St. James's Hospital
National Coagulation Centre (NCC) and the National Coagulation Laboratory, LabMed

Thrombophilia Testing Guidelines
SJH:LabMed005

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This guideline replaces all existing guidelines from January 2019 onwards and is due for review in January 2023. It will be reviewed during this time as necessary to reflect any changes in best practice, law, and organisational, professional or academic change.

Distributed to:
Medical, Nursing and Laboratory Staff of the National Coagulation Centre (NCC), Medical Staff of St James's Hospital, HOPe Directorate Management Team, Labmed Directorate Management Team.
Posted SJH Internet and Intranet:
http://www.stjames.ie/services/laboratorymedicinelabmed/http://www.stjames.ie/services/laboratorymedicinelabmed/
http://www.stjames.ie/media/SJHLabMed005.pdf

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 families [1]. 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
  - Anti cardiolipin antibodies
  - Beta 2 glycoprotein 1 antibodies

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, anti cardiolipin antibodies, anti-beta 2 glycoprotein 1 antibodies) **is recommended** in the following clinical circumstances:

4.1.4.1 History of recurrent first trimester miscarriage (>/= 3 consecutive miscarriages)

4.1.4.2 >/=1 unexplained deaths of a morphologically normal foetus at or beyond 10/40

4.1.4.3 >/=1 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 anticoagulation is discontinued (note that these patients generally warrant longterm anticoagulation

and if it has already been decided to continue longterm anticoagulation, then testing is not indicated).

4.1.5 Antiphospholipid antibody 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 the diagnostic work-up for Systemic Lupus Erythematosus by specialist secondary care services e.g. Rheumatology, Dermatology

4.1.6 Thrombophilia testing in pregnancy[2]

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

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

- Women with a history of an unprovoked VTE (not on long term 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 screened for inherited thrombophilias including factor V Leiden, factor II (prothrombin) gene mutation and protein S[3]

4.1.6.3 Thrombophilia testing **may be considered** 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 under 50 years. This will be more informative if the relative has a known thrombophilia.
- Women with a previous event due to a minor provoking factor, e.g. travel (if thromboprophylaxis is not already indicated by clinical risk assessment)

4.2 Clinical Advice on Thrombophilia Testing

4.2.1 For clinical cases under consideration (See 4.1.3, 4.1.5 and 4.1.6.3 above), clinical advice may be obtained from the Consultant Haematologist at the National Coagulation Centre by phoning 01-4162141.

4.2.2 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 Haematologists at the National Coagulation Centre.

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. Six Trisodium Citrate (Coagulation) samples and one EDTA (FBC) sample should be sent to the National Coagulation laboratory for the thrombophilia screen. One Serum sample should be sent separately to the Immunology laboratory for anti-cardiolipin and Beta 2-Glycoprotein 1 antibody testing.

4.3.2 The local laboratory request Thrombophilia Request Form or the NCL Thrombophilia Request Form can be used for samples sent from referral agencies.

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

- **Patient demographics**
- Patient's Name
- Patient's Date Of Birth
- Medical Record Number
- Name of Referring Clinician
- Name of Referring Hospital
- Order number / external laboratory number (external agencies only)

- **Request details**
- Clinical indication for testing, including number and timing of pregnancy loss
- Number of months post-partum or pregnancy loss if appropriate
- Anticoagulant therapy
- Specific tests 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 demographic or clinical information as detailed above 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 the NCC.

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 Limited thrombophilia testing, in the form of Lupus Anticoagulant testing, may be done after review by the Consultant Haematologist in the NCC of the clinical details provided.

4.3.8 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 National Coagulation Laboratory (01-4162956) in the event that such a patient requires testing.

References

[1] Clinical Guidelines for testing for heritable Thrombophilia: Baglin et al; British Journal of Haematology (2010), 149; 209 – 220. www.BCSHguidelines.com

[2] Reducing the risk of Venous Thromboembolism during Pregnancy and the Puerperium. The Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guideline No. 37a, April 2015. www.rcog.org.uk

[3] The investigation and treatment of couples with recurrent first trimester and second trimester miscarriage The Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guideline No. 17a, April 2011. www.rcog.org.uk

[4] Guidelines on the investigation and management of antiphospholipid syndrome: Keeling et al; British Journal of Haematology (2012), 157; 47-58.

Document Log			
Document Title: Thrombophilia Testing Guidelines			
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Document Status i.e. New or Revision etc.	**Version Number**	**Revision Date**	**Description of changes**
Revision	2	Dec. 2012	Section 4.1.4.4 and 4.1.4.5 removed from section 4.1.4 and changed to section 4.1.5.1 and 4.1.5.2. New additions to section 4.1.4.4 and 4.1.4.5 in version 2 Section 4.1.6 added describing guidelines for thrombophilia testing in pregnancy Layout of 4.3.3 amended to split into 2 groups (demographics and request details). New requirement added as: Number of months post-partum or pregnancy loss if appropriate.
Revision	3	March 2016	Section 4.1.4 detailing antiphospholipid testing to include anticardiolipin antibodies. 4.1.5: Antiphospholipid testing considered in work up for SLE by rheumatology and dermatology 4.1.6 amended to take into account guidelines issued by the Royal College of Obstetricians and Gynaecologists 4.3 updated to inform users of occasions when thrombophilia testing is limited to Lupus Anticoagulant testing following review by consultant
Revision	4	July 2016	Section 4.1.6.2 detailing thrombophilia testing in women with second trimester miscarriage as per RCOG greentop guideline No. 17 Section 4.3.1 updated to include details on sample requirements for testing and the requirement to send ACA and anti-Beta 2 Glycoprotein 1 tests separately to Immunology Section 4.3.3 updated to include the requirement for clinical information regarding the number and timing of pregnancy when thrombophilia testing is requested Updated the name of the NCHCD to NCC, updated the name of the coagulation laboratory to NCL Updated the web address for both internet and intranet hosting of thrombophilia testing guidelines
Revision	5	Jan 2019	New SJH Document Number assigned to reflect updated SJH PPG Register. Ownership of document changed from Dr N O'Connell to Dr K Ryan, as per change in Laboratory Consultant for NCL. Document reviewed by Dr K Ryan, Jan 2019, no changes to practice required.
Revision	6	March 2021	Section 4.3.2 stating that a local laboratory Thrombophilia Request Form or the NCL Thrombophilia Request Form can be used for samples from external agencies. Reference 4 added Updated link to guidelines for the intranet and the SJH website