

## Overview

### Useful For

Evaluating patients at-risk of rheumatoid arthritis (RA) or features of inflammatory arthritis

Differentiating the antibody isotype profile in patients positive for rheumatoid factor (RF)

Aid in the risk stratification of RF-seropositive patients with RA

### Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
RFA	Rheumatoid Factor IgA, S	No	Yes
RFM	Rheumatoid Factor IgM, S	No	Yes

### Highlights

This test is useful for the differentiation of rheumatoid factor (RF) antibodies based on the presence of IgM or IgA antibody isotypes in patients with or at-risk for rheumatoid arthritis (RA).

The combination of RF IgM and RF IgA results provides the highest sensitivity for RA while IgA isotype results provide the highest specificity and positive likelihood ratio for RA diagnosis. The presence of RF IgA isotype may also be relevant in the risk stratification of RA for erosive joint disease.

Together with anti-citrullinated peptide/protein IgG antibody testing, isotype analysis may be an alternative to RF testing.

### Method Name

Chemiluminescent Immunoassay

### NY State Available

Yes

## Specimen

### Specimen Type

Serum

### Additional Testing Requirements

Rheumatoid factor (RF) IgA and RF IgM should be tested in combination with CCP / Cyclic Citrullinated Peptide Antibodies, IgG, Serum; or following positive or equivocal results for either RHUT / Rheumatoid Factor, Serum; or RAPAN / Rheumatoid Arthritis Panel, Serum.

**Specimen Required**

**Supplies:** Sarstedt Aliquot Tube, 5 mL (T914)

**Collection Container/Tube:**

**Preferred:** Serum gel

**Acceptable:** Red top

**Submission Container:** Plastic vial

**Specimen Volume:** 1 mL

**Collection Instructions:** Centrifuge and aliquot serum into a plastic vial.

**Forms**

If not ordering electronically, complete, print, and send a [Kidney Transplant Test Request](#) with the specimen.

**Specimen Minimum Volume**

0.3 mL

**Reject Due To**

Gross hemolysis	Reject
Gross lipemia	Reject
Gross icterus	Reject
Heat-treated specimens	Reject

**Specimen Stability Information**

Specimen Type	Temperature	Time	Special Container
Serum	Refrigerated (preferred)	14 days	
	Ambient	48 hours	
	Frozen	28 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%.<sup>(1)</sup> Clinically, RA is typified by progressive damage of synovial joints, inflammation, production of diverse autoantibodies, and variable extra-articular manifestations.<sup>(1,2)</sup> To facilitate early diagnosis, the American College of Rheumatology/European League Against Rheumatism 2010 RA classification criteria recommend testing for rheumatoid factors (RF) and anti-citrullinated protein antibodies (ACPA).<sup>(2)</sup> 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.<sup>(3,4)</sup> In addition to the defined interpretations for anti-cyclic citrullinate peptide (CCP) and RF antibodies, the classification criteria also endorse the combination of

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specific clinical features and inflammatory markers for RA diagnosis.

The clinical symptoms in the early phase of RA may be nonspecific with some patients demonstrating relatively low levels of antibodies to RF or anti-CCP antibodies, which may not fulfill the diagnostic criteria for disease. In addition, some patients with clinical features of RA may test negative for criteria antibodies, a phenomenon referred to as seronegative or ACPA-negative. While alternative diagnoses may be implicated in at-risk RA patients, determination of autoantibody isotypes for RF and other RA-associated autoantibodies have been reported to improve diagnostic accuracy and/or provide prognostic clues.(5-8) Thus, determination of multiple analytes of diverse antibody isotypes in patients seropositive for RA may be useful in risk stratification for joint erosive disease and other clinical manifestations such as cardiovascular or lung involvements.(5,7,8)

In routine clinical laboratory evaluation for RA, RF antibodies are generally detected and quantified using IgM RF or total (isotype-nonspecific) RF immunoassays and CCP IgG antibodies with a variety of solid-phase immunoassays, such the enzyme linked immunosorbent assay, chemiluminescence immunoassay (CIA), fluorescent enzyme immunoassay (FEIA), multiplexed immunoassay using manual or automated platforms.(5,6,9,10) With respect to RF antibody measurements, it has been established that separate determination of RF IgA and RF IgM antibodies is important in RA evaluation, as severe joint erosive disease is seen more in patients with significantly elevated IgA RF than in those who are IgA RF negative.(5,8,9) However, IgA RF is generally less sensitive than IgM RF for RA, and double positivity for IgM RF and IgA RF has a higher specificity for RA than either IgM RF or IgA RF.(9) Both tests should be offered in a panel, which is not intended to replace RF tests that detect IgA, IgG and IgM autoantibodies. The relevance of IgG RF in addition to IgA or IgM RF is of limited clinical value and not available for testing on the CIA or FEIA platforms due to this clinical limitation.

### **Reference Values**

#### RHEUMATOID FACTOR, IgA

Negative: <20 CU

Positive: > or =20 CU

Reference values apply to all ages.

#### RHEUMATOID FACTOR, IgM

Negative: <5.0 IU/mL

Positive: > or =5.0 IU/mL

Reference values apply to all ages.

### **Interpretation**

The presence of rheumatoid factor (RF) IgM or IgA at abnormal levels in association with anti-citrullinated peptide/protein antibodies has high specificity for a diagnosis of rheumatoid arthritis (RA). However, the presence of RF isotypes in any combination may be found in a variety of conditions, including Sjogren syndrome and hepatitis infections.

### **Cautions**

Some patients with rheumatoid arthritis (RA) may be negative for rheumatoid factor (RF) IgM or RF IgA but positive for RF antibody by nephelometry or anti-citrullinated peptide IgG antibodies. Negative results do not rule out a diagnosis of RA. All results must be interpreted in the appropriate clinical context and in association with other recommended laboratory tests disease evaluation. The performance characteristics of this assay have not been established for matrices other than serum.

**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. 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
4. Derkzen VFAM, Huizinga TWJ, van der Woude D. The role of autoantibodies in the pathophysiology of rheumatoid arthritis. *Semin Immunopathol.* 2017;39(4):437-446
5. Sieghart D, Platzer A, Studenic P, et al. Determination of autoantibody isotypes increases the sensitivity of serodiagnosis in rheumatoid arthritis. *Front Immunol.* 2018;9:876
6. Brink M, Hansson M, Mathsson-Alm L, et al. Rheumatoid factor isotypes in relation to antibodies against citrullinated peptides and carbamylated proteins before the onset of rheumatoid arthritis. *Arthritis Res Ther.* 2016;18:43
7. Kelmenson LB, Wagner BD, McNair BK, et al. Timing of Elevations of Autoantibody Isotypes Prior to Diagnosis of Rheumatoid Arthritis. *Arthritis Rheumatol.* 2020;72(2):251-261
8. Oka S, Higuchi T, Furukawa H, et al. Serum rheumatoid factor IgA, anti-citrullinated peptide antibodies with secretory components, and anti-carbamylated protein antibodies associate with interstitial lung disease in rheumatoid arthritis. *BMC Musculoskelet Disord.* 2022;23(1):46
9. Van Hoovels L, Vander Cruyssen B, Sieghart D, et al. IgA rheumatoid factor in rheumatoid arthritis. *Clin Chem Lab Med.* 2022;60(10):1617-1626
10. Van Hoovels L, Vander Cruyssen B, Sieghart D, et al. Multicentre study to improve clinical interpretation of rheumatoid factor and anti-citrullinated protein/peptide antibodies test results. *RMD Open.* 2022;8(1):e002099

**Performance****Method Description**

The Inova BIO-FLASH system uses paramagnetic beads as the solid surface upon which to bind the targeted antibody. The beads used in the rheumatoid factor (RF) IgA and IgM kits are coated with rabbit polyclonal antibodies as the capture antigen. The serum sample is diluted by the instrument and combined in a cuvette with the beads and assay buffer for 10 minutes at 37 degrees C. The beads are magnetized, and unbound materials are washed away. Detection antibody conjugated with isoluminol is added to the cuvette for another incubation at 37 degrees C. The RF IgA kits contain anti-human IgA conjugate, while the RF IgM kits contain anti human IgM conjugate. After an additional wash, trigger reagents are added to the cuvette to initiate a light reaction proportional to the amount of bound isoluminol conjugate. The light produced by the reaction is measured by a detector as relative light unit (RLU). The RLU is applied to the working curve on the instrument. The RF IgA is reported as chemiluminescent units (CU), while the RF IgM is reported in IU/mL traceable to WHO Reference Reagent W1066.(Package inserts: QUANTA Flash RF IgA. Inova Diagnostics, Inc; V 4, 07/2019; QUANTA Flash RF IgM. Inova Diagnostics, Inc; V 3, 07/2019)

**PDF Report**

No

**Day(s) Performed**

Wednesday

**Report Available**

2 to 8 days

**Specimen Retention Time**

14 days

**Performing Laboratory Location**

Mayo Clinic Laboratories - Rochester Superior Drive

**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**

86431 x2

**LOINC® Information**

Test ID	Test Order Name	Order LOINC® Value
RFPN	Rheumatoid Factor Panel, S	106053-2

Result ID	Test Result Name	Result LOINC® Value
RFM	Rheumatoid Factor IgM, S	9338-5
RFA	Rheumatoid Factor IgA, S	33313-8