MAYO CLINIC LABORATORIES

# Test Definition: SFX

Protein S Activity, Plasma

## Overview

### Useful For

Second-order testing for diagnosis of congenital or acquired protein S deficiency, ie, as an adjunct to initial testing based on results of protein S antigen assay (free protein S antigen, with or without total protein S antigen assay)

Evaluating patients with a history of venous thromboembolism

### Special Instructions

- Coagulation Guidelines for Specimen Handling and Processing

### Method Name

Optical Clot-Based

### NY State Available

Yes

## Specimen

### Specimen Type

Plasma Na Cit

### Specimen Required

**Specimen Type:** Platelet-poor plasma
**Supplies**: Sarstedt Aliquot Tube, 5 mL (T914)
**Patient Preparation: Patient must not be receiving Coumadin.**
**Collection Container/Tube:** Light-blue top (3.2% sodium citrate)
**Submission Container/Tube:** 13-mm x 75-mm, 5-mL, plastic vial (polypropylene preferred)
**Specimen Volume:** 1 mL
**Collection Instructions:**
1. For complete instructions, see Coagulation Guidelines for Specimen Handling and Processing
2. Centrifuge, transfer all plasma into a plastic vial, and centrifuge plasma again.
3. Aliquot plasma into a plastic vial leaving 0.25 mL in the bottom of centrifuged vial.
4. Freeze specimen immediately (no longer than 4 hours after collection) below -40 degrees C.

### Forms

If not ordering electronically, complete, print, and send an Coagulation Test Request (T753) with the specimen.

### Specimen Minimum Volume

0.5 mL

### Reject Due To

| | |
|---|---|
| Gross hemolysis | Reject |
| Gross lipemia | Reject |
| Gross icterus | Reject |

### Specimen Stability Information

| Specimen Type | Temperature | Time | Special Container |
|---|---|---|---|
| Plasma Na Cit | Frozen | 14 days | |

## Clinical & Interpretive

### Clinical Information

Protein S is a vitamin K-dependent plasma glycoprotein synthesized predominantly within the liver. Protein S is also synthesized in endothelial cells and present in platelets. As a part of the plasma anticoagulant system, protein S acts as a necessary cofactor to activated protein C (APC) in the proteolytic inactivation of procoagulant factors Va and VIIIa. About 60% of the total plasma protein S antigen circulates bound to C4b binding protein (C4b-BP), while the remainder circulates as “free” protein S. Only free protein S has anticoagulant activity.

Congenital protein S deficiency is an autosomal codominant disorder that is present in 1% to 3% of patients with venous thromboembolism. Heterozygous protein S deficiency carriers have, approximately, a 10-fold increased risk of venous thromboembolism. Other phenotypic expressions of heterozygous congenital protein S deficiency include recurrent miscarriage, complications of pregnancy (preeclampsia, abruptio placentae, intrauterine growth restriction, and stillbirth) and, possibly, arterial thrombosis. Three types of heterozygous congenital protein S deficiency have been described according to the levels of total protein S antigen, free protein S antigen, and protein S (APC cofactor) activity in plasma.

Table. **Types of heterozygous protein S deficiency**

| Type | Free protein S antigen | Total protein S antigen | Protein activity |
|---|---|---|---|
| I | Decreased | Decreased | Decreased |
| II | Normal | Normal | Decreased |
| III | Decreased | Normal | Decreased |

Type I and III protein S deficiency are much more common than type II (dysfunctional) protein S deficiency. Type III protein S deficiency appears to be partly due to variants within the protein S binding region for C4b-BP.

Homozygous protein S deficiency is rare but can present as neonatal purpura fulminans, reflecting severe intravascular coagulation and fibrinolysis/disseminated intravascular coagulation (ICF/DIC) caused by the absence or near absence of plasma protein S.

Acquired deficiency of protein S is much more common than hereditary protein S deficiency and is generally of unknown

hemostatic significance (ie, uncertain thrombosis risk). Among the many causes of acquired protein S deficiency are:
-Vitamin K deficiency
-Oral anticoagulant therapy
-Acute illness (eg, acute thrombosis, recent surgery, or other disorder associated with acute inflammation)
-Liver disease
-ICF/DIC
-Thrombotic thrombocytopenic purpura
-Pregnancy, oral contraceptive, or estrogen therapy
-Nephrotic syndrome
-Sickle cell anemia

## Reference Values

Males: 65-150%
Females
<50 years: 50-150%
> or =50 years: 65-150%
Newborn infants have normal or near-normal free protein S antigen (> or =50%), although total protein S antigen is usually below the adult reference range. There are insufficient data concerning protein S activity in normal neonates, infants, and children; but normal or near-normal activity (> or =50%) probably is present by age 3 to 6 months.

## Interpretation

In type I and type III congenital deficiency, free protein S antigen is decreased, and protein S functional activity is similarly decreased. In type II congenital (dysfunctional) protein S deficiency, total and free protein S antigen levels are normal, but functional activity is decreased.

Patients with acquired free protein S deficiency associated with inflammation-related increase of C4b-binding protein typically have decreased free protein S antigen and protein S activity with normal (or elevated) total protein S antigen. Acquired protein S deficiency is of uncertain clinical hemostatic significance and is associated with a variety of conditions.

Elevated protein S levels are of uncertain clinical significance.

## Cautions

Direct-acting oral anticoagulants (eg, direct thrombin inhibitors, such as dabigatran [Pradaxa], argatroban [Acova], bivalirudin [Angiomax]) and direct factor Xa inhibitors (eg, rivaroxaban [Xarelto], apixaban [Eliquis], edoxaban [Savaysa]) may cause the protein S activity to appear spuriously normal (or elevated), when protein S activity is truly decreased (or normal). Clinical correlation is suggested, and in the absence of anticoagulation therapy, consider repeating the protein S activity and antigen assay.

Coumadin therapy may result in decreased protein S activity (and free protein S antigen).

Acute or chronic inflammation can result in decreased protein S activity (and free protein S antigen).

Interpret protein S activity results with caution when any of the above patient conditions are present.

Protein S antigen assay (free protein S antigen, with concomitant or reflexive total protein S antigen assay), rather than

protein S activity (functional) assay, is recommended as the initial testing approach for detecting congenital protein S deficiency, because of the greater variety of patient conditions that can interfere with the accuracy of functional testing as compared to antigen testing.

In general, it is preferable not to test for protein S deficiency during acute illness, pregnancy, or postpartum. Elective testing for protein S deficiency should be delayed for at least 30 days after cessation of warfarin therapy.

### Clinical Reference

1. Borgel D, Gandrille S, Aiach M. Protein S deficiency. Thromb Haemost. 1997;78(1):351-356
2. Faioni EM. Protein S activity. In: Laboratory Techniques in Thrombosis-A Manual. 2nd ed. Kluwer Academic Publishers; 1999:153-161
3. De Stefano V, Finazzi G, Mannucci PM. Inherited thrombophilia: pathogenesis, clinical syndromes, and management. Blood. 1996;87(9):3531-3544
4. Zoller B, Garcia de Frutos P, Dahlback B. Evaluation of the relationship between protein S and C4b-binding protein isoforms in hereditary protein S deficiency demonstrating type I and type III deficiencies to be phenotypic variants of the same genetic disease. Blood. 1995;85(12):3524-3531
5. Grandrille S, Borgel D, Ireland H, et al. Protein S deficiency: a database of mutations. For the Plasma Coagulation Inhibitors Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Thromb Haemost. 1997;77(6):1201-1214
6. Goodwin AJ, Rosendaal FR, Kottke-Marchant K, Bovill EG. A review of the technical, diagnostic, and epidemiologic considerations for protein S assays. Arch Pathol Lab Med. 2002;126(11):1349-1366
7. Yohe S, Olson J. Thrombophilia: assays and interpretation. In: Kottke-Marchant Wiley K, ed. Laboratory Hematology Practice. Blackwell Publishing; 2012;38:492-508
8. Favaloro EJ and Lippi G. eds. Hemostasis and Thrombosis, Methods and Protocols, Humana Press; 2017

## Performance

### Method Description

The functional activity of free protein S is performed on the instrumentation laboratory ACL TOP. It is determined by measuring the degree of prolongation of a prothrombin time in the presence of the recombinant human tissue factor, phospholipids, calcium ions, and activated protein C. Protein S activity is correlated with the prolongation of the clotting time of protein S deficient plasma to which diluted sample has been added. The clotting time is directly proportional to the amount of functional protein S in the patient's plasma and can be quantified using a standard curve.(Package insert: HemosIL Protein S Activity. Instrumentation Laboratory Company; Rev 08/2012)

### PDF Report

No

### Day(s) Performed

Monday through Friday

### Report Available

1 to 4 days

### Specimen Retention Time

7 days

### Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

## 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

85306

### LOINC® Information

| Test ID | Test Order Name | Order LOINC® Value |
|---|---|---|
| SFX | Protein S Activity, P | 27822-6 |

| Result ID | Test Result Name | Result LOINC® Value |
|---|---|---|
| SFX | Protein S Activity, P | 27822-6 |