Medical Coverage Policy | Genetic Testing for Inherited Thrombophilia

EFFECTIVE DATE: 06|01|2024
POLICY LAST REVIEWED: 03|06|2024

OVERVIEW
Inherited thrombophilias are a group of disorders that predispose individuals to thrombosis. Genetic testing is available for some of these disorders and could assist in the diagnosis and/or management of patients with thrombosis. For example, testing is available for types of inherited thrombophilia, including variants in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene, the factor V gene (factor V Leiden [FVL] variant), and the prothrombin (factor II) gene.

MEDICAL CRITERIA
Not applicable

PRIOR AUTHORIZATION
Not applicable

POLICY STATEMENT
Medicare Advantage Plans
Genetic testing for inherited thrombophilia, including testing for the *factor V Leiden* variant, prothrombin (factor II) gene variants, and variants in the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene, is not covered as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Commercial Products
Genetic testing for inherited thrombophilia, including testing for the *factor V Leiden* variant, prothrombin (factor II) gene variants, and variants in the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene, is not medically necessary as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

COVERAGE
Benefits may vary between groups/contracts. Please refer to the Evidence of Coverage or Subscriber Agreement for applicable not medically necessary/not covered benefits/coverage.

BACKGROUND
The overall U.S. incidence of venous thromboembolism (VTE) is approximately 1 per 1,000 person-years, and the lifetime clinical prevalence is approximately 5%, accounting for 100,000 deaths annually. The risk is strongly age-related, with the greatest risk in older populations. Venous thromboembolism also recurs frequently; the estimated cumulative incidence of first VTE recurrence is 30% at 10 years. These figures do not separate patients with known predisposing conditions from those without.

Risk factors for thrombosis include clinical and demographic variables, and at least 1 risk factor can be identified in approximately 80% of patients with thrombosis. The following list includes the most important risk factors:

- Malignancy
- Immobility
- Surgery
- Obesity
- Pregnancy

- Hormonal therapy such as estrogen/progestin or selective estrogen modulator products
- Systemic lupus erythematosus and/or other rheumatologic disorders
- Myeloproliferative disorders
- Liver dysfunction
- Nephrotic syndrome
- Hereditary factors.

Pregnancy often is considered a special circumstance because of its frequency and unique considerations for preventing and treating VTE. Pregnancy is associated with a 5- to 10-fold increase in VTE risk, and absolute VTE risk in pregnancy is estimated to be 1 to 2 per 1000 deliveries.2, In women with a history of pregnancy-related VTE, risk of recurrent VTE with subsequent pregnancies is increased greatly at approximately 100-fold.

Treatment
Treatment of thrombosis involves anticoagulation for a minimum of 3 to 6 months. After this initial treatment period, patients deemed to be at a continued high risk for recurrent thrombosis may continue on anticoagulation therapy for longer periods, sometimes indefinitely. Anticoagulation is effective for reducing the subsequent risk of thrombosis but carries its own risk of bleeding.

Inherited Thrombophilia
Inherited thrombophilias are a group of clinical conditions characterized by genetic variant defects associated with a change in the amount or function of a protein in the coagulation system and a predisposition to thrombosis. Not all individuals 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 VTE risk.

A number of conditions fall under the classification of inherited thrombophilias. Inherited thrombophilias include the following conditions, which are defined by defects in the coagulation cascade:
- Activated protein C resistance (factor V Leiden [FVL] variant)
- Prothrombin (*factor II*) gene variant (G20210A)
- Protein C deficiency
- Protein S deficiency
- Prothrombin deficiency
- Hyper-homocysteinemia (5,10-methylenetetrahydrofolate reductase [*MTHFR*] variant).

The most common type of inherited thrombophilia is FVL, which accounts for up to 50% of inherited thrombophilia syndromes. Generally, routine testing for hypercoagulable disorders is not recommended in unselected patients.3, For those considered at risk (eg, strong family history, recurrent thromboses), the prevalence of identifying an inherited thrombophilia ranges from 5% to 40%; the prevalence is estimated at 12% to 40% for FVL and 6% to 18% for prothrombin G20210A variant in this population.

Genetic Testing
Genetic testing for gene variants associated with thrombophilias is available for FVL, the prothrombin G20210A variant, and *MTHFR*. Genetic testing for inherited thrombophilia can be considered in several clinical situations. Clinical situations addressed herein include the following:
- Assessment of thrombosis risk in asymptomatic patients (screening for inherited thrombophilia)
- Evaluation of a patient with established thrombosis, for consideration of a change in anticoagulant management based on results
- Evaluation of close relatives of patients with documented inherited thrombophilia or with a clinical and family history consistent with an inherited thrombophilia
- Evaluation of patients in other situations who are considered at high-risk for thrombosis (eg, pregnancy, planned major surgery, exogenous hormone use).

For individuals who are asymptomatic with or without a personal or family history of venous thromboembolism (VTE) or who are asymptomatic with increased VTE risk (eg, due to pregnancy) who receive genetic testing for variants in *MTHFR*, or genetic testing for coagulation *factor V* and coagulation factor II, the evidence includes a large randomized controlled trial (RCT), prospective cohort analyses, retrospective family studies, case-control studies, and meta-analyses. Relevant outcomes are morbid events and treatment-related morbidity. The clinical validity of genetic testing has been demonstrated by the presence of an FVL variant or a prothrombin gene variant, and an association with an increased risk for subsequent VTE across various populations studied. However, the magnitude of the association is relatively modest, with odds ratios most commonly between 1 and 2, except for family members of individuals with inherited thrombophilia, for whom odds ratios are somewhat higher. The clinical utility of testing for FVL or prothrombin variants has not been demonstrated. Although the presence of inherited thrombophilia increases the risk for subsequent VTE events, the increase is modest, and the absolute risk of thrombosis remains low. Available prophylactic treatments (eg, anticoagulation) have defined risks of major bleeding and other adverse events that may outweigh the reduction in VTE and therefore result in net harm. Currently, available evidence has not defined a role for thrombophilia testing for decisions on initiation of prophylactic anticoagulation or the length of anticoagulation treatment. For *MTHFR* testing, clinical validity and clinical utility of genetic testing are uncertain. Because clinical utility of testing for elevated serum homocysteine itself has not been established, the utility of genetic testing also has not been established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

CODING

Medicare Advantage Plans and Commercial Products

The following code(s) are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products:

81240 F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant

81241 F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant

81291 MTHFR (5, 10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)

RELATED POLICIES

Genetic Testing Services

PUBLISHED

Provider Update, April 2024

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