Test Definition: RAPAN

Rheumatoid Arthritis Panel, Serum

Overview

Useful For

Evaluating patients suspected of having rheumatoid arthritis (RA)

Differentiating RA from other inflammatory arthritis or connective tissue diseases

Diagnosis and stratification of rheumatoid arthritis

Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
CCP	Cyclic Citrullinated Peptide Ab, S	Yes	Yes
RHUT	Rheumatoid Factor, S	Yes	Yes

Special Instructions

- Connective Tissue Disease Cascade

Method Name

CCP: Enzyme-Linked Immunosorbent Assay (ELISA)
RHUT: Turbidimetry

NY State Available

No

Specimen

Specimen Type

Serum

Ordering Guidance

This test is the optimal first-line antibody panel for evaluating patients at-risk for rheumatoid arthritis.
The following testing may also be useful:
ENAE / Antibody to Extractable Nuclear Antigen Evaluation, Serum
ADNA1 / Double-Stranded DNA (dsDNA) Antibodies , IgG, Serum
NAIFA / Antinuclear Antibodies, HEp-2 Substrate, IgG, Serum
CTDC / Connective Tissue Diseases Cascade, Serum

Specimen Required

Supplies: Sarstedt Aliquot Tube, 5 mL (T914)

Collection Container/Tube:
Preferred: Serum gel
Acceptable: Red top
Submission Container/Tube: Plastic vial
Specimen Volume: 2 mL
Collection Instructions: Centrifuge and aliquot serum into a plastic vial.

Specimen Minimum Volume

1.2 mL

Reject Due To

Gross hemolysis	Reject
Gross lipemia	Reject
Gross icterus	OK
Heat-treated specimen	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum	Refrigerated (preferred)	14 days	
	Frozen	14 days	

Clinical & Interpretive

Clinical Information

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by interactions between the environment, specific genetic risk factors, and the human immune system. It affects about 0.6% of the United States population with a global prevalence of 0.24%.(1) Clinically, RA is typified by progressive damage of synovial joints, inflammation, production of diverse autoantibodies, and variable extra-articular manifestations.(2-4) To facilitate early diagnosis, the American College of Rheumatology/European League Against Rheumatism 2010 RA classification criteria recommend testing for rheumatoid factors (RF) and anticitrullinated protein antibodies (ACPA).(2) RF are autoantibodies directed against the Fc portion of immunoglobulin, while ACPA are directed against peptides and proteins containing citrulline, a modified form of the amino acid arginine.(5,6)

Rheumatoid factor is a heterogeneous group of autoantibodies and can be found in other inflammatory rheumatic and nonrheumatic conditions with increased prevalence in healthy individuals 60 years and older. More than 75% of patients with RA have an IgM antibody to RF. The titer of RF correlates poorly with disease activity, but those patients with high titers tend to have more severe disease and, thus, a poorer prognosis than seronegative patients. Compared to early serologic tests for RA, including RF, several studies have demonstrated that ACPA have much improved specificity for RA.(4,5,7) A systemic review and meta-analysis of 33 studies, including patients with RA and healthy or disease controls, demonstrated the sensitivity of anti-mutated citrullinated vimentin, anticyclic citrullinated peptide, and RF of 71%, 71%,

77%, with the specificity of 89%, 95%, 73%, and the area under the curve of the summary receiver operating characteristic of 89%, 95%, 82%, respectively.(7) Based on these studies, there exist a subset of patients with RA who are negative for RF and ACPA IgG (seronegative) who must be diagnosed clinically or with use of emerging diagnostic tests.(4,6,8)

In addition to the use of RF and ACPA IgG to diagnose RA, RF and ACPA isotype antibodies and other serologic biomarkers have been used to predict if, and when, an individual who has inflammatory arthritis (IA) may develop future clinically apparent IA and assess genetic and environmental risks.(3,4,8,9) Furthermore, patients with RA may be categorized based on the phase of disease (early versus established), presence or absence of antibodies (seropositive versus seronegative), clinical manifestations (joint erosion, interstitial lung disease, or cardiovascular), or specific risks (genes, sex, or smoking).(2-4) Delayed diagnosis of RA is associated with joint erosion, destruction or deformities, poor response to treatment with ultimate increase in morbidity, and mortality.(3,4) Although late RA prognosis may be linked to adverse consequences, early diagnosis has been reported to improve outcomes; notably reduced joint destruction or deformity, delayed radiologic progression, and decreased functional disability.(3,4,10)

For more information see Connective Tissue Disease Cascade.

Reference Values

Cyclic Citrullinated Peptide Antibodies, IgG
<20.0 U (negative)
20.0-39.9 U (weak positive)
40.0-59.9 U (positive)
> or =60.0 U (strong positive)
Reference values apply to all ages.

Rheumatoid Factor
<15 IU/mL

Interpretation

Cyclic Citrullinated Peptide Antibodies:
A positive result for cyclic citrullinated peptide (CCP) antibodies may be suggestive of rheumatoid arthritis (RA) if compatible clinical features of disease are present.

Significantly elevated levels of CCP antibodies may be useful to identify RA patients with erosive joint disease.

A Mayo Clinic prospective clinical evaluation of the CCP antibody test showed a diagnostic sensitivity for RA of 78% with fewer than 5% false-positive results in healthy controls (see Cautions).

Rheumatoid Factor:
Positive results may be suggestive of RA if compatible clinical features of disease are present.

Cautions

Cyclic Citrullinated Peptide Antibodies:
Positive results for cyclic citrullinated peptide (CCP) antibodies may occur in some patients with systemic lupus erythematosus or other autoimmune, connective tissue diseases. In a Mayo Clinic study (see Interpretation), the false-positive rate in this subgroup was approximately 10%.

Antirheumatic therapy should not be initiated based solely on a positive test for CCP antibodies, and changes in treatment should not be based upon the levels of CCP antibodies.

Rheumatoid Factor:
The presence of rheumatoid factor (RF) antibodies is not specific to rheumatoid arthritis. Antibodies may be found in other systemic autoimmune rheumatic diseases as well as nonrheumatic conditions, including infectious diseases. These diseases include Sjogren syndrome, mixed connective tissue disease, systemic lupus erythematosus, polymyositis, tuberculosis, syphilis, viral hepatitis, infectious mononucleosis, and influenza. RF antibodies have been observed in nonaffected individuals, particularly in patients 60 years of age or older.

Clinical Reference

1. Cross M, Smith E, Hoy D, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1316-1322
2. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-2581
3. Burgers LE, Raza K, van der Helm-van Mil AH. Window of opportunity in rheumatoid arthritis - definitions and supporting evidence: from old to new perspectives. RMD Open. 2019;5(1):e000870
4. Deane KD, Holers VM. Rheumatoid arthritis pathogenesis, prediction, and prevention: An emerging paradigm shift. Arthritis Rheumatol. 2021;73(2):181-193
5. Schellekens GA, Visser H, de Jong BA, et al. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum. 2000;43(1):155-163
6. Derksen VFAM, Huizinga TWJ, van der Woude D. The role of autoantibodies in the pathophysiology of rheumatoid arthritis. Semin Immunopathol. 2017;39(4):437-446
7. Zhu JN, Nie LY, Lu XY, Wu HX. Meta-analysis: compared with anti-CCP and rheumatoid factor, could anti-MCV be the next biomarker in the rheumatoid arthritis classification criteria? Clin Chem Lab Med. 2019;57(11):1668-1679
8. Verheul MK, Bohringer S, van Delft MAM, et al. Triple positivity for anti-citrullinated protein autoantibodies, rheumatoid factor, and anti-carbamylated protein antibodies conferring high specificity for rheumatoid arthritis: Implications for very early identification of at-risk individuals. Arthritis Rheumatol. 2018;70(11):1721-1731
9. Hedstrom AK, Ronnelid J, Klareskog L, Alfredsson L. Complex relationships of smoking, HLA-DRB1 genes, and serologic profiles in patients with early rheumatoid arthritis: Update from a Swedish population-based case-control study. Arthritis Rheumatol. 2019;71(9):1504-1511
10. Emery P, Breedveld FC, Dougados M, Kalden JR, Schiff MH, Smolen JS. Early referral recommendation for newly diagnosed rheumatoid arthritis: evidence based development of a clinical guide. Ann Rheum Dis. 2002;61(4):290-297
11. Cush JJ. Rheumatoid arthritis: Early diagnosis and treatment. Rheum Dis Clin North Am. 2022;48(2):537-547

Performance

Method Description

Cyclic Citrullinated Peptide Antibodies:
Cyclic citrullinated peptide (CCP) antibodies in serum are detected by binding to the wells of a commercial microtiter plate coated with synthetic CCP. During the first incubation, serum antibodies bind to adsorbed, solid phase CCP. The wells are then washed to remove unbound serum constituents, and horseradish peroxidase-labeled goat anti-human IgG

is added. After further incubation and washing to remove unbound conjugate, substrate (3,3',5,5' tetramethylbenzidine) is added, and to the mixture incubated. The reaction between enzyme and substrate is stopped, and color in the wells measured in a microtiter plate reader. The concentration of CCP antibodies is determined by comparison to a 5-point standard curve (15.6-250 U). Testing is performed on the Agility instrument by Dynex.(Package insert: Quanta Lite CCP3 IgG ELISA. INOVA Diagnostics; 02/2020)

Rheumatoid Factor:
The Roche rheumatoid factors (RF-II) assay is an immunoturbidimetric assay. Latex-bound heat-inactivated IgG (antigen) reacts with the rheumatoid factor (RF) antibodies in the sample to form antigen/antibody complexes that, following agglutination, are measured turbidimetrically. Rheumatoid factors are autoantibodies that are directed against the Fc fragment of IgG. The autoantibodies occur in all immunoglobulin classes (IgA, IgG, and IgM). The Roche RF II assay measures all 3 types of autoantibodies. However, as the IgA and IgG types typically exhibit lower concentrations, the reaction against IgM autoantibodies predominates in this assay.(Package insert: RF-II, Rheumatoid Factors II. Roche Diagnostics; V 9.0 English, 02/2020)

PDF Report
No

Day(s) Performed
Monday through Friday

Report Available
2 to 3 days

Specimen Retention Time
14 days

Performing Laboratory Location
Mayo Clinic Jacksonville Clinical Lab

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
This test has been cleared, approved, or is exempt by the US Food and Drug Administration and is used per manufacturer's instructions. Performance characteristics were verified by Mayo Clinic in a manner consistent with CLIA requirements.

CPT Code Information
86200

86431

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
RAPAN	Rheumatoid Arthritis Panel, S	46437-0

Result ID	Test Result Name	Result LOINC® Value
CCP	Cyclic Citrullinated Peptide Ab, S	33935-8
RHUT	Rheumatoid Factor, S	11572-5