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":*

**Cyclic Citrullinated Peptide (CCP):**

<table>
<thead>
<tr>
<th>CPT codes covered for indications listed in the CPB:</th>
</tr>
</thead>
<tbody>
<tr>
<td>86200 Cyclic citrullinated peptide (CCP), antibody</td>
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</table>
**ICD-10 codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>M05.00</td>
<td>Rheumatoid arthritis and other inflammatory poliarthropathies</td>
</tr>
<tr>
<td>M14.89</td>
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</table>

**Myositis Antibody Panel:**

**CPT codes covered for indications listed in the CPB:**

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<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>83516</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method [Myositis Antibody Panel]</td>
</tr>
</tbody>
</table>

**CPT codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>81490</td>
<td>Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score</td>
</tr>
<tr>
<td>83520</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified [anti mutated citrullinated vimentin (MCV) antibodies (e.g., the Avise MCV test)]</td>
</tr>
</tbody>
</table>

**ICD-10 codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>G72.49</td>
<td>Other inflammatory and immune myopathies, NEC</td>
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</table>

**ICD-10 codes not covered for indications listed in the CPB:**

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<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>M15.0</td>
<td>Osteoarthritis and allied disorders</td>
</tr>
<tr>
<td>M19.93</td>
<td></td>
</tr>
<tr>
<td>M32.0</td>
<td>Systemic lupus erythematous (SLE)</td>
</tr>
<tr>
<td>M32.9</td>
<td></td>
</tr>
</tbody>
</table>

The above policy is based on the following references:

3. Targoff IN. Laboratory testing in the diagnosis and


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.


23. Safi MA, Attar SM, Fathaldin OA, Safi OM. Anti-mutated citrullinated vimentin antibody and rheumatoid factor (prevalence and association) in rheumatoid arthritis
patients; Saudi and non-Saudi. Clin Lab. 2015;61(3-4):259-267


32. Weiss PF. Polyarticular juvenile idiopathic arthritis: Clinical manifestations, diagnosis, and complications.
33. Weiss PF. Oligoarticular juvenile idiopathic arthritis. UpToDate Inc., Waltham, MA. Last reviewed July 2016b.


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