Medical Policy

PARAMOUNT

HMO AND PPO
ELITE (MEDICARE ADVANTAGE)
MARKETPLACE

Genetic Testing for Hereditary Thrombophilia

Policy Number: PG0355
Last Review: 04/25/2022

GUIDELINES:

- This policy does not certify benefits or authorization of benefits, which is designated by each individual policyholder terms, conditions, exclusions, and limitations contract. It does not constitute a contract or guarantee regarding coverage or reimbursement/payment. Self-Insured group specific policy will supersede this general policy when group supplementary plan document or individual plan decision directs otherwise.
- Paramount applies coding edits to all medical claims through coding logic software to evaluate the accuracy and adherence to accepted national standards.
- This medical policy is solely for guiding medical necessity and explaining correct procedure reporting used to assist in making coverage decisions and administering benefits.

SCOPE:

X Professional
X Facility

DESCRIPTION:

Thrombophilia (or hypercoagulability) is the propensity to develop thrombosis due to either an acquired or an inherited defect in the coagulation system. Acquired thrombophilia risk factors include but are not limited to advancing age (> 50), trauma, malignancy, chemotherapy, major surgery, immobilization, pregnancy, estrogen, inflammation, antiphopholipid antibody syndrome, myeloproliferative disorders, heparin-induced thrombocytopenia, liver disease, nephrotic and prolonged air travel. Inherited thrombophilia risk factors include deficiencies in antithrombin, Protein C, Protein S, mutation in Factor V Leiden and prothrombin, and dysfibrinogenemias. Mixed or unknown risk factors include hyperhomocysteinemia, elevated levels of Factor VIII, acquired Protein C resistance in the absence of Factor V Leiden, and elevated levels of Factors IX and XI.

Thrombophilia in pregnancy is often considered a special circumstance because of its frequency and unique considerations of preventing and treating venous thromboembolism (VTE). Pregnancy is associated with a 5-10-fold increase in VTE risk, and the absolute VTE risk in pregnancy has been estimated to be 1-2 per 1,000 deliveries. In women with a history of pregnancy-related VTE, risk of recurrent VTE with subsequent pregnancies is increased greatly at approximately 100-fold.

Specific variants in the genes F2, F5, and MTHFR have all been linked to increased risk for thrombophilia in the literature. Genetic testing is available for a number of types of inherited thrombophilia, including mutations in the Factor V Leiden (FVL) gene, the Factor II Prothrombin (PT) gene and the MTHFR (methyltetrahydrofolate reductase) gene. However, the clinical utility of testing is uncertain. The clinical utility of genetic testing depends on the ability of testing results to change management that results in improved clinical outcomes. The clinical utility of genetic testing for thrombophilia is based on the overall risk of thromboembolism and the risk/benefit ratio of treatment, primarily with anticoagulants.

There is insufficient evidence in the published peer-reviewed scientific literature to determine how testing for mutations in the MTHFR gene would guide decisions in the clinical setting related to disease treatment, management or prevention. Furthermore, it is not known whether health outcomes are improved as a result of clinical decision-making based on this gene test. Consequently, genetic testing for inherited thrombophilia, specifically testing for MTHFR mutations are considered investigational.

POLICY:

Paramount Commercial Insurance Plans and Elite (Medicare Advantage) Plans, Paramount Medicaid Advantage
Genetic testing for hereditary thrombophilia (81240, 81241) requires prior authorization.

Paramount Commercial Insurance Plans and Elite (Medicare Advantage) Plans
MTHFR (methyltetrahydrofolate reductase) gene testing (81291) is non-covered.

Paramount Medicaid Advantage
Genetic testing for hereditary thrombophilia (81291) requires prior authorization.

COVERAGE CRITERIA:

Paramount Commercial Insurance Plans and Elite (Medicare Advantage) Plans, Paramount Medicaid Advantage

Clinical findings that increase the suspicion for an inherited thrombophilia in an individual with a VTE that may prompt molecular testing include:

- Idiopathic VTE (where no underlying cause or triggering event can be identified) at an early age,
- Recurrent VTE,
- VTE occurring at unusual sites,
- VTE during pregnancy or with the use of estrogen containing medications, or
- Family history of VTE.

Treatment of VTE is traditionally divided into 3 phases:

- The acute phase, which attempts to halt the thrombolytic process, typically involves treatment with heparinoid agents or direct oral anticoagulants (DOACs).
- The intermediate phase focuses on reducing the risk of a VTE recurrence, typically lasts up to 3 months, and includes treatment with warfarin and DOAC agents.
- The extended phase of treatment focuses on secondary prevention of a VTE recurrence using an anticoagulant or antiplatelet agent.

After a first VTE, the duration of secondary prophylaxis using anti-vitamin K agents or oral anticoagulants after initial treatment can be established by weighing the risk of a major hemorrhagic complication against the risk of a novel unprovoked VTE event. In patients with a second unprovoked VTE, treatment recommendations are often based on bleeding risk; patients with a low risk of bleeding are typically recommended an extended anticoagulant therapy schedule over 3 months; patients with a high risk of bleeding are typically recommended to end anticoagulation therapy at 3 months.

There is general consensus by a number of professional societies/organizations that testing for Factor V Leiden (FVL) and Prothrombin G20210A (F2) is appropriate in selected individuals as an option to inform treatment, (i.e. pregnant women member's with an unprovoked VTE, member's whom have a first-degree relative with Factor V Leiden thrombophilia or F2 G2021A (prothrombin) thrombophilia, not an all-inclusive listing). The decision to test should be based on clinical utility, that is, the likelihood that test results will influence clinical management. Testing allows for prophylactic and/or ongoing clinical management including thromboprophylaxis and/or modification of risk factors.

Genetic testing for hereditary thrombophilia is considered medically necessary when BOTH criteria in items 1 and 2 are met:

1. The result of the testing will directly impact the treatment being delivered to the member; AND
2. Member has ANY of the medical conditions listed in item a. or item b.:
    a. An asymptomatic female of reproductive age who is planning pregnancy or is currently pregnant and not taking anticoagulation therapy and whose results will influence clinical decision-making and who have any of the following criteria in items (i.) through (iii.):
        i. A first-degree relative (i.e., parent, full-sibling or child) with unprovoked VTE or VTE provoked

by pregnancy or contraceptive use; OR
   ii. A first-degree relative with a history of VTE who is a known carrier for factor V Leiden and/or factor II c.97*G>A variant; OR
   iii. Personal history of VTE associated with a transient risk factor (pregnancy, estrogen-progestin contraceptive use, femoral fracture, surgery, or prolonged immobilization); OR

b. Member has a personal history of single or multiple venous thromboembolism (VTE) of unknown etiology and ANY of the criteria in items (i.) through (vii.) is met:
   i. Member has had a VTE of unknown etiology before age 50 (with or without a family history of known thrombophilia or thrombosis, i.e., VTE or pulmonary embolism); OR
   ii. Member has had a VTE of unknown etiology (at any age) and either:
      - At least ONE (1) first-degree relative with a documented genetic thrombophilia diagnosis; OR
      - At least ONE (1) first-degree relative with a history of thrombosis (VTE or pulmonary embolism) of presumed unknown etiology before age 50; OR
   iii. Member has had a VTE at unusual sites (such as hepatic portal, mesenteric, and cerebral veins); OR
   iv. Member with history of recurrent venous thrombosis (VTE); OR
   v. Females under the age of 50 who smoke tobacco and have a history of acute myocardial infarction; OR
   vi. Low activated protein C (APC) resistance activity; OR
   vii. Member has a full sibling known to be homozygous for factor V Leiden or factor II c.*97G>A

Genetic testing for hereditary thrombophilia for ANY of the following indications is considered not medically necessary (this list may not be all-inclusive):

- Not meeting the above criteria
- General population screening
- Testing for an asymptomatic member without a family history of recurrent VTE
- Routine screening during pregnancy or prior to the use of oral contraceptives, hormone replacement therapy (HRT), or selective estrogen receptor modulators (SERMs)
- Newborn testing, or routine testing in an asymptomatic child
- Testing for a member less than age 50 years of age with the first incident of venous thrombosis with a known etiology unrelated to thrombophilia, and the member has no history of a first degree relative with thrombosis
- Testing for a member age 50 years of age or older with the first incident of venous thrombosis with a known etiology unrelated to thrombophilia, and the member has no family history of recurrent venous thrombosis and no history of a first degree relative with thrombosis
- Routine testing for patients with a personal or family history of arterial thrombotic disorders (such as coronary artery disease or ischemic stroke) is considered not medically necessary, as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure
- Testing of an asymptomatic first-degree relative of an individual with proven symptomatic VTE and a proven coagulation Factor V Leiden or Factor II Prothrombin mutation, for the purpose of considering primary prophylactic anticoagulation
- Neonate or child with asymptomatic central venous catheter-related thrombosis

Note: A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children.

Paramount Commercial Plans, Elite (Medicare Advantage) Plans

Genetic testing of methylenetetrahydrofolate reductase (MTHFR) to diagnose hereditary thrombophilia is considered experimental and investigational or NOT medically necessary due to limited evidence demonstrating the clinical utility and clinical validity of testing.

Paramount Medicaid Advantage
MTHFR (methyltetrahydrofolate reductase) gene testing may be covered with prior authorization following the criteria listed above per the Ohio Department of Medicaid guidelines.

CODING/BILLING INFORMATION:
The appearance of a code in this section does not necessarily indicate coverage. Codes that are covered may have selection criteria that must be met. Payment for supplies may be included in payment for other services rendered.

CPT CODES	
81240	F2 (prothrombin, coagulation factor II)(e.g., hereditary hypercoagulability) gene analysis, 20210G>A variant
81241	F5 (coagulation Factor V)(e.g., hereditary hypercoagulability) gene analysis, Leiden variant
81291	MTHFR (5, 10-methylenetetrahydrofolate reductase)(e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)

REVISION HISTORY EXPLANATION: ORIGINAL EFFECTIVE DATE: 04/22/2016

Date	Explanation & Changes
04/22/16	• Policy created to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).
11/14/17	• Genetic testing for hereditary thrombophilia (81240, 81241) is now covered with prior authorization for HMO, PPO, Individual Marketplace, & Elite • Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG)
02/22/18	• Updated indications to include: a significant family history, in first degree family members, of recurrent thromboembolic events or of a hypercoagulable state, prior to surgery, planned pregnancy or starting oral contraceptives • Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG)
12/22/2020	• Medical policy placed on the new Paramount Medical Policy Format
04/25/2022	• Policy updated to reflect most current clinical evidence and industry standards • Coverage criteria updated
02/23/2023	• Medical Policy updated to reflect Medicaid coverage to Anthem as of 02/01/2023
03/11/2024	• Medical policy placed on the new Paramount Medical Policy Format

Paramount reserves the right to review and revise our policies periodically when necessary. When there is an update, we will publish the most current policy to
https://www.paramounthealthcare.com/providers/medical-policies/policy-library

REFERENCES/RESOURCES

Centers for Medicare and Medicaid Services, CMS Manual System and other CMS publications and services https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs

American Medical Association, *Current Procedural Terminology (CPT®)* and associated publications and services https://www.ama-assn.org/amaone/cpt-current-procedural-terminology

Centers for Medicare and Medicaid Services, Healthcare Common Procedure Coding System, HCPCS Release and Code Sets https://www.cms.gov/Medicare/Coding/HCPCSReleaseCodeSets/HCPCS-Quarterly-Update

U.S. Preventive Services Task Force, https://www.uspreventiveservicestaskforce.org/uspstf/
Industry Standard Review

Hayes, Inc., https://www.hayesinc.com/

Industry Standard Review