Quest Diagnostics™

# Osteoarthritis and Rheumatoid Arthritis

## Laboratory Markers for Diagnosis and Prognosis

## CLINICAL BACKGROUND

Osteoarthritis (OA) is the most common form of arthritis in the United States, affecting over 30 million adults.[1] It is characterized by loss of hyaline cartilage in the joints and radiographic changes, such as decreased joint space and osteophytes. Rheumatoid arthritis (RA) is much less common, affecting approximately 1.3 million adults in the United States.[2] In contrast to OA, RA is an autoimmune disease characterized by chronic, systemic inflammation that predominantly affects the synovial membranes and articular structures in joints but may also damage organs such as the heart and lungs.[3] Both diseases appear to have a genetic component, but the exact causes are unknown.[1,3]

Differential diagnosis of OA and RA is important because treatments differ. OA is often treated with drugs such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) that alleviate symptoms but do not change the disease course.[4] For RA, drugs such as NSAIDs may be used to treat symptoms, but other options are available that can favorably alter the disease course. Disease-modifying anti-rheumatic drugs (DMARDs) (eg, methotrexate, leflunomide) or biological therapies (eg, abatacept, etanercept, infliximab) can often ameliorate RA, improve the clinical outcome, and, in some cases, achieve remission.[5] Early diagnosis of RA is important because effective treatment early in the course of the disease can prevent or reduce irreversible joint damage and help maintain overall well-being.[6-9]

Many symptoms of OA and RA overlap, including pain, swelling, and stiffness in the joints. These similarities can cause difficulty when differentiating the diseases. However, some symptoms and laboratory markers can assist with differentiation. For example, in OA patients, joint pain often worsens with use and is relieved with rest, but in RA patients, joint pain is worse in the morning and improves with activity during the day.[10] In addition, some laboratory markers are elevated in RA patients but normal in OA patients.

This Clinical Focus discusses laboratory tests available to assist in differentiating RA from OA and other conditions that manifest with polyarthritis. The associations between test results and disease progression are also discussed. This material is provided for educational purposes only and is not intended as medical advice. Test selection and interpretation, diagnosis, and patient management decisions should be based on the physician's education, specialization, clinical expertise, and clinical and laboratory assessment of the patient.

## Disease Classification Criteria

### Osteoarthritis

The American College of Rheumatology (ACR) has published guidelines for the classification of OA in different joints.[11-13] Depending on the joint, classification criteria may include joint symptoms (pain, stiffness, swelling, enlargement, deformation), age, erythrocyte sedimentation rate (ESR), radiologic findings (presence of osteophytes or narrowing of joint space), synovial fluid tests (color, appearance, white blood cell count), and the sensation of crackling in the joint (crepitus) **(Table 1)**. Sensitivity and specificity of classification criteria for OA vary based on 1) the joint (knee, hand, hip); 2) the classification method (traditional vs classification tree); and 3) the type of criteria (clinical vs clinical and radiographic vs clinical and laboratory).

### Rheumatoid Arthritis

Diagnosis of RA relies on patient history, physical examination, laboratory testing, and radiographic evidence of joint damage. The ACR/European League Against Rheumatism (EULAR) 2010 Rheumatoid Arthritis Classification Criteria are based on clinical presentation (synovitis, joint swelling), serology, acute-phase reactants, and duration of symptoms.[6] The criteria are designed to identify early-stage patients who are at high risk of persistent and/or erosive disease.[6] Once other conditions such as OA, systemic lupus erythematosus, psoriatic arthritis, gout, and arthritis caused by viral infection (eg, parvovirus B19, rubella, hepatitis C virus) have been ruled out, a patient is classified as having RA if a score of ≥6 out of a possible 10 is reached. Details of the scoring system and classification criteria can be found in the **Figure** and **reference 6**.

**Table 1. Criteria for Classification of Osteoarthritis in Different Joints[a]**

| Knee (Clinical and Laboratory)[11] | Hand[12] | Hip (Clinical and Radiographic)[13] |
|---|---|---|
| • Knee pain<br><br>**Plus ≥5 of the following**<br>• Age >50 years<br>• Joint stiffness <30 minutes<br>• Crepitus<br>• Bony tenderness<br>• Bony enlargement<br>• No palpable warmth<br>• ESR <40 mm/hour<br>• RF <1:40<br>• Synovial fluid clear, viscous, or white blood cell count <2,000/mm$^3$ | • Hand pain, aching, or stiffness<br><br>**Plus ≥3 of the following**<br>• Hard tissue enlargement of ≥2 of 10 selected joints[b]<br>• Hard tissue enlargement of ≥2 distal interphalangeal joints<br>• <3 swollen metacarpophalangeal joints<br>• Deformity of ≥1 of 10 selected joints[b] | • Hip pain<br><br>**Plus ≥2 of the following**<br>• ESR <20 mm/hour<br>• Osteophytes (femoral or acetabular)<br>• Joint space narrowing (superior, axial, and/or medial) |
| Sensitivity: 92%<br>Specificity: 75% | Sensitivity: 94%<br>Specificity: 87% | Sensitivity: 89%<br>Specificity: 91% |

ESR, erythrocyte sedimentation rate; RF, rheumatoid factor

[a] Schema presented are in traditional format. Depending on the joint, schema may also be available in traditional or classification tree format for clinical criteria alone or in combination with radiographic criteria.[11-13] Other schema have different sensitivities (86% to 95%) and specificities (69% to 98%).

[b] Selected joints include 1st carpometacarpal and 2nd and 3rd distal and proximal interphalangeal joints of each hand.

## INDIVIDUALS SUITABLE FOR TESTING

- Individuals with symptoms of arthritis not attributed to other diagnosed conditions
- Individuals with arthritis requiring differential diagnosis of OA from RA
- Individuals with established RA

## TEST AVAILABILITY

A list of tests that may be useful for OA or RA diagnosis, assessment of prognosis, and follow-up is provided in **Table 2**.

## TEST SELECTION

### Diagnosis

Laboratory testing can help with the differential diagnosis of OA or RA from other conditions that manifest with polyarthritis. These tests can be especially useful early in the disease course for establishing a diagnosis.

#### Osteoarthritis

##### ESR

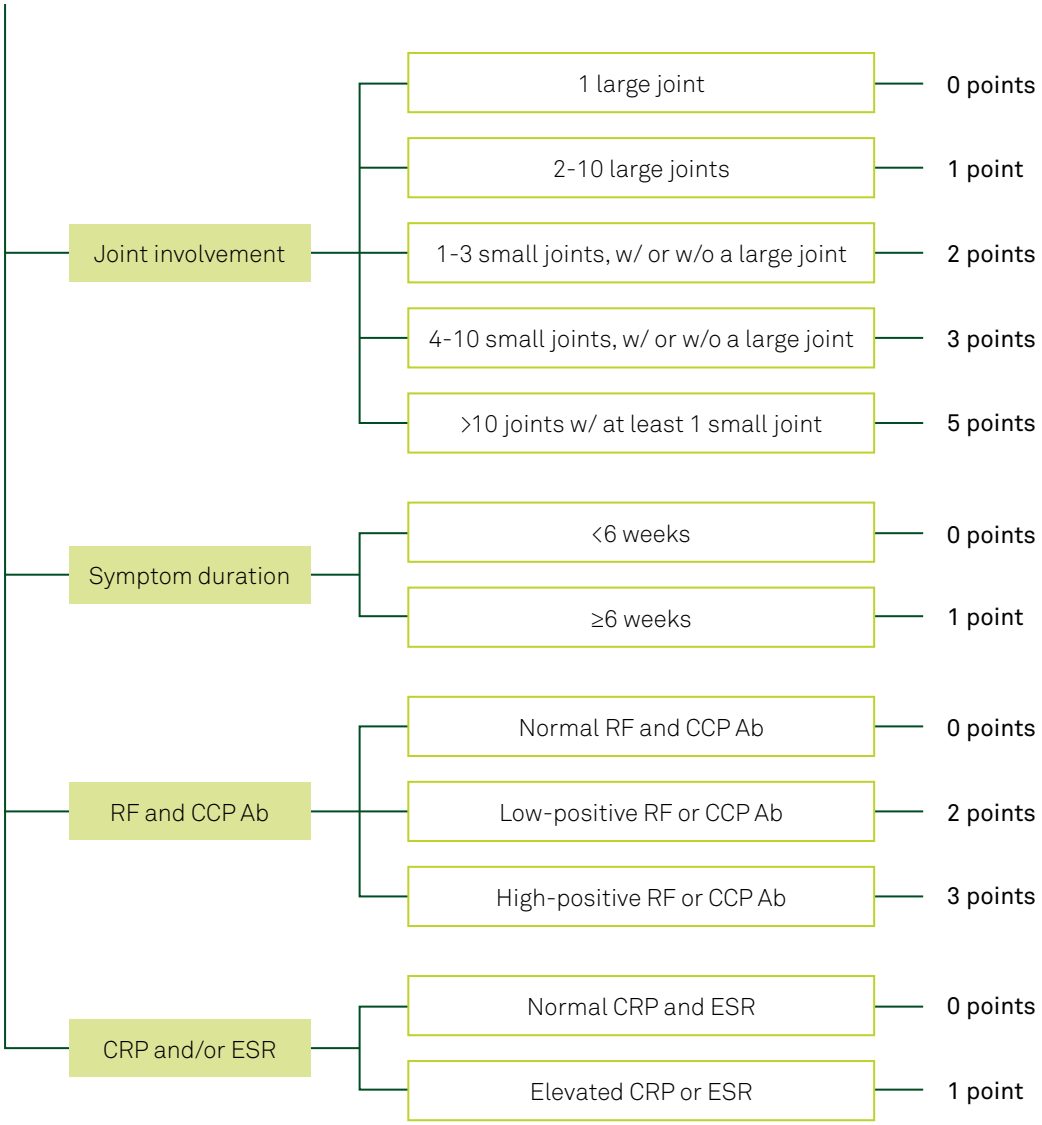
Erythrocyte sedimentation rate (ESR), also known as sed rate, measures the rate at which red blood cells fall through plasma and is an acute-phase marker of inflammation. According to the ACR criteria for the classification and reporting of OA **(Table 1)**, ESR can help classify OA in the hip and knee joints. ESR thresholds vary by joint: ≤20 mm/hour for hip, <40 mm/hour for knee; ESR is not recommended for the classification of OA in the hand.[11-13]

##### Synovial fluid

Analysis of synovial fluid from an affected joint is useful for the differential diagnosis of OA and is included in the ACR criteria for the classification of OA in the knee **(Table 1)**.[11] Testing of synovial fluid, using techniques such as Gram stain, white blood cell counts, and biochemical assays,

**Figure.** ACR/EULAR Classification Criteria for Rheumatoid Arthritis

**Patient With Swollen Joint(s) Not Explained by Another Condition**




Add points. Patient with ≥6 points (out of 10 possible) is classified as having RA.

ACR/EULAR, American College of Rheumatology/European League Against Rheumatism; CCP Ab, cyclic citrullinated peptide antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; and RF, rheumatoid factor.

This figure was developed by Quest Diagnostics based on reference 6. It is provided for informational purposes only and is not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on his/her education, clinical expertise, and assessment of the patient.

**Table 2. Tests Available to Support Diagnosis, Prognosis, and Follow-up of Rheumatoid Arthritis**

| Test Code | Assay | Method | Clinical Use |
|---|---|---|---|
| 91472 | Rheumatoid Arthritis Diagnostic IdentRA® Panel 2[a]<br>Includes RF IgM, CCP antibody IgG), and 14-3-3η protein | Immunoturbidimetry (RF); ELISA (CCP antibody and 14-3-3η protein) | Provides additional diagnostic and prognostic value relative to each assay alone |
| 19878 | Rheumatoid Arthritis Diagnostic Panel 3<br>Includes RF (IgG), RF (IgA), RF (IgM), CCP antibody (IgG), Sjögren antibody (SS-A), Sjögren antibody (SS-B) | ELISA (RF IgG/A/M, CCP); Immunobead-based enzyme immunoassay (SS-A, SS-B) | Assist in diagnosis and determining prognosis of RA; may help differentiate RA from primary Sjögren syndrome versus RA with secondary Sjögren syndrome |
| 92812 | Rheumatoid Arthritis Diagnostic IdentRA Panel 4[a]<br>Includes RF (IgG), RF (IgA), RF (IgM), CCP antibody (IgG), 14-3-3η protein, Sjögren antibody (SS-A), Sjögren antibody (SS-B) | ELISA (RF IgG/A/M, CCP, 14-3-3η); Immunobead-based enzyme immunoassay (SS-A, SS-B) | Assist in diagnosis and determining prognosis of RA; may help differentiate RA from primary Sjögren syndrome versus RA with secondary Sjögren syndrome |
| 90071 | ANA Screen, IFA, with Reflex to Titer and Pattern/Rheumatoid Arthritis Panel 1[b]<br>Includes ANA screen, IFA with Reflex to Titer and Pattern; RF; CCP antibody (IgG) | IFA (ANA, Titer and Pattern); Immunoturbidimetry (RF); ELISA (CCP antibody) | Assist in diagnosis of RA |
| 92813 | ANA Screen, IFA, with Reflex to Titer and Pattern/ Rheumatoid Arthritis Panel 2[a,b]<br>Includes ANA screen, IFA with Reflex to Titer and Pattern; RF; CCP antibody (IgG); 14-3-3η protein | IFA (ANA, Titer and Pattern); Immunoturbidimetry (RF); ELISA (CCP antibody, 14-3-3η protein) | Assist in diagnosis of RA |
| 94954 | ANA Screen, IFA, Reflex Titer/ Pattern, Reflex Mplx 11 Ab Cascade with IdentRA[a,b]<br>Includes ANA screen, IFA, with Reflex Titer/Pattern and Reflex to Multiplex 11 Ab Cascade; RF; CCP antibody (IgG); 14-3-3η protein | IFA (ANA, Titer and Pattern); Multiplex immunoassay (11 Ab Cascade); Immunoturbidimetry (RF); ELISA (CCP antibody, 14-3-3η protein) | Assist in diagnosis of RA and other ANA-positive systemic autoimmune diseases |
| 36378 | ANAlyzeR™ ANA, IFA with Reflex Titer/Pattern, Systemic Autoimmune Panel 1<br>Includes 14-3-3η protein; ANA screen, IFA, with Reflex to Titer and Pattern; beta-2-glycoprotein I antibodies (IgG, IgA, IgM); cardiolipin antibodies (IgA, IgG, IgM); CCP antibody (IgG); centromere B antibody; chromatin (nucleosomal) antibody; complement component C3 and C4; DNA (ds) antibody, Crithidia IFA with Reflex to Titer; Jo-1 antibody; scleroderma antibody (Scl-70); Sjögren antibodies (SS-A and SS-B), Sm antibody; Sm/RNP antibody; RF (IgG, IgA, IgM); thyroid peroxidase antibodies (TPO) | ELISA (14-3-3η protein); IFA (ANA, Titer and Pattern; DNA (ds) antibody, Crithidia with Titer); Immunoassay (beta-2-glycoprotein I IgG/IgA/IgM, cardiolipin IgG/A/M, CCP, centromere B antibody, chromatin antibody, Jo-1, RF IgG/IgA/IgM, Scl-70, Sm antibody, Sm/RNP antibody, SS-A, SS-B, TPO); Immunoturbidity (complement component C3 and C4) | Assist in diagnosis of RA and other systemic autoimmune diseases, some of which (eg, thyroiditis) commonly co-occur with RA |

*(Continued)*

**Table 2. Tests Available to Support Diagnosis, Prognosis, and Follow-up of Rheumatoid Arthritis *(Continued)***

| Test Code | Assay | Method | Clinical Use |
|---|---|---|---|
| 4418 | Rheumatoid Factor | Latex agglutination/ immunoturbidimetry | Assist in diagnosis and determining prognosis of RA; detects primarily IgM RF |
| 15682 | Rheumatoid Factor (IgA) | ELISA | Provides added specificity when used in combination with other RF or CCP antibody assays; may help predict severity of disease course |
| 15683 | Rheumatoid Factor (IgG) | ELISA | Provides added specificity when used in combination with other RF or CCP antibody assays |
| 19705 | Rheumatoid Factor (IgA, IgG, IgM) | ELISA | Assist in diagnosis of RA; detecting all 3 isotypes improves the specificity and predictive value |
| 11173 | Cyclic Citrullinated Peptide (CCP) Antibody (IgG) | ELISA | Assist in diagnosis and determining prognosis of RA |
| 91455 | 14.3.3 eta Protein[a] | ELISA | Assist in diagnosis and determining prognosis of RA |
| 809 | Sed Rate by Modified Westergren | Modified Westergren | Assist in diagnosis of RA and assessing disease activity |
| 4420 | C-Reactive Protein (CRP) | Immunoturbidimetry | Assist in diagnosis of RA and assessing disease activity |
| 15384 | Rheumatoid Factor Screen with Reflex to Titer, Synovial Fluid[b] | Latex agglutination | Assist in diagnosis and prognosis of RA |
| 6398 | Synovial Fluid Analysis, Complete<br>Includes color, appearance, microscopic cell differential, crystals, and mucin clot | Microscopy/polarized light | Assist in diagnosis of disorders of the joints and joint fluid |
| 4562 | Cell Count and Differential, Synovial Fluid<br>Includes color, appearance, total nucleated cell count, and percentage of neutrophils, lymphocytes, monocytes/macrophages, eosinophils, and synoviocytes | Microscopic visualization | |
| 4563 | Crystals, Synovial Fluid | Microscopy/polarized light | Exclude pathologic crystals |
| 17658 | LD, Synovial Fluid | Ultraviolet kinetic | Differentiate OA from RA, infectious arthritis, and gout |
| 657 | Mucin Clot, Synovial Fluid | Macroscopic examination/ Ropes test | Assist in differential diagnosis of diseases of joints and joint fluid |
| 4446 | Culture, Aerobic and Anaerobic<br>Includes aerobic culture, anaerobic culture, and Gram stain | Direct microscopy; bacterial culture; aerobic and anaerobic isolation | |
| 6641 | Susceptibility Panel, Aerobic Bacterium | Varies | |

*(Continued)*

**Table 2. Tests Available to Support Diagnosis, Prognosis, and Follow-up of Rheumatoid Arthritis *(Continued)***

| Test Code | Assay | Method | Clinical Use |
|---|---|---|---|
| 6642 | Susceptibility Panel, Anaerobic Organism | Microdilution panel | Assist in differential diagnosis of diseases of joints and joint fluid |
| 17597 | Complement C3, Synovial Fluid | Immunoturbidimetry | Assist in diagnosis of immunologic disorders |
| 17598 | Complement Component C4, Synovial Fluid | Immunoturbidimetry | |
| 4943 | C4d Fragment, EIA | Enzyme immunoassay | |

ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; LD, lactate dehydrogenase.
[a] This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics. It has not been cleared or approved by the US Food and Drug Administration. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.
[b] Reflex tests are performed at an additional charge and are associated with an additional CPT code.

can help distinguish between inflammatory arthritis and noninflammatory types of arthritis such as OA.[14] Synovial fluid analysis can also help exclude the possibility of gout through the absence of monosodium urate crystals.[14]

## Rheumatoid Arthritis

### RF and CCP

Rheumatoid factor (RF) and cyclic citrullinated peptide (CCP) antibody are established biomarkers that are integrated into ACR/EULAR criteria for RA classification.[6] Sensitivity of RF ranges from 57% to 78% for early RA[15,16] and from 58% to 84% for established RA.[15-18] Specificity ranges from 81% to 97% for early and established RA.[15-18] However, patients with certain other rheumatic diseases, such as Sjögren syndrome, often have positive RF results.[18]

RF titer is most often assessed using latex agglutination or immunoturbidimetry, which primarily detects IgM RF. IgM RF, as well as IgA RF and IgG RF, can also be measured individually with specific immunoassays. The presence of IgA RF, IgG RF, or both in patients with IgM RF and joint disease markedly increases the likelihood that the patient has RA; these combinations are not typically found in patients with other rheumatic diseases that may be accompanied by IgM RF. However, IgA RF and IgG RF are not highly sensitive and are not widely used in the initial diagnosis of RA.

CCP antibody is assessed by immunoassay. The sensitivity of CCP antibody (55%-88%) is comparable to that of RF for early and established RA.[15-20] However, CCP antibody is highly specific (89%-99%) for RA.[15-20] Because of this high specificity, patients who are healthy or have other rheumatic diseases, such as OA, test positive for CCP antibody less often than for RF.[18] Moreover, side-by-side comparisons demonstrate that CCP antibody has similar sensitivity and greater specificity than RF in various clinical situations.[15,17-19] To increase sensitivity for RA, CCP antibody can be combined with RF; specificity tends to remain comparable or decrease modestly.[16,17]

### 14-3-3η

The 14-3-3η protein is a newer marker for RA that is elevated in serum and synovial fluid during joint inflammation.[16] The reported sensitivity of 14-3-3η for early RA is 60%, with a specificity of 85%.[21] The sensitivity for established RA is 77%, with a specificity of 93%.[16] 14-3-3η testing may be particularly helpful to differentiate RA from OA; when comparing patients with early RA to those with OA, the sensitivity of 14-3-3η for early RA was 64%, with a specificity of 83%.[16]

The addition of serum 14-3-3η measurement to RF and CCP antibody testing increases sensitivity for RA.[21,22] Increasing sensitivity is important to detect RA in patients who test negative for RF and CCP antibody. In one study, 28% of patients with early RA tested negative for RF and CCP antibody (ie, these patients were seronegative).[21] However, 14-3-3η measurement detected early RA in 19% of seronegative patients, which increased sensitivity for early RA from 72% to 77%.[21] This increased sensitivity may translate into treatment earlier in the course of disease, which can reduce irreversible joint damage.

### CRP and ESR

C-reactive protein (CRP) and ESR are serological acute-phase markers of inflammation that are included in the ACR/EULAR classification criteria for RA **(Figure)**.[6] CRP is produced by the liver in response to tissue injury, infection, and inflammation. Levels increase during periods of heightened RA disease activity, but elevations may also reflect inflammation due to other causes such as infection or injury. The ESR depends primarily on the concentration of fibrinogen, a clotting factor that increases during an inflammatory response. Therefore, the ESR provides an indirect measure of inflammation. The ESR typically increases with increased RA disease activity, but it can also be affected by plasma components independent of degree of inflammation.[23] CRP and ESR are often both elevated or not elevated in a patient; however, one study reported discordant levels in 26% of patients with active RA.[24]

## Prognosis

### Osteoarthritis

The clinical course of OA is variable, and disease characteristics (eg, joint space narrowing, osteophyte formation) are useful for assessing OA progression.[25] No laboratory biomarkers have been validated for determining prognosis, but some are under investigation, including serum hyaluronic acid and urinary CTX-II.[25]

### Rheumatoid Arthritis

Like OA, RA has a variable clinical course. Some patients have self-limiting disease whereas others develop progressive joint damage. Predicting which RA patients will experience progressive disease helps direct aggressive treatment with DMARDs and/or biological agents to patients who need it most, and spare others from unnecessary exposure to the potential adverse effects of these drugs.[5,26]

### RF and CCP

RF and CCP antibody are included as indicators of poor prognosis in the ACR recommendations for treatment of early and established RA.[5] A positive RF or CCP antibody test result is predictive of radiographic progression and more severe disease.[20,27-29] In addition, RF and especially CCP antibody are predictive of the development of RA and can be detected years before disease onset.[30-32] In studies of blood donors, the sensitivity of CCP antibody detection for future development of RA ranged from 32% to 34%, with a specificity of ≥97%.[30,31] CCP antibody levels may be associated with time to disease onset, with high levels predicting shorter time to onset.[31] CCP antibody testing may also predict a future diagnosis of RA in patients with undifferentiated arthritis.[32]

RF and CCP antibody may be predictive of clinical response to certain therapies. Patients positive for RF and/or CCP antibody have a greater clinical response to the biological therapeutic rituximab than do seronegative patients.[33,34] In addition, patients who are positive for RF and/or CCP antibody may be less likely to prematurely discontinue the biological therapeutic abatacept because of inefficacy or safety.[35,36]

### 14-3-3η

Elevated levels of 14-3-3η are associated with radiographic progression and increased disease activity.[37-39] The predictive capability of 14-3-3η may be useful for identifying high-risk patients before onset of RA because levels are often elevated early in the course of disease. For instance, in a study of 331 patients with early undifferentiated polyarthritis, elevated levels of 14-3-3η at baseline predicted radiographic progression of joint damage over 5 years, and fewer patients with elevated baseline 14-3-3η achieved remission of disease activity.[39]

### CRP and ESR

Elevated levels of the acute-phase markers of inflammation are associated with more severe disease in subsequent years. Baseline levels of CRP are predictive of radiographic progression at 5 and 10 years.[27,39] Baseline ESR is predictive of radiographic damage and progression at 2 and 5 years.[20,27] Each of these acute-phase markers can also be incorporated into common disease assessment tools (eg, Disease Activity Score) that are used to monitor RA disease activity.[40]

## Supportive Testing

### Osteoarthritis

Laboratory tests are not typically used in supportive testing for OA.

### Rheumatoid Arthritis

A complete blood count with white blood cell differential can help document the mild anemia, leukocytosis, and other hematologic abnormalities sometimes associated with RA. More severe anemia may reflect gastrointestinal bleeding resulting from steroidal and non-steroidal anti-inflammatory drugs. Urinalysis typically yields normal results. Liver and kidney function should be assessed before starting therapy with non-steroidal anti-inflammatory drugs and/or DMARDs, to establish baseline values, and at intervals thereafter.

## TEST INTERPRETATION

The result of each assay should be evaluated in conjunction with clinical and radiographic findings and other serological test results.

### Diagnosis

In patients requiring differential diagnosis of OA from RA, a positive/elevated result for RF, CCP, or 14-3-3η suggests inflammatory arthritis, such as RA. However, RA may coexist with OA.

#### RF

Positive RF results provide evidence for the presence of RA **(Figure)** but do not indicate a definitive diagnosis because positive results are also common in patients with other rheumatic diseases and conditions.[18] Very high titers may be associated with more severe joint disease, Felty syndrome, rheumatoid nodules, peripheral neuropathy, skin ulcers, scleritis, and vasculitis. Negative results are consistent with conditions other than RA but do not rule out RA. Though rare, seroconversion of RF-negative patients can occur[41]; thus, follow-up testing at intervals until disease pattern and activity stabilize may be useful if the initial result is negative. Positive results for IgA RF and/or IgG RF are also suggestive of RA. However, negative results do not rule out RA owing to relatively low sensitivity.

#### CCP Antibody

Positive CCP antibody results provide evidence for the presence of RA **(Figure)**. Though this assay is generally more specific than RF, patients with other rheumatic diseases may have elevated titers.[18] Negative results suggest that other rheumatic diseases may be responsible for the patient's symptoms but do not rule out a diagnosis of RA.

#### 14-3-3η

Elevated levels of 14-3-3η are suggestive of RA; however, normal levels do not rule out RA. Patients with erosive psoriatic arthritis may also have elevated levels of 14-3-3η, although serum levels are typically lower than those observed in patients with RA.[16]

#### Combination of RF, CCP Antibody, and 14-3-3η Protein

In patients with suspected RA, a positive/elevated result for RF, CCP antibody, and/or 14-3-3η protein suggests an RA diagnosis.[16] Negative/normal results for all 3 markers indicate that an RA diagnosis is less likely.

The combination of a positive IgM RF and CCP antibody result is highly suggestive of RA. However, this test result may be found in some patients with other rheumatic diseases. Patients with positive CCP antibody and negative RF results are also likely to have RA. Patients with positive RF and negative CCP results are less likely to have RA, but RA remains a possibility. A negative result on both assays indicates a low likelihood of RA but does not exclude the diagnosis. In RF-positive patients with chronic hepatitis C virus (HCV) or other infections associated with polyarticular arthritis, a positive CCP antibody result suggests a likely diagnosis of coexisting RA.[42]

#### CRP and ESR

Elevated levels of CRP or ESR provide evidence for the presence of RA **(Figure)**. In patients with RA, elevated levels of CRP or ESR suggest heightened disease activity.[23] However, elevations may also be due to other inflammatory conditions. Normal levels of CRP and ESR suggest relatively low disease activity in patients with RA.

### Prognosis

#### RF and CCP

A positive RF or CCP antibody test result at baseline suggests long term radiographic progression and more severe joint damage.[28,29] The combination of a positive IgM RF and CCP antibody result is also associated with an aggressive disease course.[28]

#### 14-3-3η

Elevated levels of 14-3-3η are predictive of radiographic progression.[37,39]

#### CRP and ESR

Elevated levels of CRP or ESR during early RA may be predictive of long-term (5- to 10-year) disease progression.[27]

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