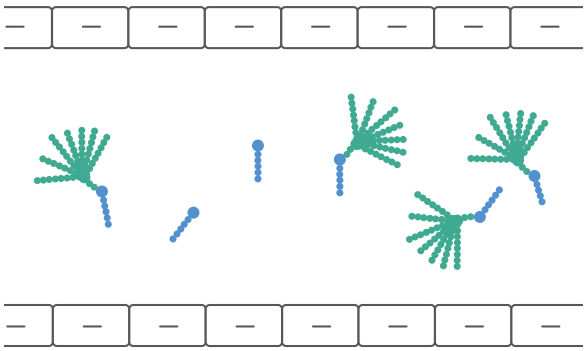
NORDIC BIOMARKER

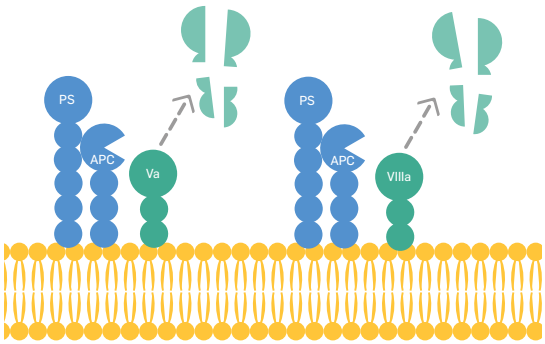
Protein S

Protein S and Its Functions

Protein S is a small vitamin K-dependent protein, acting as a cofactor to protein C. It functions as an anticoagulant by increasing the activity of protein C facilitated degradation of factor Va and VIIIa. Protein S exists in two forms in circulation, bound to the protein C4BP or free. Only the free form of protein S has anticoagulant activity. Approximately 60% of the circulating protein S is bound to C4BP. The amount of free protein S in circulation is dependent on the amount of C4BP, as protein S is in excess.



Protein S (blue) in the circulation can be free or bound to C4BP (green).



Protein S (PS) acts as a cofactor to activated protein C (APC) and facilitates the degradation of factor Va and VIIIa.

Protein S Deficiency

Approximately 2-3% of patients seeking medical attention with first time thrombosis have protein S deficiency. Characteristics are unprovoked thrombosis at a young age, at uncommon locations in the body. Family history is often considered if the patient has recurring thromboses. Late miscarriages are also an indication for protein S deficiency. Severe deficiency is very rare but very critical, often leading to DIC, or purpura fulminans in newborn infants.

Protein S deficiency can be inherited or acquired. Common acquiring causes are oral anticoagulant therapy (e.g. warfarin), oral contraceptives, nephritic syndrome, DIC and pregnancy. Protein S deficiency increases the risk for thrombosis by 2–11 times.

There are three types of protein S deficiency.

Type	Protein S activity	Total Protein S	Free Protein S	% of total cases
Type I	Lowered	Lowered	Lowered	<80%
Type II (IIa)	Lowered	Normal	Normal	0.1–5%
Type III (IIb)	Lowered	Normal	Lowered	<20%

Treatment

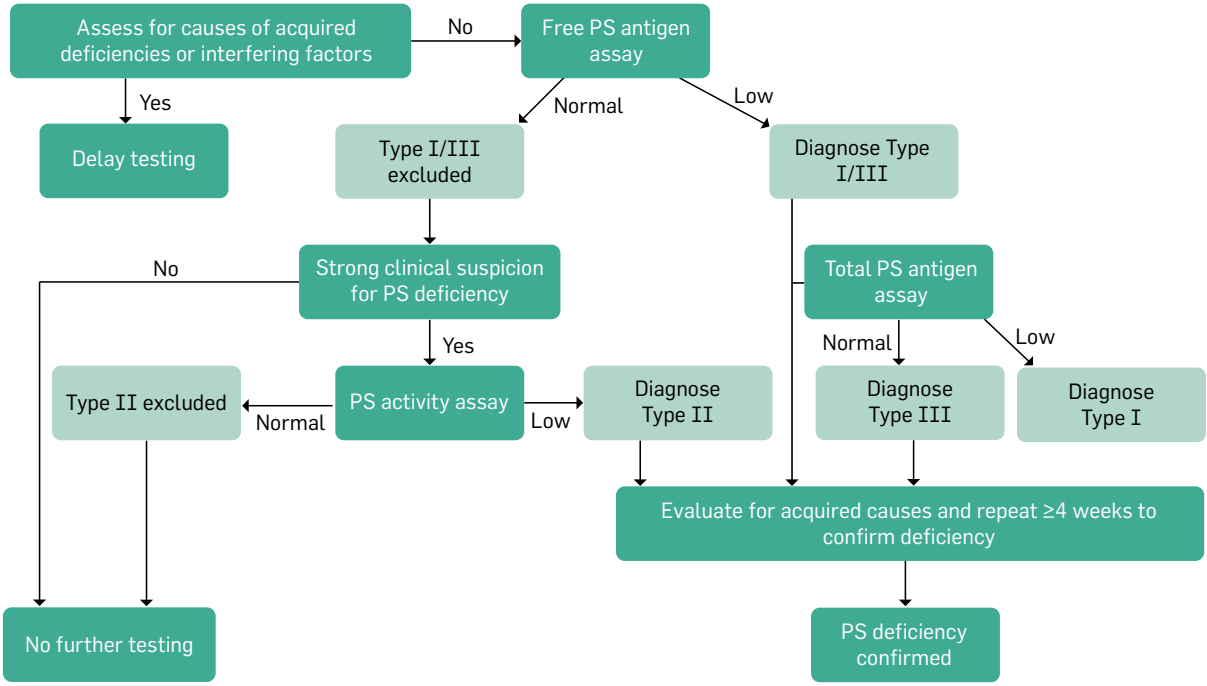
Hereditary protein S deficiency is a lifelong ailment, whereas acquired deficiency with temporary causes (pregnancy, oral anticoagulant therapy, etc.) are temporary. However, there are ways to lower healthrisks for patients with protein S deficiency. Anticoagulant therapy is used to lower the risk of thrombosis after a first occurrence. In known thrombosis risk situations such as surgery, trauma, pregnancy etc anticoagulant therapy is administered prophylactically. Oral contraceptives are strongly discouraged for patients with known protein S deficiency.

Testing for Protein S Deficiency

There are three assays for identification of protein S deficiency.

- Free protein S: Immunological assay, which measure the concentration of free protein S in circulation.
- Total protein S: Immunological assay, which measure the concentration of total protein S (both free and bound) in circulation.
- Protein S activity: Clotting assay, which measures the function of protein S.

Unfortunately, the activity assay is riddled with interference problems and sporadic, unexplainable false positive results. Total protein S cannot diagnose type III deficiency but can be used for differentiation between types in conjunction with the other assays. Therefore, ISTH guidelines recommend free protein S as the first line assay to be used when there is a clinical suspicion of protein S deficiency as it catches most cases, with the lowest number of falsely positive results.



Classification and clinical testing algorithms for protein S deficiencies. Source: ISTH

A Closer Look: MRX Free Protein S

MRX Free Protein S consists of free protein S specific monoclonal antibodies coupled to sub-micron sized polystyrene particles.

When the reagent is exposed to a plasma sample containing free protein S, the particles will agglutinate, giving rise to increased light-scattering. When exposed to the appropriate wavelength of light, the increase in measured turbidity, or light-scattering, is proportional to the amount of free Protein S in the sample. The assay is of course calibrated against the WHO international standard and correlates well to existing assays on the market.

MRX Blue Free Protein S is suitable for instruments operating at 400–600 nm.
MRX Red Free Protein S is suitable for instruments operating at 600–800 nm.