



RHEUMATOLOGY NURSE PRACTICE

NEWSLETTER

Inside this Issue

ISSUE 3 | VOLUME 1

- » Which laboratory tests are most commonly utilized in patients with rheumatoid arthritis (RA)? Which tests are used to assess disease activity? Monitor safety? Rule out infection and other diseases? Predict response to therapy?
- » What do the terms “sensitivity,” “specificity,” and “predictive value” mean in regards to laboratory test results?
- » How are multi-test panels being used today, and what is their future potential in the diagnosis and assessment of RA disease progression?
- » How do laboratory results tell the truth, lie, or provide more information in specific patient cases?

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Learning Objectives

1. Define key terms such as specificity, sensitivity, and positive predictive value as they relate to the diagnostic and prognostic value of individual laboratory tests
2. Explain the utility and limitations of specific laboratory tests commonly ordered in patients with RA
3. Describe the differences in prognosis between patients with seronegative vs. seropositive disease
4. Identify future opportunities with laboratory testing that may improve the ability to predict patients' response to treatment

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Breaking Down Lab Reports in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disease that causes joint destruction and chronic inflammation throughout the body. The clinical course of RA can vary widely, from a mild form with little or no joint destruction to an aggressive phenotype associated with severe debilitation. When used in combination with a patient history and physical examination, laboratory testing is essential to confirm the diagnosis of RA, to predict the clinical course of disease, and to monitor the effect of treatment.

Laboratory Tests: The Unique Challenge of RA Management

In many chronic diseases such as dyslipidemia and diabetes, laboratory tests can be the most important type of information collected in the process of care. Patients are often diagnosed on the basis of

elevated cholesterol and blood glucose levels alone, and laboratory values drive decisions about when to start or adjust treatment. However, the story is quite different in RA where positive laboratory tests for RA are insufficient to determine a diagnosis on their own, and negative test results are not enough to rule out the disease entirely.¹

NEWSLETTER SUMMARY

In this issue of Rheumatology Nurse Practice, we will explore the rationale for ordering various laboratory tests, from the initial diagnostic work-up through ongoing monitoring, and explore how test results influence the management of patients with RA.

Criteria	Points
<i>CLINICAL FEATURES</i>	
Joint Involvement	1-5 points are given based on the size and number of joints
Duration of Symptoms	1 point is given for duration greater than 6 weeks
<i>LABORATORY TESTS</i>	
Autoantibodies	2-3 points are given based on low-positive or high-positive RF or ACPA
Acute Phase Reactants	1 point is given for abnormal ESR or CRP

ACPA = anti-citrullinated protein antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor

Table 1
ACR/EULAR
Classification
Criteria for RA²

The current RA classification criteria from the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) are centered around a points-based system in which patients are scored on the presence of clinical and laboratory features of RA (Table 1). Patients are considered to have RA if they score at least 6 out of a possible 10 points; one point must be from synovitis that cannot be explained by another disease. Patients can earn up to 4 of the 6 points needed for an RA diagnosis based on positive laboratory tests. Conversely, a patient can meet the diagnostic criteria for RA based solely on joint involvement and duration of symptoms without a single abnormal laboratory result.²

The Growing Role of Evidence-Based Laboratory Medicine

Evidence-based laboratory medicine (EBLM) describes an approach to patient care that emphasizes the use of laboratory tests to guide treatment decisions. EBLM is becoming increasingly important in today's healthcare environment due to the growing emphasis on the efficient use of resources to achieve quality care.³ However, it is a common misperception that laboratory tests used in RA assessment are more "scientific" than subjective measures such as joint tenderness and pain. In reality, studies have shown that patient-reported measures of physical function, pain, and global health status are more likely than laboratory tests to be abnormal at the time of diagnosis, and are more predictive of long-term disability.¹

The following sections of this newsletter explore the roles of individual laboratory tests in the diagnosis, prognostic evaluation, and management of RA. The reference ranges that define "normal" test results may vary depending on the individual assay and your specific practice (Table 2). Ideally, laboratory test results and subjective measures of

RA disease activity should be considered together to gain a full understanding of each patient's symptoms.¹

Laboratory Tests for RA Disease Activity

Autoantibodies

Autoantibodies are a hallmark feature of RA that reflect the underlying autoimmune process. Activation of the autoimmune response is an early event in the pathogenesis of RA, resulting in autoantibodies that may be detectable in the blood several years before clinical symptoms develop.¹⁰ **Rheumatoid factor (RF)** was the first autoantibody identified in patients with RA. RF is present in up to 70% of RA patients, but it is also commonly found in healthy individuals and in patients with other autoimmune diseases, chronic infections, and cancer. The sensitivity of RF is approximately 69%, and the specificity is 85%. Higher RF levels are associated with more severe RA disease activity.¹

Compared with RF, the **anti-citrullinated peptide antibodies (ACPAs)** correlate more strongly with RA.¹¹ In a large review of studies, the sensitivity of ACPAs for RA ranged from 57% for patients with early disease to 77% for those with established RA. The specificity of ACPAs for RA was 96% for all patients.¹² Higher ACPA levels predict more severe RA disease activity, as measured by higher ultrasound synovitis scores, disease activity score with 28 joint count (DAS28), and Simplified Disease Activity Index (SDAI) scores.¹³

Patients who test positive for either RF or ACPA, or both, are described as having '**seropositive**' RA. Conversely, '**seronegative**' RA describes the absence of both autoantibodies. Seropositive RA is associated with more aggressive disease, including an increased likelihood of joint destruction.

A recent study examining the rates of orthopedic surgery in patients with RA illustrates the prognostic differences between seropositive and seronegative RA. The retrospective study included more than 2,000 patients with RA; seropositive patients were defined as those with high RF levels (>34 IU/mL), high ACPA levels (>4.1 IU/mL), or both. The rate of orthopedic surgery in this group ranged from 14.3% to 19.9%. By comparison, only 5.1% of patients with seronegative RA required orthopedic surgery ($P < 0.001$) (Figure 1).¹⁴

The definition of seronegative RA has become a moving target, as improved testing techniques can detect smaller concentrations of a wider variety of autoantibody subtypes. In general, approximately 20% of patients with RA will be seronegative throughout the course of their disease.¹⁵ Although seronegative RA is considered the less aggressive phenotype, patients with this form of RA can experience substantial disease activity that requires careful management.¹⁵

Ordering tests for both RF and ACPA is critical for a patient's initial diagnostic work-up, as the severity of RA is best understood when the status of both of these antibodies is known.¹⁶ However, repeat antibody testing is not necessary, given that it can be costly and test results rarely change over the course of time. Indeed, autoantibody tests should not be used to monitor disease activity or assess response to treatment.¹⁶ This is why tests for RF and ACPA are not included in composite measures of disease activity such as the DAS28 or SDAI. The only exceptions involve cases where test results are borderline positive or negative and repeat testing can provide clarity around antibody serology.¹⁶

Despite these best practices, repeat antibody testing appears to be common in patients with

RA. In a study of 100 patients, 65 patients (65%) tested positive for RF on their first test. Among patients with a positive result, 78% had at least 1 repeat RF test, and 34% had 4 or more RF tests. Among all patients, only 2 RF results changed with repeat testing, with 1 each switching from negative to positive and vice versa. Repeat ACPA testing was also common, with 25% of patients having at least 2 ACPA tests, and 5% being tested 4 times or more.¹⁶

Multiple other autoantibodies have been detected in RA, including antibodies against carbamylated proteins (anti-CarP), nuclear antigens (e.g., anti-RA33), and collagen, although none of these are yet part of standard autoantibody testing.¹⁷

Antinuclear antibodies

Antinuclear antibodies (ANAs) are often present in patients with certain autoimmune and connective tissue diseases. Nearly 100% of patients with drug-induced lupus or systemic lupus erythematosus (SLE) will test positive for ANAs. In addition, more than 95% of patients with scleroderma or Sjögren's syndrome will have a positive ANA test. By comparison, only 40% of patients with RA will test positive for ANA. Therefore, ANA testing is not particularly useful for the diagnosis of RA.⁶

Markers of inflammation

Acute phase reactants (APRs), including **erythrocyte sedimentation rate (ESR)** and **C-reactive protein (CRP)**, are inflammatory markers that increase in response to tissue injury and acute or chronic inflammation. The sedimentation rate describes the rate at which red blood cells suspended in plasma settle when placed in a vertical tube. The rate can be elevated in the presence of inflammation

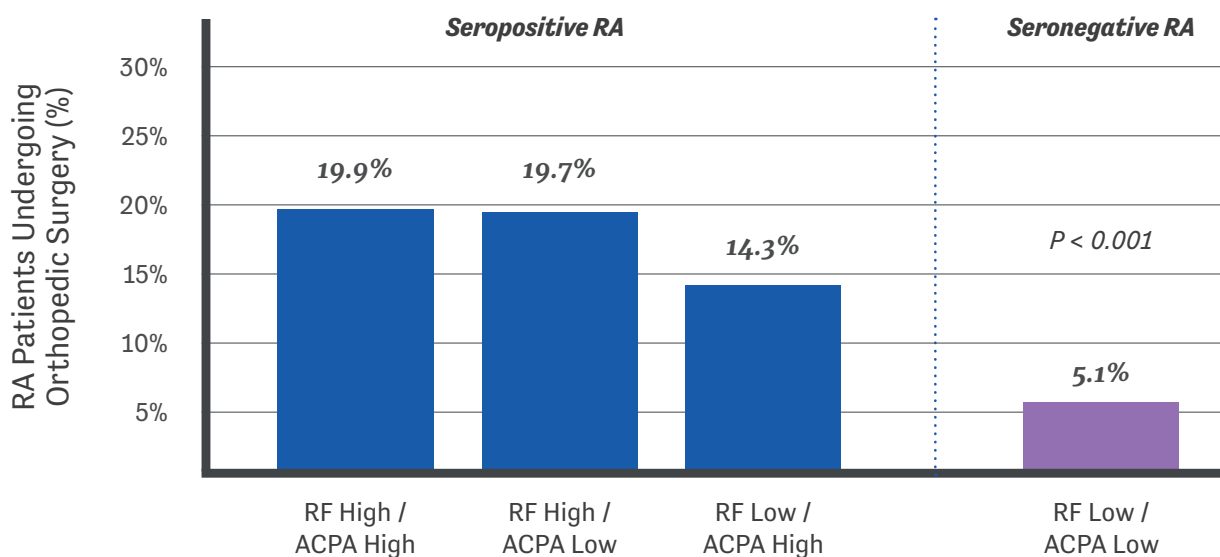


Figure 1
Orthopedic Surgery in Seropositive and Seronegative RA¹⁴

ACPA = anti-citrullinated protein antibody; RF = rheumatoid factor

or infection, regardless of the underlying cause. ESR is also influenced by factors unrelated to inflammation, including changes in the size, shape, and number of erythrocytes. As a result, ESR can be abnormal in patients who are older, obese, or female, and in patients with chronic diseases such as kidney disease and anemia.⁶ CRP is a serum protein synthesized by the liver in response to chemical signals released by macrophages and adipocytes (fat cells). A range of acute and chronic inflammatory stimuli can cause an increase in CRP levels, including infections, inflammatory diseases, cancer, injury, necrosis, and aging.¹⁸

Both of these APRs correlate with RA disease activity, although increased levels of ESR and CRP reflect different underlying pathologic mechanisms. Therefore, ESR and CRP can show discordant values, with only one measure presenting as elevated.^{19,20} In one study of patients with RA (N = 400), 27% of patients had elevated levels of either ESR or CRP.¹⁹ In general, CRP is a stronger measure of inflammatory disease activity, whereas ESR tends to reflect immunologic disorder.²⁰ ESR and CRP levels tend to decrease in response to therapy, although the magnitude of reduction can vary for individual patients. Patients with RA must achieve normal ESR or CRP levels to meet the criteria for clinical remission.¹

Test	Normal Results*
AUTOANTIBODIES	
ACPA	<25 IU/mL
ANA	Negative
RF	<5 IU/mL
ACUTE PHASE REACTANTS	
CRP	<10 mg/dL
ESR	Male: <22 mm/hr Female: <29 mm/hr
CBC, DIFFERENTIAL, AND PLATELET COUNT	
Hb	Male: 13.5-17.5 gm/dL Female: 12.0-15.5 gm/dL
HCT	Male: 38.8-50.3% Female: 34.9-44.5%
Platelets	150,000-450,000 platelets/mcL
RBC	Male: 4.3-5.7 cells/mcL Female: 3.9-5.0 cells/mcL
WBC	3,500-10,500 cells/mcL

* Reference ranges for individual assays may vary

Table 2
Reference Ranges for Common RA Laboratory Tests^{4,5}

ACPA = anti-citrullinated protein antibody;
ANA = anti-nuclear antibody; CBC = complete blood count;
CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; Hb = hemoglobin; HCT = hematocrit; RBC = red blood cell; RF = rheumatoid factor; WBC = white blood cell

Approximately 40% of patients with RA will present with normal ESR or CRP levels.¹ These patients often have a milder disease course, require less aggressive treatment, and experience better clinical outcomes than patients with elevated ESR or CRP levels.¹⁹ One recent study examined treatment patterns and outcomes among patients with RA according to baseline ESR and CRP levels. In the first 2 years after diagnosis, patients with normal baseline APR levels were less likely to be treated with glucocorticoids or biologic agents. Despite the use of less aggressive therapy, more than half of patients with normal APR levels achieved clinical remission, compared with approximately one-third of patients with abnormal ESR and/or abnormal CRP levels ($P=0.0003$).¹⁹ Although these findings are helpful for understanding general patterns in RA severity, it is important to remember that individual patients can experience aggressive disease despite testing “negative” for markers of poor prognosis.

Laboratory Tests for Safety Monitoring

Complete Blood Count

The complete blood count (CBC) is an important component of any laboratory evaluation of patients with RA. Clinicians should order a CBC prior to starting RA treatment to establish baseline values. A standard CBC includes a red blood cell (RBC) count, white blood cell (WBC) count, hematocrit (Hct), and hemoglobin (Hb) level. In patients with RA, the WBC count may be elevated due to inflammation or a disease flare. In addition, chronic diseases such as RA can reduce the bone marrow’s ability to produce red blood cells, resulting in a low RBC due to anemia of chronic disease. Several medications commonly used to treat RA, including methotrexate (MTX) and other disease modifying antirheumatic drugs (DMARDs), can also cause bone marrow suppression that results in anemia.¹¹

Anemia is emerging as an important potential predictor of erosive joint disease and radiographic progression in patients with RA.²¹ In 2 recent phase 3 trials, the baseline prevalence of anemia was 41% in patients with early RA and 18% in patients with established disease. Among those with normal hemoglobin levels at baseline, 30% had at least 1 episode of anemia during the 2-year study period. Anemia correlated with significant worsening of radiographic progression, as measured by the modified total Sharp x-ray score (mTSS). Each additional week of anemia was associated with a mean mTSS increase of 0.111 in patients with early RA ($P < 0.001$) and 0.26 in patients with established RA ($P = 0.047$).²¹ Therefore, patients with RA and chronic anemia may be candidates for more aggressive therapy aimed at reducing the risk of radiographic progression.

Platelets counts

Platelet counts can range from abnormally high to abnormally low in patients with RA. The presence of inflammation throughout the body can elevate platelet counts.¹¹ In one study of patients with RA, a higher mean platelet volume significantly correlated with worse disease activity ($P = 0.007$).²² Conversely, treatment with agents such as MTX and tumor necrosis factor (TNF) inhibitors is associated with a reduction in platelet count.^{22,23} Patients with prolonged thrombocytopenia (low platelets) may be at risk for immune thrombocytopenia purpura (ITP), a condition that develops in patients with many systemic autoimmune diseases, including RA.²⁴

Kidney and liver function tests

Prior to starting treatment for RA, a comprehensive metabolic profile should be obtained to establish baseline kidney and liver function. Standard renal function testing includes urinalysis, glomerular filtration rate (GFR), blood urea nitrogen (BUN) levels, and serum creatinine levels.¹¹ Serum levels of alanine transaminase (ALT) and aspartate transaminase (AST) are commonly used to evaluate baseline liver function.²⁵

Kidney and liver function should be monitored for the duration of RA treatment.²⁵ Dose adjustments or other treatment modifications may be required for patients with abnormal serum

Sensitivity, Specificity, and Predictive Values

Diagnostic tests can vary in their ability to correctly identify patients with a disease (i.e., sensitivity) and to correctly identify patients without it (i.e., specificity) (Table 3). To understand whether a test is useful in the clinical setting, it is important to understand multiple test features. For instance, a test that is highly sensitive for RA will yield positive test results in nearly all patients with RA. However, a highly sensitive test with low specificity may also yield positive test results for patients with a range of other diagnoses. In such cases, interpreting a positive test result would be difficult.

For example, antinuclear antibody (ANA) is highly sensitive (99%) for systemic lupus erythematosus (SLE). Nearly all patients with SLE will test positive for ANA. However, the specificity of ANA for SLE is low (57%), because ANA is also found in many healthy persons and individuals with other connective tissue disorders. In addition, SLE is a rare condition; there are many more healthy individuals who have naturally occurring ANA than patients with SLE who have ANA as a result of their disease. Therefore, most patients who test positive for ANA will not have SLE.^{6,7}

Table 3
Interpreting Test Results⁸

Term	Definition	Example
Sensitivity	The ability of a test to correctly detect the presence of a disease. Also called the true-positive rate.	A test is 95% sensitive for RA. Of 100 patients with RA, 95 will have a positive result on this test. Five will have false-negative results.
Specificity	The ability of a test to correctly detect the absence of a disease. Also called the true-negative rate.	A test is 95% specific for RA. Of 100 patients without RA, 95 will have a negative result on this test. Five will have false-positive results.
Positive Predictive Value (PPV)	The rate at which a positive test result can confirm the presence of disease.	A test has an 85% PPV for RA. Of 100 positive tests, 85 are true positives and 15 are false-positives.
Negative Predictive Value (NPV)	The rate at which a negative test result can confirm the absence of disease.	A test has an 85% NPV for RA. Of 100 negative tests, 85 are true negatives and 15 are false-negatives.

The ideal diagnostic test is both highly sensitive and highly specific for the suspected diagnosis.⁸ As an example, the current approach to HIV testing—which involves both a preliminary antibody screen and a confirmatory test—is both highly sensitive (>99.5%) and highly specific (>99.5%) for HIV infection, making it an excellent diagnostic test.⁹

creatinine or liver transaminase levels.²⁵ Some patients may develop elevated liver enzymes as a result of treatment with MTX, leflunomide, or chronic nonsteroidal antiinflammatory drug (NSAID) therapy.¹¹

Laboratory Tests to Rule Out Infection and Other Diseases

Tuberculosis

All patients with RA should be screened for tuberculosis (TB) prior to starting treatment with prednisone or biologic agents. The ACR recommends TB screening with the tuberculin skin test (TST) or an interferon-gamma release assay (IGRA) such as QuantiFERON-TB Gold. The IGRA is the preferred screening test for patients with a history of vaccination against TB.²⁶

Patients who test positive on TST or IGRA screening will require additional evaluation with a chest radiograph and possibly a sputum analysis. If latent or active TB infection is confirmed, patients will require TB treatment prior to starting biologic therapy or high-dose (>20 mg/day) prednisone.²⁶

Hepatitis B and C

Patients with RA should be screened for the presence of hepatitis B virus (HBV) and hepatitis C virus (HCV).^{11,25} Both chronic HBV and HCV infection can trigger positive RF results.²⁷ In addition, patients who are diagnosed with HBV or HCV may have to avoid certain RA medications that may irritate or cause increased stress to the liver.¹¹

HIV

The Centers for Disease Control and Prevention (CDC) recommends that all individuals aged 13 to 65 years undergo screening for the human immunodeficiency virus (HIV) at least once.²⁸ Therefore, it is reasonable to add an HIV test to the standard baseline RA work-up that includes HBV and HCV testing.²⁹ Interpreting baseline laboratory results can be tricky in patients with RA and HIV, as HIV can increase RF and ACPA positivity. In rare cases, RA can cause false-positive HIV test results.³⁰

The presence of HIV infection can influence the choice of RA therapy. In particular, patients with HIV are vulnerable to interactions between antiviral agents and rheumatology medications such as glucocorticoids and MTX.²⁹ Given the potential complexity of treatment, patients with both RA and HIV are best managed in collaboration with an HIV practitioner.²⁹



Laboratory tests are used not only to diagnose and assess RA, but to rule out other infections and diseases.

Synovial fluid analysis

Patients with an unclear diagnosis of RA may require an arthrocentesis, which involves aspirating the synovial fluid from an affected joint. Analyzing the synovial fluid for the presence of immune system cells and uric acid crystals is important for ruling out infection and gout.¹¹

Uric acid

An elevated uric acid level indicates the presence of gout.¹¹

Vitamin D

Patients with vitamin D deficiency and RA may be at increased risk of radiographic progression and functional disability. In a study of 813 patients with RA, baseline serum vitamin D levels significantly correlated with several measures of RA disease activity, including the DAS28 score, mTSS, and Health Assessment Questionnaire (HAQ) score. The presence of severe vitamin D deficiency (< 10 ng/mL) at baseline doubled the risk of disability at 6 months (OR, 2.01; $P = 0.025$) and

doubled the risk of radiographic progression at 12 months (OR, 1.95; $P = 0.038$). The interaction between serum vitamin D levels and RA outcomes highlights the role of environmental risk factors in the development and progression of RA.³¹

There are two primary lab tests that measure vitamin D levels – the 25-hydroxy vitamin D and 1,25-dihydroxyvitamin D tests. It is important to be able to differentiate the two tests.

The 25-hydroxy vitamin D blood test is the more accurate measurement of vitamin D levels. A level of 20–to–50 ng/mL is considered adequate for healthy individuals. Vitamin D insufficiency is associated with levels between 21–29 ng/mL. A level of <12 ng/mL indicates vitamin D deficiency.³²

The 25-hydroxy vitamin D test is often requested before an individual begins drug therapy for osteoporosis. It may also be indicated for individuals known to be at risk of vitamin D deficiency. These includes the following groups:³²

- Older adults
- Individuals who are institutionalized or homebound and/or have limited sun exposure
- Obese individuals
- Individuals who have undergone gastric bypass surgery and/or who have fat malabsorption
- Individuals with darker skin
- Breastfed infants

When an individual’s calcium is high or someone a disease that might produce excess amounts of vitamin D—such as sarcoidosis or some forms of lymphoma—1,25-dihydroxyvitamin D may be ordered.³²

Multi-Test Panels for RA Assessment

Multi-test panels incorporate several individual laboratory tests into a single assay. Currently, a handful of multi-test panels are available to support the diagnosis of RA and/or assist with ongoing disease activity monitoring.

Multi-biomarker disease activity score

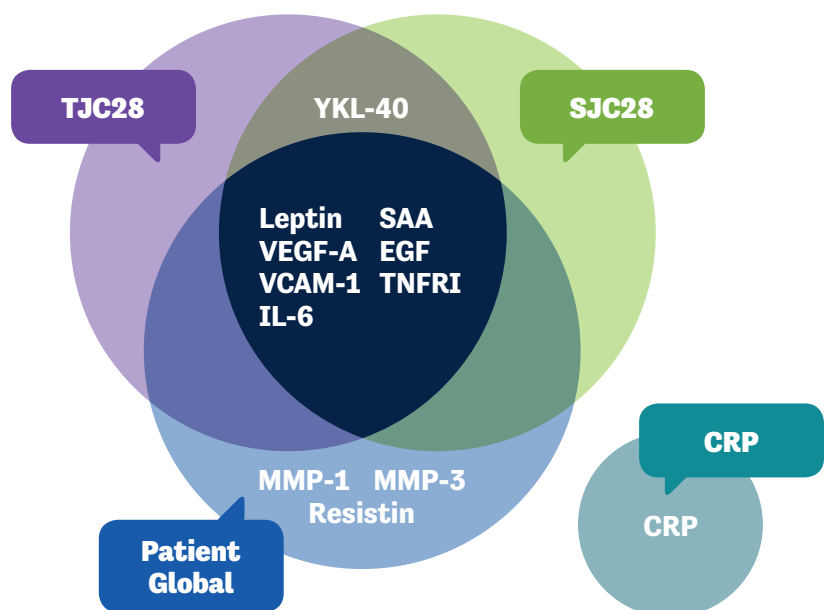
The multi-biomarker disease activity (MBDA) score provides a snapshot of RA disease activity based on the serum concentrations of 12 biomarkers.³³ The MBDA test measures the concentrations of each biomarker and uses an algorithm to determine a total score of 1 to 100. The MBDA score is able to track the activity of a heterogenous disease like

RA because the 12 biomarkers represent a wide spectrum of pathologic mechanisms, including cytokine signaling, synovial invasion, cartilage and tissue remodeling, and immune response. The MBDA biomarkers correspond with the specific signs and symptoms of RA captured by the DAS28–CRP score, including 28 tender-joint count (TJC28), 28 swollen-joint count (SJC28), patient global assessment, and CRP (Figure 2).³³

As a complement to clinical assessment, the MBDA assay offers rheumatology providers an objective tool for monitoring RA disease activity.³⁴ To date, the MBDA score is the only validated marker of disease activity that differentiates between high and low risk of radiographic progression in patients with early RA.³⁵ In a study of hypothetical RA patient cases that included data on physical findings and standard laboratory test results, the MBDA score offered additional prognostic information that influenced rheumatologists’ treatment decisions.³⁶

The MBDA test is also used to track response to RA treatment. In a study of patients treated with anti-TNF therapy, the MBDA score differentiated responders and nonresponders as accurately as DAS28–ESR and DAS28–CRP scores.³⁷ Another study examined the role of the MBDA score in determining next steps for patients with a poor response to first-line MTX therapy. Patients who had a change in their MBDA score of at least 22 points while on MTX were more likely to respond to second-line treatment with non-biologic triple therapy (MTX, sulfasalazine, and hydroxychloroquine). By comparison, patients with a smaller change in their MBDA score while on MTX were more likely to respond to second-line treatment with an anti-TNF agent.³⁸

Figure 2
Biologic MBDA Biomarkers and Components of the DAS28 Score³³



Rheumatology providers are increasingly incorporating the MBDA score assay into clinical practice. Financial data shows an increase in assay usage of more than 230% within the past year.³⁹ However, although the MBDA is a cost-effective tool for aiding RA disease management, limited reimbursement coverage for the assay remains a barrier to more widespread use.^{34,40} In the future, the MBDA score may be further developed as a tool

to guide treatment decisions by identifying which patients are more likely to benefit from intensive therapy and which patients can safely avoid treatment intensification.^{34,35}

14-3-3eta

The 14-3-3 proteins are an abundant family of intracellular proteins involved in diverse biologic processes such as cellular signaling and protein transport. Although these proteins normally reside within cells, they can become externalized in response to certain disease triggers. One subtype of 14-3-3 called 14-3-3eta is preferentially expressed in the synovial fluid of patients with inflamed joints. The presence of extracellular 14-3-3eta activates a proinflammatory response that is highly specific for RA and easily measured with a blood test.⁴¹ Using a cut-off

of ≥ 0.19 ng/mL to define a positive result, the 14-3-3eta has a sensitivity of 77% and a specificity of 93% for RA.

In clinical practice, the 14-3-3eta test can improve the diagnostic accuracy of standard autoantibody testing. In a study of patients with early RA, the ACPA test alone correctly identified 59% of patients with RA. The diagnostic capture rate increased to 72% by combining ACPA and RF, and to 78% by adding 14-3-3eta.⁴² The 14-3-3eta test is also helpful in differentiating between RA, osteoarthritis (OA), and erosive psoriatic arthritis (PsA). One study found that median 14-3-3eta levels were higher in patients with early RA (0.76 ng/mL) and erosive PsA (0.23 ng/mL) than in patients with OA (0.00 ng/mL).⁴³ In another recent study, only 4.9% of patients with OA tested positive for 14-3-3eta.⁴⁴

One of the goals of RA management is to diagnose patients at the earliest stages of disease. In the future, the 14-3-3eta blood test may be used to identify which patients are at high risk of developing RA.⁴³ In a study of 40 patients with joint pain, most patients (82%) who tested positive for 14-3-3eta at baseline developed RA within 4 years, whereas the majority of patients who tested negative for 14-3-3eta (62%) remained free from RA.⁴⁵ Another study of 148 patients with joint pain found that those who tested highly positive for 14-3-3eta expression (≥ 0.80 ng/mL) were approximately 6 times more likely to develop RA than those with a negative test result.⁴⁶

Two options have recently become available for testing 14-3-3eta. Providers can order an individual blood test for 14-3-3eta, or a 3-test diagnostic panel that includes RF, ACPA, and 14-3-3eta (IdentRA™).⁴⁷ Usage rates of these panels in the clinical setting remain to be seen.

Laboratory Tests That Predict Treatment Response

Treatment responses to RA medications can vary widely, reflecting the diversity of pathologic mechanisms driving RA in different patients. In keeping with current ACR treatment guidelines, RA patients should start one treatment and wait approximately 3 months to determine whether that treatment is effective. If the response is inadequate after 3 months, options include adjusting the dose or switching to another regimen for another 3-month trial.²⁶ During this period of treatment trial-and-error, the patient's disease may remain poorly controlled, and RA may progress. Having a test that predicts the likelihood of response can help match the best candidates to specific treatments, and may contribute to more cost-effective care by reducing the use of ineffective therapy.

Autoantibodies

Autoantibody tests have an emerging role in predicting response to certain RA therapies. For patients with high RF and/or ACPA titres, overactive antibody-producing B cells may drive the underlying RA disease activity. Logic follows that these patients may be particularly responsive to B cell-targeted therapies such as rituximab. One study examined the likelihood of achieving a reduction disease activity—defined as a reduction in DAS28 score of at least 1.2 points—after 6 months of treatment with rituximab. Patients with high baseline ACPA levels (≥ 1000 U/mL) were 5 times more likely than patients with lower baseline ACPA levels to achieve the DAS28 endpoint (OR, 5.10; $P=0.0002$).⁴⁸

Having a test that predicts the likelihood of response can help match the best candidates to specific treatments, and may contribute to more cost-effective care by reducing the use of ineffective therapies.

References

Results in RA patients treated with other biologic therapies have been mixed. Another study evaluated the interaction between baseline ACPA levels—separated into 4 quartiles—and response to treatment with subcutaneous abatacept or adalimumab. In the abatacept treatment group, patients with the highest baseline ACPA levels (>1060 U/mL) had the greatest improvements in DAS28 score. In contrast, patients in the adalimumab group had a similar magnitude of response to treatment regardless of baseline ACPA level.⁴⁹

Methotrexate polyglutamate

MTX is a prodrug that must be metabolized to a biologically active form before it can exert its anti-inflammatory effect. As part of this process, MTX is converted to MTX polyglutamate (MTX PG). Some patients with RA harbor genetic mutations that disrupt MTX metabolism, resulting in reduced concentrations of the active form of MTX.⁵⁰ The MTX PG blood test can determine whether patients are metabolizing MTX effectively and reaching therapeutic serum concentrations of active MTX. With this information, clinicians may be able to determine whether partial or nonresponders to MTX might benefit from increasing the MTX dose or switching therapy. A blood test for measuring MTX PG levels (Avisc MTX) is currently available.⁵¹

Another emerging strategy for predicting MTX response involves genetic testing to identify the mutations responsible for disrupting MTX metabolism.⁵² Patients who harbor these mutations will not achieve an adequate response to MTX, and therefore should be treated with non-MTX regimens.⁵²

Future Perspectives

Laboratory testing is critical at every stage of RA management, from diagnosis through treatment monitoring. However, laboratory tests alone are insufficient to guide RA care. At present, there is no gold-standard laboratory test to identify the best choice of therapy for every patient with RA. Test results must be considered within the larger context of patients' histories, clinical exams, and self-reported disease measures to gain a full understanding of RA disease activity. With advances in testing technology, future multi-test panels may enable the earlier diagnosis of RA and provide definitive guidance regarding optimal RA treatment.

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When Lab Tests **Lie**

by Iris Zink, MSN, NP

Twelve years ago, I met R.T., a 35-year-old female patient who had previously been diagnosed with rheumatoid arthritis. Her rheumatoid factor was positive at 49. Her sedimentation rate and C-reactive protein were also elevated. Her joints were visibly swollen and tender on exam. Everything was indicative of significant disease activity.

After discussing treatment options, we decided to start R.T. on a titration dose of methotrexate, 3 pills (7.5 mg) a week on the first Friday and increasing by one pill every Friday until she reached a goal of 17.5 per week. One month later, her liver enzymes were 3 times the upper limits of normal on her laboratory panel, or roughly 130. I called R.T. immediately and had her come in for an evaluation.

In my head, I began running through possible explanations. Did she have a drinking problem that she was covering up? Had she failed to tell me about other medications she was taking such as acetaminophen?

When R.T. next came in, I began by asking if she had any stressors at home. “Yes, my husband is very sick with hepatitis C,” she told me.

I took a second or two to collect myself and then asked R.T. if she had ever been tested

for hepatitis C. She told me, “No,” and so I asked if I could run a hepatitis panel and viral load if the panel was positive. She reluctantly agreed.

Her viral load came back showing more than a million copies of the virus. It was then clear that the patient’s high rheumatoid factor level and other elevated test results were due to her active hepatitis C and that her joint pain was a manifestation of her viral disease and not due to rheumatoid arthritis. I referred R.T. to an infectious disease specialist after apologizing for misdiagnosing her.

The Centers for Disease Control and Prevention recommends testing all patients between the ages of 13–64 for HIV infections, and testing all individuals born between 1945–64 for hepatitis C.¹ According to the package inserts for current biologics used to treat RA, hepatitis B screening should be performed prior to the initiation of those medications in all patients.

While it is impossible to overestimate the importance of a complete physical exam—including a formal joint count—a case like this shows how lab results can be misinterpreted if we don’t ask patients the right questions.



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When Lab Tests Tell the Truth

by Iris Zink, MSN, NP



Biomarkers have been an important addition to the toolbox of rheumatology healthcare providers, which was illustrated in my interactions with G.H., a recent patient of mine with rheumatoid arthritis (RA).

When I met with G.H. for the first time, she told me that her disease activity had been stable on etanercept for approximately 10 years. She reported daily morning stiffness of less than 30 minutes and, aside from ankle pain which had been going on for years, complained of no other notable symptoms.

Though her symptoms seemed stable and she had limited complaints, I thought I might be able to help even these somewhat mild symptoms lessen or go away entirely, and so I told G.H. about the Vectra DA, a multibiomarker disease activity score. She had never had a recorded elevated C-reactive protein or erythrocyte sedimentation rate, and our practice therefore had no true measurement of how her disease was progressing except for what she was telling us.

G.H. agreed to the Vectra DA test. Somewhat surprisingly, her result was 60, which correlates to a high level of disease activity (a score above 45 is indicative of a high level of activity). After receiving this result, I called G.H., and she finally admitted that the etanercept was no longer working and had not been for “some time.” When I asked her why she didn’t say anything to me about this during her most recent visit, she said, “I don’t like change, and I remember how bad I felt before I started the etanercept. I don’t want to feel like that again.” I told her that it was dangerous to let her disease be poorly

controlled, reminding her that her RA was not just affecting her joints, but that the inflammation could also affect her organs and increase her risk of cardiovascular disease.

After our discussion, G.H. agreed to switch from etanercept to adalimumab. However, one month later when she returned for an initial check-in, she told me she had not yet started taking the adalimumab. I was exasperated. “Why?” I asked her. She said her co-pay was going to be too high if she started on adalimumab and that she would rather just stick with the etanercept. We then had another discussion about payment assistance and eventually got her a co-pay card for adalimumab. This time, she did start the medication.

Our RA patients frequently stop their medications without telling us. In one recent study of Canadian pharmacy records, 37% of patients stopped taking their first biologic medication within six months of starting it, many times for socioeconomic reasons.¹ In addition, patients are often not adherent to methotrexate regimens, yet do not admit they are not taking their medications or are taking only partial doses due to fear or embarrassment.

Without the Vectra DA, I would never have known that G.H. had a high level of disease activity, and she would likely still be silently suffering on etanercept. Rheumatology healthcare providers need to be detectives in finding the true story and real reasons that patients may not be achieving remission. Newly available tools such as the MBDA add another option to establish disease activity and even track medication adherence.



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When Lab Tests Provide Additional Information

by Elizabeth Kirchner, CNP

Is there a more confounding lab test in rheumatology than the antinuclear antibody (ANA) test? It can lead us straight to a diagnosis or set us off on a

As a result, the first step in interpreting an ANA test result is to order it on the right patient—someone with a malar rash or thickness of the skin with shortness of breath, for instance—and not on everyone who walks in the door complaining of fatigue or joint pain.

When an ANA is used correctly, it can be a valuable tool; when it is used correctly and comprehensively, it can be even more valuable.

Let me give you an example: H.C. was a 35-year-old generally healthy female sent by her primary care physician to our rheumatology clinic with complaints of severely dry eyes and stiff, aching hands. Physical exam revealed mild synovitis of several metacarpophalangeal and proximal interphalangeal joints. A Schirmer's test was positive. The combination of these results alone would have been enough for a diagnosis of Sjögren's syndrome, but an ANA was also ordered. Results showed that she had an ANA of >1:640 with positive SSA and SSB antibodies, confirming the Sjögren's diagnosis.

Further workup showed that the patient's anti-CCP was negative and her rheumatoid factor was just barely positive at 48 IU/mL. Her C-reactive protein (CRP) was normal, but her erythrocyte sedimentation rate (ESR) was elevated at 29 mm/hr. X-rays of her hands and feet were normal.

Based on these results, H.C. started treatment with hydroxychloroquine and prednisone, and after 6 weeks, she reported improvement in her symptoms. Her ESR stabilized. In many instances, this would have been the end of another success story—we made the diagnosis based upon physical exam and lab results, set a course for treatment, and the patient responded well.

wild goose-chase. Sometimes, ANA test results tell the truth and sometimes they lie, but they almost always give us additional information to consider.

The biggest problem with the ANA test is that it is too often used indiscriminately. Many healthy individuals have positive ANA tests; estimates range between 5–35%, although a 2011 review determined that approximately 13% of healthy people have a positive ANA.¹ False-positive results can be due to infection, liver disease, malignancy, type 1 diabetes, pregnancy, and healthy aging (to name just a few causes).² Some medications, including beta-blockers and minocycline, can cause a positive ANA as well.³

When an ANA is used correctly, it can be a valuable tool; when it is used correctly and comprehensively, it can be even more valuable.



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But when the patient returned for a second follow-up 6 months later, something wasn't quite right. H.C. was a busy mom and trying to conceive a third child, so she downplayed her symptoms, but her hands and feet told the story—she had marked synovitis of almost all of her joints, including her wrists. Her ESR and CRP were still normal. X-rays of her hands and feet showed multiple early erosions. Clearly, this wasn't just Sjögren's. So why did her ANA test result say that it was?

In the end, it turned out that the ANA result wasn't lying. H.C. did have Sjögren's. But this is where clinical interpretation comes into play. Remember that borderline positive RF? H.C. had

Sjögren's secondary to RA, although it was the Sjögren's that showed up first.

The progression of her RA into erosive disease called for a serious step-up in therapy. We started H.C. on methotrexate and rituximab, and 3 years later her symptoms remain under control, her MBDA score is 26 (indicating low disease activity) and recent X-rays show no further erosions.

This case illustrates how the ANA test is rarely a "one-stop shop" in rheumatology. While it can be a valuable part of patient evaluation, it almost always represents only a small piece of a much larger puzzle



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Why Vitamin D Levels Matter in Patients with Rheumatic Disease

by Sheree C. Carter, PhD, RN

Over a decade ago, I had the pleasure of hearing Michael F. Holick, MD, PhD, discuss his cutting edge research on vitamin D. At the time, Dr. Holick was a largely unknown researcher focused on very much a niche area. Since that time, however, he has become a much more visible and highly accomplished researcher regarding the vitamin D deficiency pandemic and its role not only in causing metabolic bone disease and osteoporosis in adults, but also in increasing the risk among children and adults for the development of several common cancers, autoimmune diseases, type 1 diabetes, multiple sclerosis, and heart disease. In 2010, at the annual Rheumatology Nurses Society's conference, we had the distinct honor of having him address our attendees. He was enthusiastically received.

Dr. Holick's path has not been easy. As a trailblazer in the research of vitamin D, he was often scoffed at, accused of wasting time and energy on a topic that would "never amount to anything." Due to his fervent belief and passion, though, I quickly became a fan of his and have followed the research on vitamin D since our first encounter many years ago. Based largely on his efforts, I have been thrilled to see the growing body of research on vitamin D and rheumatic disease both at national meetings and within the medical literature.

Several studies at the recent European League Against Rheumatism (EULAR) annual congress focused on vitamin D. One study of 136 patients with either rheumatic or irritable bowel diseases found that 61.8% of patients with rheumatic disease (RA, psoriatic arthritis, ankylosing spondylitis, and polymyalgia rheumatica) had vitamin D deficiency/insufficiency. This compared to 75.6% of patients with irritable bowel disease. The prevalence of vitamin D deficiency was higher in patients

treated with biologic therapies compared to those treated with nonbiologic disease modifying antirheumatic drugs.¹ Other studies presented at EULAR linked fatigue and symptom severity with low levels of vitamin D.^{2,3} These studies provide a small sample of research in recent years linking the severity of rheumatic diseases to vitamin D levels.

According to Dr. Holick, the goal in patients is to get levels of form 25-hydroxyvitamin D [25(OH)D] above 30 ng/ml.⁴ It is important to remember that, as a rule, 100 IU of Vitamin D₃ raises levels of 25(OH)D by only 1 ng/ml. As we know from the research of Dr. Holick and others, vitamin D has a causative role not only in metabolic bone disease and osteoporosis in adults, but also in increasing the risk of children and adults developing common deadly cancers, autoimmune diseases, including the arthritides, type 1 diabetes, multiple sclerosis, and heart disease. Vitamin D deficiency has also been linked to diffuse musculoskeletal pain and severity of disease in RA.⁵

Diligence is required when ordering levels of 25(OH)D, prescribing supplementation, and following up to determine if a therapeutic level has been achieved. In my experience, raising vitamin D levels can be a long process. One patient of mine required 8 weeks of 50,000 IU/week supplementation just to reach an acceptable level.

Vitamin D might not be a lab test as unique to patients with RA as rheumatoid factor or anti-CCP, but it is important for us to remember that vitamin D has immunomodulatory properties such as decreasing antigen presentation and inhibiting proinflammatory T-helper cells.^{4,5} Thus, vitamin D supplementation may be beneficial for some of our rheumatic disease population



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My Most Memorable Patient

by Jacqueline Fritz, RN, MSN, CNS

As rheumatology nurses, we are lucky to be able to touch so many lives in a memorable way. Consequently, when a patient appears in our practice clearly lost in the vortex of insurance companies and lacking continuity of care, it makes us reflect on the importance of our role as a liaison for each patient and how special our relationships are with them.

I met D.C. in our rheumatology clinic in June of this year. He came to our office with a long list of challenges, including past bouts of congenital pulmonary stenosis, hip dysplasia with surgical repair that resulted in abscess and sepsis, and likely macrophage activation syndrome (MAS). MAS is characterized by unremitting fevers, prolongation of prothrombin time, decrease of erythrocyte sedimentation rate from consumption of fibrin, and liver dysfunction.¹

D.C. was diagnosed by a pediatric rheumatologist at age 14 with juvenile idiopathic arthritis. He was started on methotrexate and eventually added etanercept. He also required prolonged systemic glucocorticoid therapy, which caused osteopenia, growth retardation, and constant fatigue. Finally, at age 15, D.C. was found to have a solitary kidney, fortunately with normal renal function.

Needless to say, D.C. was a complicated patient who had been through many ups and downs of the healthcare system.

And then things got even worse. D.C. turned 18, lost insurance coverage and access to nearly all of his medications—except for the occasional steroid—and became a victim of “the system.”

D.C. was stuck. He had no knowledge of any patient assistance programs or how he might obtain coverage, and since he no longer had a pediatric rheumatologist, had no one to help guide him (his mother, who had been his primary caregiver, had recently passed away). He and his sister looked on websites that discussed Social Security benefits, but D.C. was sure he did not qualify because he had never worked or finished school.

Predictably, D.C.’s health gradually got worse in the years after he lost insurance coverage. He presented to me at age 27 with fused elbows and severe osteoarthritis of the hip. His sister had taken on the role as his primary caregiver without receiving any external financial support. The best anyone had been able to do for D.C. was offer a manual wheelchair despite his ankylosed elbows, swan neck deformities of his fingers, and chronic hip pain. He was the kind of patient who visually is crying for help without even saying a word.

The passage of the Affordable Care Act finally gave D.C. some options, and he was able to enroll in Medicaid. While he has to drive 2 hours each way to visit our office, he is finally on a stable plan that includes home health visits for weekly injections of methotrexate and etanercept. He also had recent hip replacement surgery.

The reason that D.C. is such a memorable patient is because he put me in a real professional conundrum. Even though I am a reasonably intelligent (I think) healthcare provider, I was baffled about where I would have started had I seen him at age 19. There are programs such as the Children’s Health Insurance Program that may have helped D.C. when he was younger, but not as a 19-year-old. One of the advantages of the Affordable



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Care Act is that children can stay on their parents' health plan until age 26, regardless of whether they are in school or working, but since D.C.'s mother had passed away before his 18th birthday and his father was not a presence in his life, even that would not have been an option for him at the time he transitioned into adulthood.

To get some help, I reached out to a few colleagues for their suggestions. One person pointed me to a wonderful video that the Johns Hopkins Arthritis Center has on its website entitled "Transitioning the JRA Patient to an Adult Rheumatologist."²

Here were some other suggestions offered to help a patient such as D.C.:

- Start the transition to an adult practice early and when the patient's disease is well controlled
- Encourage the patient to visit the new rheumatology practice without parents once they reach age 18 to empower the patient to take a more active role in the management of their disease
- Discuss transferring protocols in light of the patient's current health plan

With some guidance, I was also able to find the following resources:

- National 211 Collaborative: A free service that helps in a number of areas, including health insurance referrals, homelessness, medical care, assisted living, and many others. This is a 24-hour-a-day, 7-day-a-week service to avoid crises for patients of all ages. Best of all, real humans answer the phone! (Call 211 or go to www.211.org)
- Court Appointed Special Advocates national program (CASA.org)
- Insure Kids Now.gov: State-specific regional centers
- Children's Medicaid
- In-home supportive services (IHSS)

It took me several hours and many emails to colleagues to even begin to assimilate how patients may access care when they have no income, no assets, and no real knowledge of what assistance programs they might be eligible for. It's a real challenge, and I'm grateful to have a safety net of dedicated nursing professionals with a variety of experiences to draw upon.



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