Medical Policy
Genetic Testing for Inherited Thrombophilia

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Policy Number: 802
BCBSA Reference Number: 2.04.82
NCD/LCD:
Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)
Local Coverage Determination (LCD): MolDX: Genetic Testing for Hypercoagulability/Thrombophilia (Factor V Leiden, Factor II Prothrombin, and MTHFR) (L36089)

Related Policies
Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease and Venous Thromboembolic Disease, #016

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Genetic testing for inherited thrombophilia, including testing for factor V Leiden variant, prothrombin gene variants, and variants in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene, is considered INVESTIGATIONAL.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

F2 and F5 genetic tests are not considered to be clinically efficacious. Therefore, testing is not medically necessary.

Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

This is a non-coverage policy for genetic testing for thrombophilia testing for the Factor V Leiden.

Local Coverage Determination (LCD): MolDX: Genetic Testing for Hypercoagulability/Thrombophilia (Factor V Leiden, Factor II Prothrombin, and MTHFR) (L36089)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.
Prior Authorization Information

Inpatient
- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed inpatient.

Outpatient
- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed outpatient.

<table>
<thead>
<tr>
<th>Outpatient</th>
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<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
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<tr>
<td>Medicare HMO BlueSM</td>
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<td>Medicare PPO BlueSM</td>
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CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity; Medicare HMO Blue and Medicare PPO Blue:

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81240</td>
<td>F2 (prothrombin, coagulation factor II) (e.g., hereditary hypercoagulability) gene analysis, 20210G&gt;A variant</td>
</tr>
<tr>
<td>81241</td>
<td>F5 (coagulation Factor V) (e.g., hereditary hypercoagulability) gene analysis, Leiden variant</td>
</tr>
<tr>
<td>81291</td>
<td>MTHFR (5, 10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)</td>
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</table>

Description

VENOUS THROMBOEMBOLISM

The overall U.S. incidence of venous thromboembolism (VTE) is approximately 1 per 1000 person-years, and the lifetime clinical prevalence is approximately 5%, accounting for 100,000 deaths annually. Risk is strongly age-related, with the greatest risk in older populations. VTE also recurs frequently; 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 a variety of 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 of 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. 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 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. In unselected patients with an idiopathic thrombosis, the incidence of FVL is 17% to 24%, compared with a rate of 5% to 6% in normal controls. The prothrombin G20210A variant is found less commonly, in approximately 5% to 8% of unselected patients who have thrombosis compared with 2% to 2.5% of normal controls.

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 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).
Summary
For individuals who are asymptomatic with or without a personal or family history of venous thromboembolism (VTE) or with increased venous thromboembolism risk (eg, due to pregnancy) who receive genetic testing for variants in \textit{MTHFR}, coagulation factor V, and coagulation factor II, the evidence includes 1 large RCT, prospective cohort analyses, retrospective family studies, case-control studies, and meta-analyses. Relevant outcomes are morbid events and treatment-related morbidity. The analytic validity of genetic testing for inherited thrombophilia is high. The analytic sensitivity and specificity for FVL testing both exceed 99%, and the analytic sensitivity and specificity for the prothrombin G20210A variant both exceed 98%. The clinical validity of genetic testing has been demonstrated by the presence of an FVL or a prothrombin gene variant testing 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 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 a net harm.

Currently available evidence has not defined a role for thrombophilia testing for decisions on initiation of prophylactic anticoagulation or on the length of anticoagulation treatment. For \textit{MTHFR} testing, clinical validity and clinical utility of genetic testing is uncertain. Because clinical utility of testing for elevated serum homocysteine itself has not been established, utility of genetic testing also has not been established. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>7/2017</td>
<td>BCBSA National medical policy review. “Mutations” changed to “variants” throughout policy. Policy statement otherwise unchanged. 7/1/2017</td>
</tr>
<tr>
<td>8/2015</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>7/2015</td>
<td>Coverage for Medicare Advantage clarified. Local Coverage Determination (LCD): Molecular Pathology Procedures (L34506) added.</td>
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<tr>
<td>9/2014</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>2/04/2013</td>
<td>New policy describing ongoing non-coverage.</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References


