

Title: Guidelines on testing for inherited and acquired Thrombophilia in Cork University Hospital	Reference:	INS-CUH-PAT-1861	Revision: 03
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	Approved By:	Dr Cleona Duggan	
	Author:	Dr Cleona Duggan	

Guidelines on testing for inherited and acquired Thrombophilia in Cork University Hospital

1.0 Introduction

Thrombophilia testing i.e. the testing of a patient's blood for the presence of factors that may contribute to the development of Venous Thromboembolism (VTE) has been shown to be of limited value in diagnosing, managing or determining risk in either persons who present with VTE or members of thrombosis-prone families¹. Clinical factors such as the nature of the VTE event, the presence or absence of provoking risk factors, the strength of those risk factors (e.g. major provoking risk factors such as surgery or limb immobilisation versus minor provoking risk factors such as travel) as well as family history are more important in guiding decision making than laboratory testing. Interpretation of the results of thrombophilia tests requires integration of clinical, laboratory and family data. The presence of a laboratory thrombophilia does not influence the acute management of an episode of VTE. The duration or intensity of anticoagulation, indications for thromboprophylaxis and suitability of hormonal contraception/HRT are determined by clinical factors. There is no evidence that the presence of a laboratory Thrombophilia influences the likelihood of recurrence of VTE and the risk of recurrence is better predicted by clinical factors. Accordingly in order to ensure thrombophilia testing is undertaken appropriately, safely and effectively the Coagulation Laboratory has developed these guidelines.

2.0 Aim

To assist healthcare professionals in:

- Determining appropriate clinical indications for thrombophilia testing
- The appropriate preparation of samples, labels and requests sent for Thrombophilia testing

3.0 Definitions

Thrombophilia Testing includes any or all of the following laboratory assays:

- Antithrombin
- Protein C
- Protein S
- Factor VIII
- Fibrinogen
- Activated protein C resistance
- Genetic test for the Factor V Leiden gene mutation
- Genetic test for the Prothrombin gene mutation
- Lupus anticoagulant
- Antiphospholipid antibodies
- Beta 2 glycoprotein 1 antibodies

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4.0 Standards

4.1 Appropriate Testing

(Guidelines specific to testing in pregnancy are given in section 4.1.6 below)

4.1.1 Testing for Antithrombin or Protein C or Protein S **is recommended** in the following clinical circumstances:

4.1.1.1 Asymptomatic relatives with a family history of Antithrombin, Protein C or Protein S deficiency **AND** a family history of Thrombosis

4.1.1.2 Neonates and children with purpura fulminans (severe Protein C or Protein S deficiency)

4.1.2 Thrombophilia testing is **not recommended** in the following clinical circumstances:

4.1.2.1 Unselected patients after a first venous thrombosis event

4.1.2.2 Asymptomatic relatives of patients with the Factor V Leiden or Prothrombin gene mutations

4.1.2.3 Asymptomatic relatives of patients with venous thrombosis prior to hormonal treatment

4.1.2.4 Upper limb thrombosis

4.1.2.5 Catheter related thrombosis

4.1.2.6 Retinal vein occlusion

4.1.2.7 Patients prior to assisted conception or patients with ovarian hyperstimulation

4.1.2.8 Hospitalised patients as part of risk assessment for thrombosis

4.1.2.9 Arterial thrombosis

4.1.3 Thrombophilia testing **may be considered** in the following clinical circumstances:

4.1.3.1 First venous thrombosis in a patient with a family history of unprovoked or recurrent venous thrombosis in one or more first degree relatives

4.1.3.2 Asymptomatic relatives of venous thrombosis patients with a known heritable thrombophilia prior to hormonal treatment.

4.1.3.3 Cerebral venous sinus thrombosis

4.1.3.4 Splanchnic vein thrombosis

4.1.3.5 Skin necrosis secondary to Vitamin K antagonists

4.1.4 Antiphospholipid antibody testing (Lupus anticoagulant, antiphospholipid antibodies, anti beta 2 glycoprotein 1 antibodies) **is recommended** in the following clinical circumstances:

4.1.4.1 History of recurrent first trimester miscarriage (\geq three consecutive miscarriages)

4.1.4.2 \geq 1 unexplained deaths of a morphologically normal foetus at or beyond 10/40

4.1.4.3 \geq one premature birth of a morphologically normal neonate before 34/40 because of eclampsia/severe preeclampsia or placental insufficiency

4.1.4.4 Young adults ($<$ 50 years) with ischaemic stroke

4.1.4.5 Patients with an unprovoked PE or proximal DVT if

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anticoagulation is discontinued (note that these patients generally warrant long term anticoagulation and if it has already been decided to continue long term anticoagulation, then testing is not indicated).

4.1.5 Antiphospholipid testing may be considered in the following clinical circumstances:

- 4.1.5.1 History of immune disorders and venous or arterial thrombosis
- 4.1.5.2 Unusual or extensive venous or arterial thrombosis
- 4.1.5.3 As part of diagnostic work-up for Systemic Lupus Erythematosus specialist care services e.g. Rheumatology, Dermatology

4.1.6 Thrombophilia testing in pregnancy

4.1.6.1 Thrombophilia Testing is **NOT indicated** in the following:

Women for whom thromboprophylaxis is already recommended on the clinical risk assessment alone e.g.

- previous unprovoked or oestrogen related VTE
- history of recurrent VTE

Women for whom thromboprophylaxis is not recommended e.g.

- women with a history of VTE due to a major provoking risk factor which is no longer present
- women who are asymptomatic relatives of patients with the Factor V Leiden or prothrombin gene polymorphisms
- women with a family history of thrombophilia which is not associated with thrombosis
- at the time of acute thrombosis or while on anticoagulant therapy

4.1.6.2 Targeted thrombophilia testing **is indicated** in the following:

- Women with a history of an unprovoked VTE (not on longterm anticoagulation) should be tested for antiphospholipid antibodies
- Women with prior VTE and a family history of VTE and known Antithrombin deficiency or where the specific thrombophilia has not been detected should be tested for Antithrombin deficiency
- Women with second trimester miscarriage should be tested for inherited thrombophilias including factor V Leiden, factor II (prothrombin) gene mutation and protein

4.1.6.3 Thrombophilia testing **may be indicated** in the following:

- Women with no personal history or risk factors for VTE but who have a family history of an unprovoked or oestrogen provoked VTE in a first degree relative when aged <50 years. This will be more informative if the relative has a known thrombophilia.
- Women with a history of provoked VTE, if the provoking risk factor was mild (e.g. travel) or the effect of the risk factor is unknown.

4.2 Clinical Advice on Thrombophilia Testing

4.2.1 Occasionally, it may be appropriate to test patients who fall outside the guidelines given above. The clinical details may be discussed with one of the Consultant Haematologist in the Coagulation Centre, Cork University Hospital (tel. 021/4922545)

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4.3 Laboratory Sample Preparation

4.3.1 A completed request form must be sent with all samples sent to the laboratory for Thrombophilia Testing.

4.3.2 For ICM requests, the clinical details including reason for thrombophilia testing **must** be completed, or the sample will be rejected.

4.3.3 The request form must include detailed patient and clinical information including:

- **Patient demographics**

- Patient's Name
- Patient's Date Of Birth
- MRN
- Name of Referring Clinician
- Name of Referring Hospital

- **Request details**

- Clinical indication for testing
- Number of months post partum or pregnancy loss if appropriate
- Anticoagulant therapy
- Specific tests requested (Partial thrombophilia screens can be requested)

4.3.4 The laboratory will **not** analyse samples without full clinical information.

4.3.5 In the event a sample is received which does not have the required data (above) or does not have adequate clinical details the laboratory will:

4.3.5.1 Issue a letter to the requesting doctor requesting additional clinical details and/or advise that the case is discussed with a Consultant Haematologist in Cork University Hospital

4.3.5.2 Store the sample for up to eight weeks.

4.3.6 Samples will be discarded after eight weeks if the referring clinician has not provided the required details or if it is determined that testing is not indicated.

4.3.7 Samples should **not** be sent for laboratory thrombophilia testing if patients are being treated with heparin or low molecular weight heparin or with oral anticoagulants, except in limited circumstances. Please discuss with the Haematology laboratory in the event that such a patient requires testing.

4.3.8 Protein S should not be measured during pregnancy and for up to 6 months post partum. Please discuss with the Haematology Consultant in specific cases where this is being considered.

References

- 1 Clinical Guidelines for testing for heritable Thrombophilia: Baglin et al; British Journal of Haematology (2010), 149; 209 – 220. www.BCSHguidelines.com
2. Thrombophilia Testing Guidelines, N O'Connell et al National Centre for Hereditary Coagulation Disorders, (NCHCD), Coagulation Laboratory, LabMed Directorate, St. James's Hospital, Dublin.