The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Preauthorization is not required but is recommended if, despite this Protocol position, you feel this service is medically necessary; supporting documentation must be submitted to Utilization Management. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

Description

Inherited thrombophilias are a group of disorders that predispose to thrombosis. Genetic testing is available for some of these disorders and could potentially assist in the diagnosis and/or management of patients with thrombosis.

Background

Venous thromboembolism. The overall U.S. incidence of venous thromboembolism (VTE) is approximately one per 1,000 person-years, and the lifetime clinical prevalence is about 5%, accounting for 100,000 deaths annually. (1) Risk is strongly age-related, with the greatest risk in older populations. VTE also recurs frequently; the estimated cumulative incidence of first VTE recurrence is 30% at 10 years. (1) These figures do not separate patients who had known predisposing conditions from those who do not.

Risk factors for thrombosis include a variety of clinical and demographic variables, and at least one risk factor can be identified in approximately 80% of patients with a thrombosis. The following list includes the most important risk factors:

- Malignancy
- Immobility
- Surgery
- Obesity
- Pregnancy
- Hormonal therapy with estrogen/progesterones
- Systemic lupus erythematosus (SLE), and/or other rheumatologic disorders
- Myeloproliferative disorders
- Liver dysfunction
- Nephrotic syndrome
- Hereditary factors.

Treatment of thrombosis involves anticoagulation for a minimum of three to six months. Following this initial treatment period, patients deemed to be at a continued high risk for recurrent thrombosis may be continued on anticoagulation for longer periods, sometimes indefinitely. Anticoagulation is effective in reducing the subsequent risk of thrombosis, but has its own risks of bleeding.
Pregnancy is often considered a special condition because of its frequency and the unique considerations of preventing and treating VTE in this setting. Pregnancy is associated with a five to 10-fold increase in the risk for VTE, and the absolute risk of VTE in pregnancy has been estimated to be one to two per 1,000 deliveries. In women with a previous history of pregnancy-related VTE, the risk of recurrent VTE with subsequent pregnancies is increased greatly at approximately 100-fold.

**Inherited thrombophilia.** Inherited thrombophilias are a group of clinical conditions in which there is a genetic variant defect associated with a predisposition to thrombosis. However, not all patients with a genetic predisposition to thrombosis will develop VTE. The presence of inherited thrombophilia will presumably interact with other VTE risk factors to determine an individual's risk of VTE.

There are a number of conditions that fall under the classification of inherited thrombophilias, which arise from genetic variants in the genes involved in defects in the coagulation cascade. Inherited thrombophilias include the following abnormalities:

- Activated protein C resistance (factor V Leiden mutations)
- Prothrombin gene mutation
- Protein C deficiency
- Protein S deficiency
- Prothrombin deficiency
- Hyper-homocysteinemia (*MTHFR* mutations).

The most common type of inherited thrombophilia is a factor V Leiden mutation, which accounts for up to 50% of the inherited thrombophilia syndromes. In unselected patients with an idiopathic thrombosis, the rate of factor V Leiden positivity is in the range of 17-24%, compared to a rate of 5-6% in normal controls. The prothrombin gene mutation is found less commonly, in approximately 5-8% of unselected patients with thrombosis, compared to 2-2.5% of normal controls.

Genetic testing for gene variants associated with thrombophilias is available for factor V Leiden, the prothrombin gene mutation, and the *MTHFR* gene. The use of genetic testing for inherited thrombophilia can be considered in several clinical situations. The clinical situations that will be addressed in this Protocol include the following:

- Assessment of the risk for thrombosis in asymptomatic patients (screening for inherited thrombophilia)
- Evaluation of a patient with established thrombosis, in consideration of change in anticoagulant management based on results
- Evaluation of close relatives of patients with documented inherited thrombophilia, or with a clinical and family history that is consistent with an inherited thrombophilia
- Evaluation of patients in other situations that are considered high risk for thrombosis, e.g., pregnancy, planned major surgery, or oral contraceptive use.

**Regulatory Status**

More than a dozen commercial laboratories currently offer a wide variety of diagnostic procedures for *F2* (*prothrombin, coagulation factor II*), *F5* (*coagulation factor V*), and *MTHFR* (*5, 10-methylenetetrahydrofolate reductase*) genetic testing. These tests are available as laboratory developed procedures under the U.S. Food and Drug Administration (FDA) enforcement discretion policy for laboratory developed tests.

**Related Protocol:**

Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease
Corporate Medical Guideline

Genetic testing for inherited thrombophilia, including testing for factor V Leiden mutations, prothrombin gene mutations, and mutations in the \textit{MTHFR} gene, is considered \textbf{investigational}.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. \textit{For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.}

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. \textit{Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.}

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


