Problems and pitfalls with hereditary thrombophilia screening

(1) Arterial versus venous thromboembolism (VTE)
   Testing for heritable thrombophilia is not indicated in patients with arterial
   thrombosis.\(^*\) In premature arterial disease (e.g. < 50 years), especially in the
   absence of the usual cardiovascular risk factors, as well as testing for
   antiphospholipid syndrome (see below) other screening tests to be considered
   include (raised) lipoprotein A and homocysteine (request from Biochemistry).

\(^*\) (Heritable venous thrombophilia testing is only indicated in rare cases of
   paradoxical arterial embolism e.g. due to patent foramen ovale as demonstrated on
   bubble contrast echocardiogram).

(2) Lupus anticoagulant, antiphospholipid (APL) antibodies & APL syndrome
   These represent an acquired thrombotic tendency and as such are not covered
   in this guideline - requests for the individual screening tests (lupus
   anticoagulant, anti-cardiolipin and anti-\(\beta_2\) glycoprotein I antibodies) should be
   requested separately; they are not included as a part of an hereditary
   thrombophilia screen. These requests are not vetted by this laboratory.
   Indications for these tests include: all cases of unprovoked VTE and
   (unexplained) arterial thrombosis in young patients (< 50 years of age);
   thrombosis at unusual sites; relevant obstetric problems (recurrent (\(\geq\)3)
   miscarriage; pre-eclampsia, placental abruption, Intrauterine Growth
   Retardation (IUGR), unexplained stillbirth).
   Testing should be performed prior to commencement of anticoagulation
   Consider haematology referral if screening tests are positive on two
   occasions
   >12 weeks apart.

(3) Timing of testing
   Acute thrombosis (within 1 month) and anticoagulation (heparin and warfarin)
   affect many of the thrombophilia tests, making interpretation unreliable.
   Therefore avoid routine screening during an acute episode and until off
   anticoagulation for at least 1 month\(^*\)
   Pregnancy, combined oral contraceptive pill and hormone replacement therapy
   (HRT) can also affect results – testing should be avoided in these situations
   unless there is clinical urgency (discuss with haematologist / obstetrician).

\(^*\) Rarely in paediatric purpura fulminans or catastrophic widespread VTE in patients
   aged <40 years, urgent thrombophilia testing may be indicated in liaison with a
   haematology consultant.

(4) Utility of testing
   Thrombophilia tests rarely lead to a change in patient management.
   There is no evidence that hereditary thrombophilia should influence intensity of
   anticoagulation; its presence only rarely influences duration of anticoagulation
   and does not predict the likelihood of recurrence. There is also a lack of
   evidence that testing asymptomatic affected relatives leads to better outcomes,
   although in certain high risk situations listed below e.g. pregnancy, it may be
   considered. Such limitations of testing should be discussed fully with the
   patient.

(5) Repeat testing
   There is no benefit in repeating a normal thrombophilia screens. In the event of
   an abnormal result, requests for confirmatory testing should be limited to the
   relevant deficiency only.
Testing for Hereditary Thrombophilia Screening (code = TPS)

This screen includes: Protein C, Protein S & Antithrombin levels, and a test for the prothrombin gene mutation (20210A). An ‘activated protein C resistance’ (APCR) test is also done as a screen for Factor V Leiden – if this is abnormal, then DNA analysis for Factor V Leiden is performed.

Indications for Hereditary Thrombophilia Screening
('Unprovoked' means none of the following: immobility, fracture, cancer, oestrogen therapy, pregnancy, surgery within the preceding 3 months).

Personal history of VTE / related problems:
(1) Patients with unprovoked VTE aged <40 years **
(2) Patients with unprovoked VTE and either:
   - 2 or more family members affected by unprovoked VTE, or
   - Other family member with known high risk thrombophilia e.g. antithrombin, protein C or S deficiency (not Factor V Leiden or prothrombin gene mutation)
(3) Patients with unusual site of VTE (cerebral vein, intra-abdominal), aged <60 years **
(4) History of warfarin induced skin necrosis (test after warfarin withdrawn)
(5) Women with a history of second trimester miscarriage, placental abruption, Intrauterine Growth Retardation (IUGR), unexplained stillbirth / intrauterine death** (not as part of pre IVF work up / implantation failure investigation unless other qualifying factor as above)
(6) Neonates and children with purpura fulminans (urgent – discuss with haematologist)

Family Screening
(7) Women planning pregnancy / use of combined oral contraceptive pill with either (i) a history of VTE at a young age (<45 years) in at least one first degree relative, or (ii) a family history of known thrombophilic defect
(8) In other people, testing should only be considered if there is a family history of known high risk thrombophilia; e.g. antithrombin, protein C or S deficiency (not Factor V Leiden or Prothrombin Gene mutation) WITH a history of unprovoked VTE in affected members, AND if clinical management would be influenced, e.g.
   - Woman considering hormone replacement therapy (HRT)
   - Patient planned for major operation with a family history of thromboprophylaxis failure in affected family members in whom extended thromboprophylaxis would be considered

** At discretion of clinician in individual cases. Testing for these indications has uncertain predictive value and there is currently no clear evidence that results should influence therapy.

Sample Requirements

Hereditary Thrombophilia Screen:
x3 Clotting bottles (adult size) for functional factor assays
x1 FBC bottles (adult size) for molecular tests (PT gene mutation +/- FV Leiden)

Antiphospholipid Screen:
x2 clotting bottle (adult size) for lupus anticoagulant
x1 biochemistry (SST) (adult size) for anti-cardiolipin and β2-glycoprotein I antibodies