Test Summary

Rheumatoid Arthritis Diagnostic Panel IdentRA™ with 14-3-3 eta

Test Code: 91472(X)

Specimen Requirements: 3 mL refrigerated serum (red-top tube [no gel]); 1.5 mL minimum

CPT Codes*: 86431; 86200; 83520

Clinical Use

- Diagnose rheumatoid arthritis (RA)
- Diagnose erosive psoriatic arthritis in patients with psoriasis
- Differentiate osteoarthritis from RA or erosive psoriatic arthritis

Clinical Background

The prevalence of RA in the United States is 0.5% to 1% (over 1.5 million adults), and approximately 165,000 new cases are diagnosed annually.[1] If the disease is diagnosed early (ie, before significant joint erosion occurs), treatment can prevent irreversible joint damage. However, early diagnosis is difficult for several reasons: joint symptoms and signs are limited, physical findings to suggest synovitis may be absent, and laboratory test results may be seronegative in some patients. This Test Summary discusses laboratory markers available for the diagnosis of RA, including rheumatoid factor (RF), cyclic citrullinated peptide (CCP) antibody, and the 14-3-3η protein.

RF is an autoantibody that targets the Fc region of IgG. It is widely used as a laboratory marker of RA because serum levels are often elevated in RA patients. The sensitivity of RF testing is 60% to 86% for established RA and 57% for early RA.[2-4] However, the usefulness of RF testing is somewhat limited by its low specificity: 70% to 85% for established and early RA.[2,4] This limitation is less of a concern when using newer serology markers.

In 2010, cyclic citrullinated peptide (CCP) antibody was added to the classification criteria for RA from the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR).[5] CCP testing identifies autoantibodies to citrullinated peptides, which are often elevated in RA patients.[6] Compared to RF testing, CCP testing has similar sensitivity for established RA (64% to 88%)[2,7] and early RA (59%)[4]; however, specificity (90% to 99%) is higher for both established and early RA.[4,8] Indeed, most side-by-side comparisons demonstrate that CCP antibody testing is at least as sensitive as and more specific than RF testing in various clinical situations.[2-4,7]

Although CCP testing is more specific than RF testing, it is not considered a replacement for RF testing. Serology tests for both markers are included in the ACR/EULAR classification criteria for RA,[5] and studies show that the combined use of the markers provides greater sensitivity than the use of either alone.[2,3] Despite this increased sensitivity, between 28% and 44% of patients with *early* RA test negative for both RF and CCP antibody,[4,9] and patients who develop erosive RA may remain negative for both markers.[9,10] Thus, other markers for RA have been sought.

The 14-3-3η protein represents a novel biomarker for the detection of RA.[4] It may play a role in stimulating tumor necrosis factor alpha, metalloproteinases, and other inflammatory mediators critical to the joint erosive process.[4] The 14-3-3η protein is found in the central nervous system and synovial joint tissue.[11,12] It is released into the extracellular space (eg, synovial fluid and peripheral blood) when synovial inflammation associated with joint erosion is present in RA and psoriatic arthritis.[6,7] Thus, blood levels of 14-3-3η tend to be elevated in patients with RA, but not in other diseases including osteoarthritis, osteoporosis, gout, psoriasis, Crohn's disease, ulcerative colitis, type 1 diabetes, systemic lupus erythematosus, primary Sjögren's syndrome, scleroderma, and multiple sclerosis.[11,12]

One of the advantages of 14-3-3η as an RA marker is that it can improve identification rates of *early* RA. Maksymowych and colleagues found that adding 14-3-3η (cutoff ≥0.19 ng/mL) to RF and CCP antibody testing increased diagnostic sensitivity for early RA patients (n=99)[4] (Table 1). For the diagnosis of RA, the benefit of increased sensitivity allows earlier detection and treatment in the course of disease, which can minimize irreversible joint damage. Furthermore, a separate study indicated that 14-3-3η serum concentration is correlated with the presence

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Table 1. Sensitivity and Specificity of RF, CCP, and 14-3-3η Biomarkers for Detecting RA[4]

	Early RA[a] (n=99)		Established RA[a] (n=135)	
Marker(s)	Sensitivity	Specificity	Sensitivity	Specificity
Only RF+	57	85	84	85
Only CCP+	59	99	79	99
Only 14-3-3η+	64	93	77	93
RF+ and/or CCP+	72	84[b]	88	84[b]
14-3-3η+ and/or RF+ and/or CCP+	78	78[b]	90	78[b]

[a] Comparison with healthy controls

[b] For multi-marker tests in which a positive result in any of the markers leads to a positive result for the overall test, specificity declines relative to tests of the individual markers.

of joint damage; the median concentration was 6.13 ng/mL in early RA patients with joint damage (n=13) and 1.30 ng/mL in those without joint damage (n=20).[9]

The 14-3-3η protein is also a novel biomarker for the detection of erosive psoriatic arthritis.[13] Like RA, psoriatic arthritis can be difficult to diagnose clinically early in the disease process and can be associated with early joint erosion.[13] It affects approximately 30% of patients with psoriasis.[14] In patients with psoriatic arthritis, 14-3-3η positivity may help differentiate those with joint damage from those without joint damage. Maksymowych and colleagues found that median 14-3-3η levels were higher in patients with erosive psoriatic arthritis (0.23 ng/mL) than nonerosive psoriatic arthritis (0.0 ng/mL).[4]

In addition, RF, CCP, and 14-3-3η results may help differentiate RA from osteoarthritis. In 2 studies (n=30 and n=40), 12.5% to 17% of OA patients tested positive for RF and approximately 7% of patients tested positive for CCP.[4,15] One of these studies also found that median 14-3-3η serum levels were 0.76 ng/mL in early RA patients (n=99) versus 0.00 ng/mL in osteoarthritis patients (n=30).[4]

Individuals Suitable for Testing

- Individuals suspected of having RA
- Individuals with psoriatic arthritis
- Individuals with arthritis requiring differential diagnosis of osteoarthritis from RA or erosive psoriatic arthritis

Method

- This panel includes tests for RF, CCP antibody, and 14-3-3η protein.
  - –CCP antibody and 14-3-3η protein: enzyme-linked immunosorbent immunoassay (ELISA)
  - –RF: Immunoturbidimetric assay
- Panel components can be ordered separately (Table 2).

Reference Range

RF: <14 IU/mL

CCP antibody (IgG):
- Negative: <20 units
- Weak positive: 20-39 units
- Moderate positive: 40-59 units
- Strong positive: >59 units

14-3-3η protein: <0.2 ng/mL

Interpretive Information

In patients with suspected RA, a positive/elevated result of 1 or more markers is suggestive of an RA diagnosis. The diagnosis is less likely when all 3 markers are negative/normal.

In patients with psoriatic arthritis and an elevated 14-3-3η protein level, joint damage is likely. A concentration within the reference range, however, does not rule out erosive psoriatic arthritis.

In patients requiring differential diagnosis of osteoarthritis from RA or erosive psoriatic arthritis, a positive/elevated result of 1 or more markers is suggestive of inflammatory arthritis. However, RA or erosive psoriatic arthritis may coexist with osteoarthritis.

Table 2. Individual Tests Included in the Rheumatoid Arthritis Diagnostic Panel IdentRA™ with 14-3-3 eta

Test Code	Test Name	CPT Code
4418	Rheumatoid Factor	86431
11173	Cyclic Citrullinated Peptide (CCP) Antibody (IgG)	86200
91455	14-3-3 eta Protein[a]	83520

[a] This test was developed and its performance characteristics have been determined by Quest Diagnostics Nichols Institute. It has not been cleared or approved by the US Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. Performance characteristics refer to the analytical performance of the test.

References

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*The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed.

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