Medical Coverage Policy | Genetic Testing for Inherited Thrombophilia

EFFECTIVE DATE: 06|01|2024
POLICY LAST REVIEWED: 05|06|2026

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.

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

Commercial Products

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. §27-19-81 described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing ser-vices are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies.

Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate section of the Benefit Booklet, 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 to 2 per 1,000 person-years, and the lifetime clinical prevalence is approximately 8%. After VTE, 1-year survival varies greatly by underlying VTE cause, with lower survival rates seen for cancer-associated VTE (~47%) and higher survival among patients with provoked (84%) or unprovoked (93%) VTE. 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. Pregnant women experience 10 to 14 VTE events per 10,000 deliveries. Furthermore, approximately half of all pregnancy-associated VTEs occur postpartum, most within 6 weeks after delivery. Compared to similarly aged nonpregnant controls, the daily risk of VTE during pregnancy and postpartum is 3 to 10 times higher and 12 to 35 times higher, respectively. Additionally, up to a quarter of pregnancy-associated VTEs are recurrent events.

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. 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. In a 2024 systematic review and meta-analysis of 107 studies (N=107,130), VTE risk in adults with hereditary thrombophilia was highest in homozygous FVL (odds ratio [OR], 5.58; 95% CI, 4.61 to 6.74) and homozygous prothrombin G20210A (OR, 5.16; 95% CI, 3.12 to 8.52).

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

Biomarker Mandate
Genetic Testing Services

PUBLISHED

Provider Update, July 2026
Provider Update, August 2025
Provider Update, April 2024

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2. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: Molecular Pathology Procedures (A56199); https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=35000&ver=149&bc=0. Accessed April 14, 2026
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