Test Definition: AATHR

Thrombophilia Profile, Plasma and Whole Blood

Overview

Useful For

Evaluating patients with thrombosis or hypercoagulability states

Detecting a lupus-like anticoagulant; dysfibrinogenemia; disseminated intravascular coagulation/intravascular coagulation and fibrinolysis

Detecting a deficiency of antithrombin, protein C, or protein S

Detecting activated protein C resistance (and the factor V Leiden [p.Arg534Gln, historically known as R506Q] variant if indicated)

Detecting the prothrombin F2 c.*97G>A variant (historically known as G20210A)

Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
AATHI	Thrombophilia Interpretation	No	Yes
PTSC	Prothrombin Time (PT), P	Yes, (order PTTP)	Yes
APTSC	Activated Partial Thrombopl Time, P	Yes, (order APTTP)	Yes
DRV1	Dilute Russells Viper Venom Time, P	Yes, (order DRVI1)	Yes
TTSC	Thrombin Time (Bovine), P	Yes	Yes
CLFIB	Fibrinogen, Clauss, P	Yes, (order FIBTP)	Yes
DIMER	D-Dimer, P	Yes, (order DDITT)	Yes
ATTF	Antithrombin Activity, P	Yes	Yes
CFX	Protein C Activity, P	Yes	Yes
PSF	Protein S Ag, Free, P	Yes, (order PSTF)	Yes
APCRV	Activated Protein Resistance V, P	Yes	Yes
PTNT	Prothrombin G20210A Mutation, B	Yes	Yes

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
ATTI	Antithrombin Antigen, P	Yes	No
FACTV	Coag Factor V Assay, P	Yes	No

F_7	Coag Factor VII Assay, P	Yes	No
F_9	Coag Factor IX Assay, P	Yes	No
F_10	Coag Factor X Assay, P	Yes	No
F_11	Coag Factor XI Assay, P	Yes	No
F_12	Coag Factor XII Assay, P	Yes	No
F8A	Coag Factor VIII Activity Assay, P	Yes	No
RTSC	Reptilase Time, P	Yes	No
F_2	Coag Factor II Assay, P	Yes	No
PCAG	Protein C Ag, P	Yes	No
F5DNA	Factor V Leiden (R506Q) Mutation, B	Yes	No
PNP	Platelet Neutralization Procedure	No	No
PTMSC	PT Mix 1:1	No	No
APMSC	APTT Mix 1:1	No	No
PST	Protein S Ag, Total, P	No	No
DRV2	DRVVT Mix	No	No
DRV3	DRVVT Confirmation	No	No
SOLFM	Soluble Fibrin Monomer	No	No
PTFIB	PT-Fibrinogen, P	No	No
HEXLA	HEX LA, P	No	No
SFX	Protein S Activity, P	Yes	No

Testing Algorithm

Initial testing includes prothrombin time (PT); activated partial thromboplastin time (aPTT); dilute Russell's viper venom time (dRVVT); thrombin time (bovine); fibrinogen; D-dimer; antithrombin activity; protein C activity; protein S antigen, free; prothrombin *G20210A* variant; activated protein resistance V; and thrombophilia interpretation.

If the PT is greater than 13.9 seconds, then the PT mixing study will be performed at an additional charge.

If the aPTT is 38 seconds or more, then the aPTT mixing study will be performed at an additional charge.

If the aPTT mix result is 38 seconds or more and thrombin time is less than 35.0 seconds (no evidence of heparin), then the platelet neutralization procedure will be performed at an additional charge.

If the dRVVT ratio is 1.20 or more, then the dRVVT mixing study and dRVVT confirmation will be performed at an additional charge.

If the thrombin time is 25.0 or more seconds, then the reptilase time will be performed at an additional charge.

If the fibrinogen result is less than 150 mg/dL or clinically indicated, then PT-fibrinogen will be performed at an additional charge.

If the D-dimer result is greater than 500 ng/mL fibrinogen equivalent units (FEU), then soluble fibrin monomer testing will be performed at an additional charge.

If the free protein S antigen result is less than 65% for men and women 50 years of age or older and less than 50% for women and girls younger than 50 years of age, then the total protein S antigen test will be performed at an additional charge.

If the protein C activity is less than 70% with no evidence for an acquired decrease in protein C activity, then protein C antigen testing may be performed at an additional charge.

If the antithrombin activity is less than 80% with no evidence of an acquired decrease in antithrombin activity, then antithrombin antigen testing will be performed at an additional charge.

If the activated protein C resistance (APC) ratio is less than 2.3 or the baseline APC aPTT is prolonged, then factor V Leiden (R506Q) variant analysis will be performed at an additional charge.

If appropriate, protein S activity, coagulation factor assays, or hexagonal lupus anticoagulant will be performed, at an additional charge, to clarify significant abnormalities in the screen test results.

For more information see Thrombophilia Profile

Special Instructions

- Coagulation Guidelines for Specimen Handling and Processing
- Informed Consent for Genetic Testing
- Coagulation Patient Information
- Thrombophilia Profile
- Informed Consent for Genetic Testing (Spanish)
- Coagulation Profile Comparison

Method Name

PTSC, APTSC, DRV1, TTSC, APCRV: Optical Clot-Based
CLFIB: Clauss
DIMER, PSF: Latex Immunoassay (LIA)
ATTF, CFX: Chromogenic
PTNT: Direct Variant Analysis
AATHI: Medical Interpretation

NY State Available

Yes

Specimen

Specimen Type

Whole blood
Plasma Na Cit

Ordering Guidance

Multiple coagulation profile tests are available. See Coagulation Profile Comparison for testing that is performed with each profile.

Shipping Instructions

Send all specimens in the same shipping container.

Specimen Required

Both blood and plasma are required.

Patient Preparation:
1. Patient **should not** be receiving Coumadin (warfarin), heparin, direct thrombin inhibitors (argatroban, dabigatran), or direct factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban).
2. Specimen must be collected prior to initiation of anticoagulants and thrombolytic therapy.
3. If patient has been recently transfused, it is best to perform this study pretransfusion, if possible.

Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA)
Acceptable: Yellow top (ACD), light-blue top (3.2% sodium citrate)
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**
3. Label specimen as whole blood.

Specimen Type: Platelet-poor plasma
Collection Container/Tube: Light-blue top (3.2% sodium citrate)
Submission Container/Tube: Plastic vial (polypropylene preferred)
Specimen Volume: 5 mL in 5 plastic vials; each containing 1 mL
Collection Instructions:
1. Specimen must be collected prior to factor replacement therapy.
2. For complete instructions, see Coagulation Guidelines for Specimen Handling and Processing.
3. Centrifuge, transfer all plasma into a plastic vial, and centrifuge plasma again.
4. Aliquot plasma (1-2 mL per aliquot) into 5 separate plastic vials leaving 0.25 mL in the bottom of centrifuged vial.
5. Freeze plasma immediately (no longer than 4 hours after collection) at -20 degrees C or, ideally, -40 degrees C or below.
Additional Information: Double-centrifuged specimen is critical for accurate results as platelet contamination may cause spurious results.

Forms

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

Specimen Minimum Volume

Plasma: 5 mL total, 5 plastic vials each containing 1 mL, Whole blood: 1 mL

Reject Due To

Gross hemolysis	Reject
Gross lipemia	Reject
Gross icterus	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole blood	Ambient (preferred)	14 days	
	Refrigerated	14 days	
	Frozen	14 days	
Plasma Na Cit	Frozen	14 days	

Clinical & Interpretive

Clinical Information

Thrombophilia is defined as an acquired or familial disorder associated with thrombosis. The clinical presentation of an underlying thrombophilia predominantly includes venous thromboembolism (deep vein thrombosis, pulmonary embolism, superficial vein thrombosis). Other manifestations that have been linked to thrombophilia include recurrent miscarriage and complications of pregnancy (eg, severe preeclampsia, abruptio placentae, intrauterine growth restriction, stillbirth). Thrombophilia does not predict arterial thrombosis. Demographic or environmental exposures that compound the risk of venous thromboembolism among persons with a thrombophilia include increasing age, male gender, obesity, surgery, trauma, hospitalization for medical illness, malignant neoplasm, prolonged immobility during travel (eg, prolonged airplane travel), oral contraceptive use, estrogen therapy (both oral and transdermal), tamoxifen and raloxifene therapy, and infertility drugs. Central venous catheters and transvenous pacemaker wires increase the risk for upper extremity deep vein thrombosis; this risk is unrelated to thrombophilia.

Inherited thrombophilias include:
-Deficiency due to reduced plasma protein level or dysfunctional protein of:
-Antithrombin
-Protein C
-Protein S
-Dysfibrinogenemias (rare)
-Activated protein C resistance due to the factor V Leiden variant (F5 c.1601G>A; p.Arg534Gln, historically known as R506Q)

-Prothrombin F2 c.*97G>A variant (historically known as G20210A)

Acquired thrombophilias include a lupus-like anticoagulant (antiphospholipid antibodies) and disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF). DIC/ICF may cause thrombotic as well as hemorrhagic events. Positive tests for DIC/ICF can also occur as consequences of thrombosis.

Acquired deficiencies of fibrinogen, protein C, protein S, and antithrombin may be found in conjunction with liver disease (they are produced by the liver) or DIC/ICF and are of uncertain significance with respect to thrombosis risk.

Acquired deficiencies of protein C and protein S are also found in patients with liver disease who are being treated with oral anticoagulants (eg, warfarin, Coumadin), since both proteins are dependent upon the action of vitamin K for normal function.

Acquired protein S deficiency also occurs in thrombotic thrombocytopenic purpura, pregnancy or estrogen therapy, nephrotic syndrome, and sickle cell anemia. In acute illness, the levels of acute-phase reactants rise (including C4b binding protein, which binds and inactivates protein S in the plasma), and the portion of bound protein S also rises, leaving a lower proportion of free protein S. The significance of acquired protein S deficiency with respect to thrombosis risk is unknown.

Reference Values

An interpretive report will be provided.

Interpretation

An interpretive report will be provided when testing is completed, noting the presence or absence of thrombophilia.

Cautions

To obtain the most useful information, this testing is best performed in medically stable patients who are not receiving an oral vitamin K inhibitor (eg, warfarin, Coumadin), heparin, low-molecular-weight heparin, hirudin (Refludan), argatroban, fibrinolytic agents (eg, streptokinase, tissue plasminogen activator), or platelet GPIIbIIIa (alpha IIb beta3) inhibitors (abciximab [ReoPro], tirofiban [Aggrastat]). However, useful information can be obtained in patients receiving anticoagulation therapy.

Clinical Reference

1. Pengo V, Tripodi A, Reber G, et al. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2009(10):1737-1740. doi:10.1111/j.1538-7836.2009.03555.x
2. Keeling D, Mackie I, Moore GW, Greer IA, Greaves M, British Committee for Standards in Haematology: Guidelines on the investigation and management of antiphospholipid syndrome. Br J Haemotol. 2012;157(1):47-58. doi:10.1111/j.1365-2141.2012.09037.x
3. Clinical and Laboratory Standards Institute (CLSI). Laboratory Testing for the Lupus Anticoagulant; Approved Guideline. CLSI document H60-A. CLSI; 04/2014
4. Favaloro EJ and Lippi G. eds. Hemostasis and Thrombosis, Methods and Protocols. Humana Press; 2017

Performance

Method Description

Prothrombin Time:
The prothrombin time (PT) assay is performed on the Instrumentation Laboratory ACL TOP. Patient plasma is incubated and combined with a PT reagent containing recombinant human tissue factor, synthetic phospholipids, calcium chloride, polybrene, and buffer. The tissue thromboplastin-factor VII/VIIa complex activates factor X. Activated factor X (factor Xa) forms a complex with factor Va, calcium, and phospholipid to activate factor II (prothrombin) to thrombin. Thrombin then acts on fibrinogen (factor I) to form fibrin which clots, the time to clot formation is measured optically using a wavelength of 671 nm providing the assay endpoint (the "prothrombin time").(Package insert: HemosIL RecombiPlasTin 2G. Instrumentation Laboratory Company; R4, 03/2019)

Activated Partial Thromboplastin Time:
The activated partial thromboplastin time (aPTT) assay is performed on the Instrumentation Laboratory ACL TOP. Patient plasma is combined and incubated with an aPTT reagent containing phospholipid, a negatively charged contact factor activator, and buffer. After a specified incubation time, calcium is added to trigger the coagulation process in the mixture. Subsequently, the time to clot formation is measured optically using a wavelength of 671 nm. Mixing studies (see APMSC / Activated Partial Thromboplastin Time [APTT] Mix 1:1, Plasma) using normal pooled plasma are performed on samples with a prolonged aPTT to assist in discriminating between factor deficiency states and coagulation inhibitors, unless further testing is not indicated.(Package insert: HemosIL SynthASil. Instrumentation Laboratory Company; R11, 06/2017)

Dilute Russell's Viper Venom Time:
The dilute Russell's viper venom time (dRVVT) screening assay is performed on the Instrumentation Laboratory ACL TOP. Patient plasma is incubated for a specified time and then combined with a dRVVT screening reagent containing Russell's viper venom, phospholipids, heparin neutralizing agents, calcium, buffers, and stabilizers to trigger the coagulation process. Subsequently, the time to clot formation is measured optically using a wavelength of 671 nm. The patient dRVVT screening clotting time is normalized by dividing the patient result by the mean dRVVT screening clotting time of normal pooled plasma to yield a ratio (dRVVT screen ratio).(Package insert: LA CHECK DRVVT. Precision Biologic; R14, 03/2012)

Thrombin Time:
The thrombin time assay is performed on the Instrumentation Laboratory ACL TOP. Patient plasma is combined with a bovine thrombin reagent containing bovine albumin, calcium chloride, and buffer, immediately triggering the coagulation process in the mixture. Time to clot formation is measured optically using a wavelength of 671 nm.(Package insert: HemosIL Thrombin Time. Instrumentation Laboratory Company; R1, 12/2018)

Fibrinogen:
The Clauss fibrinogen assay is performed using the HemosIL Fibrinogen-C kit on the Instrumentation Laboratory ACL TOP. Patient plasma, containing fibrinogen, is mixed with reagent containing excess thrombin. The excess thrombin converts the fibrinogen in the patient plasma to fibrin. The amount of time it takes to form a clot is inversely proportional to the amount of fibrinogen present in the patient plasma.(Package insert: HemosIL Fibrinogen-C. Instrumentation Laboratory Company; R7, 06/2017)

D-Dimer:
The D-dimer assay is performed using the HemosIL D-Dimer HS 500 kit on the Instrumentation Laboratory ACL TOP instrument. D-dimer is assayed in plasma by adding polystyrene latex particles coated with monoclonal antibodies specific for D-dimer domain. The latex particles agglutinate in the presence of soluble fibrin degradation products containing the D-dimer domain. The degree of agglutination is directly proportional to the concentration of D-dimer in the sample and is determined by measuring the decrease of transmitted light caused by the aggregates (turbidimetric immunoassay).(Package insert: HemosIL D-Dimer HS 500. Instrumentation Laboratory Company; R6, 04/2018)

Antithrombin Activity:
This assay is performed using the HemosIL Liquid Antithrombin Kit on the Instrumentation Laboratory ACL TOP instrument. Patient plasma, containing antithrombin, is mixed and incubated with reagent containing factor Xa and excess heparin. Factor Xa activity in the reagent is rapidly inhibited by antithrombin. Residual factor Xa activity is then measured using an amidolytic activity assay. This occurs when residual factor Xa lyses chromogenic substrate S-2765 (N-alpha-Z-D-Arg-Gly-Arg-pNA 2HCl) and subsequently releases para-nitroaniline (pNA) (detected at 405 nm) in a level that is inversely proportional to the amount of antithrombin in the sample. This method is based on inhibition of factor Xa and, therefore, only higher amounts of heparin cofactor II, alpha-2-macroglobulin, or alpha-1-antitrypsin will influence the assay.(Package insert: HemosIL Liquid Antithrombin. Instrumentation Laboratory Company; R8, 06/2017)

Protein C Activity:
This assay is performed using the HemosIL Protein C kit on the Instrumentation Laboratory ACL TOP. Protein C in plasma is activated by a specific enzyme (Protein C activator) from copperhead snake venom (*Agkistrodon contortrix contortrix*). The amount of activated protein C is determined by the rate of hydrolysis of the chromogenic substrate, S-2366 (pyroGlu Pro-Arg-pNA-HCL). The pNA release is measured kinetically at 405 nm and is directly proportional to the protein C level in the plasma.(Package insert: HemosIL Protein C. Instrumentation Laboratory; R8, 06/2017)

Protein S Free:
This assay is performed using the HemosIL Free Protein S kit on the Instrumentation Laboratory ACL TOP. The assay uses latex immunoassay methodology to determine the presence of free protein S. It consists of 2 latex reagents, one being latex particles coated with purified human C4b-binding protein (C4BP), and the other is latex particles coated with a monoclonal antibody directed against human protein S. Patient plasma is combined with the purified C4BP that reacts with a high affinity for free protein S in the patient plasma. The free protein S adsorbed on the C4BP latex triggers the agglutination reaction with the second latex reagent. The aggregates form diameters greater than the wavelength of the light (405nm) passing through, causing absorption of the light. This change in absorption is measured over time and reported as delta optical density. The increase in absorption is proportional to the concentration of free protein S antigen present in the patient plasma. (Package insert: HemosIL Free Protein S. Instrumentation Laboratory; R15, 04/2019)

Activated Protein C Resistance:
This assay is performed using the HemosIL Factor V Leiden (APC Resistance V) Kit on the Instrumentation Laboratory ACL TOP instrument. The method uses a modified aPTT test to detect activated protein C (APC) resistance. The plasma specimen is prediluted in factor V-deficient plasma. Then the aPTT test is performed by incubating patient plasma with a standardized amount of platelet-like phospholipids and activator of the contact factors of the intrinsic coagulation pathway, followed by recalcification of plasma and measurement of clotting time. The ratio of the aPTT test with and

without added APC is reported as the APC resistance (or sensitivity) ratio.(Package insert: HemosIL Factor V Leiden [APC Resistance V]. Instrumentation Laboratory Company; R12, 11/2017)

Prothrombin G20210A Variant:
An allelic discrimination assay is set up using TaqMan chemistry. End-products are analyzed using the Roche LightCycler 480 System for genotype detection.(User guide: TaqMan SNP Genotyping Assays. Applied Biosystems; 09/29/2017)

PDF Report
No

Day(s) Performed
Weekly

Report Available
4 to 7 days

Specimen Retention Time
Plasma: 7 days; Whole blood: 2 weeks

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
See Individual Test IDs

CPT Code Information
81240-F2 PTNT
85300-ATTF
85303-CFX
85306-PSF
85307-APCRV
85379-DIMER
85384-CLFIB
85390-26-AATHI
85610-PTSC
85613-DRV1

85670-TTSC
85730-APTSC
81241-F5 (coagulation factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant (if appropriate)
85210-Factor II (if appropriate)
85220-Factor V (if appropriate)
85230-Factor VII (if appropriate)
85240-Factor VIII (if appropriate)
85250-Factor IX (if appropriate)
85260-Factor X (if appropriate)
85270-Factor XI (if appropriate)
85280-Factor XII (if appropriate)
85301-Antithrombin antigen (if appropriate)
85302-Protein C antigen (if appropriate)
85305-Protein S antigen, total (if appropriate)
85306-Protein S activity (if appropriate)
85366-Soluble fibrin monomer (if appropriate)
85385-PT-Fibrinogen (if appropriate)
85597-Platelet neutralization for lupus inhibitor (if appropriate)
85598-Hex LA (if appropriate)
85611-PT mix 1:1 (if appropriate)
85613-DRVVT mix (if appropriate)
85613-DRVVT confirmation (if appropriate)
85635-Reptilase (if appropriate)
85732 - APTT Mix 1:1 (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
AATHR	Thrombophilia Prof	98125-8

Result ID	Test Result Name	Result LOINC® Value
ATTF	Antithrombin Activity, P	27811-9
CFX	Protein C Activity, P	27818-4
PSF	Protein S Ag, Free, P	27821-8
APCR	APCRV Ratio	13590-5
INT55	Interpretation	48591-2
21803	Prothrombin G20210A Mutation, B	24475-6
21804	PTNT Interpretation	69049-5
21806	PTNT Reviewed By	18771-6
APTSC	Activated Partial Thrombopl Time, P	14979-9
CLFIB	Fibrinogen, Clauss, P	48664-7
TTSC	Thrombin Time (Bovine), P	46717-5
DIMER	D-Dimer, P	In Process
INRSC	INR	6301-6

PTSEC	Prothrombin Time (PT), P	5902-2
603184	Thrombophilia Interpretation	69049-5
603325	Reviewed by	18771-6
RVR1	DRVVT Screen Ratio	15359-3