MAYO CLINIC LABORATORIES

Test Definition: CRGSP

Cryoglobulin and Cryofibrinogen Panel, Serum and Plasma

Overview

Useful For

Evaluating patients with vasculitis, glomerulonephritis, and lymphoproliferative diseases

Evaluating patients with macroglobulinemia or myeloma in whom symptoms occur with cold exposure

This test is **not useful for** general screening of a population without a clinical suspicion of cryoglobulinemia.

Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
CRY_S	Cryoglobulin, S	Yes	Yes
CRY_P	Cryofibrinogen, P	No	Yes

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
IMFXC	Immunofixation Cryoglobulin	No	No

Testing Algorithm

If cryoglobulin has a positive result after 1 or 7 days, then immunofixation will be performed at an additional charge. Immunofixation will only be performed once when positive cryoglobulin results are 0.1 mL of precipitate or greater.

Method Name

CRY_S, CRY_P: Quantitation and Qualitative Typing Precipitation
IMFXC: Immunofixation

NY State Available

Yes

Specimen

Specimen Type

Plasma EDTA
Serum Red

Specimen Required

Both plasma and serum are required.
Patient Preparation: Fasting: 12 hours, preferred but not required

Specimen Type: Plasma
Collection Container/Tube: Lavender top (EDTA)
Submission Container/Tube: Plastic vial
Specimen Volume: 1 mL Plasma
Collection Instructions:
1. Tube must remain at 37 degrees C.
2. Centrifuge at 37 degrees C. **Do not use a refrigerated centrifuge.** If absolutely necessary, ambient temperature is acceptable. It is very important that the specimen remains at 37 degrees C until after separation of plasma from red blood cells.
3. Place plasma into an appropriately labeled plastic vial.

Specimen Type: Serum
Collection Container/Tube: Red top (serum gel/SST are **not acceptable**)
Submission Container/Tube: Plastic vial
Specimen Volume: 5 mL Serum
Collection Instructions:
1. Tube must remain at 37 degrees C.
2. Allow blood to clot at 37 degrees C.
3. Centrifuge at 37 degrees C. **Do not use a refrigerated centrifuge.** If absolutely necessary, ambient temperature is acceptable. It is very important that the specimen remains at 37 degrees C until after separation of serum from red blood cells.
4. Place serum into an appropriately labeled plastic vial.
Additional Information: Analysis cannot be performed with less than 3 mL of serum. Smaller volumes are insufficient to detect clinically important trace (mixed) cryoglobulins. Less than 3 mL will require collection and submission of a new specimen.

Forms

If not ordering electronically, complete, print, and send a Benign Hematology Test Request Form (T755) with the specimen.

Specimen Minimum Volume

Plasma: 0.5 mL; Serum: 3 mL

Reject Due To

Gross hemolysis	OK
Gross lipemia	OK
Gross icterus	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Plasma EDTA	Refrigerated (preferred)		
	Frozen		
Serum Red	Refrigerated (preferred)		
	Frozen		

Clinical & Interpretive

Clinical Information

Cryoglobulins are immunoglobulins that precipitate when cooled and dissolve when heated. Because these proteins precipitate when cooled, patients may experience symptoms when exposed to the cold. Cryoglobulins may be associated with a variety of diseases including plasma cell disorders, autoimmune diseases, and infections. Cryoglobulins may also cause erroneous results with some automated hematology instruments.

Cryoglobulins may be classified as type I, type II, and type III. Type I is composed of a monoclonal immunoglobulin: IgG or IgM, or rarely IgA or free monoclonal light chains. Type II cryoglobulins consist of a monoclonal component and a polyclonal component. Finally, type III cryoglobulins are composed of only polyclonal immunoglobulins.

The majority of patients with cryoglobulins are asymptomatic. The type or quantity of cryoglobulin does not reliably predict whether or which symptoms will be present. The concentration of cryoglobulins tends to vary by type with the majority of cases of type III, being less than 1 mg/mL; of type II, greater than 1 mg/mL; and of type I, greater than 5 mg/mL. Even though the type I cryoglobulin concentrations tend to be the highest, they are the least likely to cause symptoms. The thermal amplitude (temperature at which the cryoglobulin precipitates) is a better predictor of symptoms than quantity or type.

Symptoms of cryoglobulinemia include purpura, Raynaud phenomenon, cyanosis, skin ulceration, gangrene, kidney failure, peripheral neuropathy, fever, and malaise.

Type I cryoglobulinemia is associated with monoclonal gammopathy of undetermined significance, macroglobulinemia, or multiple myeloma.

Type II cryoglobulinemia is associated with autoimmune disorders such as vasculitis, glomerulonephritis, systemic lupus erythematosus, rheumatoid arthritis, and Sjogren syndrome. It may be seen in infections such as hepatitis, infectious mononucleosis, cytomegalovirus, and toxoplasmosis. Type II cryoglobulinemia may also be essential, ie, occurring in the absence of underlying disease.

Type III cryoglobulinemia usually demonstrates trace levels of cryoprecipitate, may take up to 7 days to appear, and is associated with the same disease spectrum as type II cryoglobulinemia.

A cryoprecipitate that is seen in plasma but not serum is caused by cryofibrinogen. Cryofibrinogens are extremely rare and can be associated with vasculitis. Patients with cryofibrinogenemia often present asymptomatically, but this disorder can also be secondary to numerous conditions that include, but are not limited to, malignancies, infection, inflammation, or thrombotic disorders. Of those with symptoms, primary or essential cryofibrinogenemia can present

with systemic manifestations or with a more specific clinical picture that typically includes cold intolerance and thrombotic/hemorrhagic manifestations, such as purpura, necrosis, ulcers, and gangrene. Due to the rarity of clinically significant cryofibrinogenemia, testing for cryoglobulins is usually sufficient for investigation of cryoproteins.

Reference Values

CRYOGLOBULIN
Negative
Positive results are reported as a percentage or trace amount.

CRYOFIBRINOGEN
Negative

Interpretation

Type I cryoglobulins are composed of monoclonal protein, often linked to plasma cell disorders such as monoclonal gammopathy of undetermined significance, macroglobulinemia, or multiple myeloma.

Type II cryoglobulins have both monoclonal and polyclonal component and can be associated with associated with autoimmune disorders such as vasculitis, glomerulonephritis, systemic lupus erythematosus, rheumatoid arthritis, and Sjogren syndrome. It may be seen in infections such as hepatitis, infectious mononucleosis, cytomegalovirus, and toxoplasmosis.

Type III cryoglobulins consist of only polyclonal protein and are associated with the same diseases as type II cryoglobulins. Clinical severity depends more on thermal amplitude than concentration or type.

Cryofibrinogen precipitates in plasma only and is associated with vasculitis and thrombotic disorders.

Cautions

Failure to follow specimen handling instructions may cause false-negative results.

Clinical Reference

1. Kyle RA, Lust JA. Immunoglobulins and laboratory recognition of monoclonal proteins. Section III. Myeloma and related disorders. In: Wiernik PH, Canellos GP, Dutcher JP, Kyle RA, eds. Neoplastic Diseases of the Blood. 3rd ed. Churchill Livingstone; 1996:453-475
2. Desbois AC, Cacoub P, Saadoun D. Cryoglobulinemia: An update in 2019. Joint Bone Spine. 2019;86(6):707-713. doi:10.1016/j.jbspin.2019.01.016

Performance

Method Description

Normal proteins in plasma and serum do not precipitate in the cold. An aliquot of plasma and of serum are incubated for 24 hours at 1 degree C. If a precipitate develops in the serum, the specimen is centrifuged, and the percentage of precipitate is reported. Negative specimens are kept at 1 degree C for 7 days and rechecked. All positive cryoglobulins are analyzed by immunofixation to determine if the precipitate is a monoclonal protein, polyclonal protein, or a mixed

cryoglobulin. Precipitates that occur in plasma and not serum are reported as positive for cryofibrinogen. Cryofibrinogen-positive specimens are not quantitated or immunotyped. Slowly forming fibrin clots (as may occur in hemophilia) are distinguished from cryoprecipitates by their inability to redissolve on warming.(Lerner AB, Watson CJ. Studies of cryoglobulins; unusual purpura associated with the presence of a high concentration of cryoglobulin [cold precipitable serum globulin]. Am J Med Sci. 1947;214[4]:410-415; Desbois AC, Cacoub P, Saadoun D. Cryoglobulinemia: An update in 2019. Joint Bone Spine. 2019;86(6):707-713. doi:10.1016/j.jbspin.2019.01.016)

PDF Report
No

Day(s) Performed
Monday through Friday

Report Available
2 to 10 days

Specimen Retention Time
Serum: Negative: 7 days post receipt; Positive: Until reported up to 10 days; Plasma: Not retained

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
82585
82595
86334-Immunofixation (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
CRGSP	Cryo Panel, S and P	74352-6

Result ID	Test Result Name	Result LOINC® Value
2685	Cryofibrinogen, P	11043-7
2684	Cryoglobulin, S	12201-0