Geisinger

# Geisinger Health Plan Policies and Procedure Manual

**Policy: MP336**

**Section: Medical Benefit Policy**

**Subject: Genetic Testing for Inherited Thrombophilia/ Hypercoagulability**

**Applicable Lines of Business**

| | | | |
|---|---|---|---|
| **Commercial** | **X** | **CHIP** | **X** |
| **Medicare** | **X** | **ACA** | **X** |
| **Medicaid** | **X** | | |

**I. Policy:** Genetic Testing for Inherited Thrombophilia/ Hypercoagulability

**II. Purpose/Objective:**

To provide a policy of coverage regarding Genetic Testing for Inherited Thrombophilia/ Hypercoagulability

**III. Responsibility:**

A. Medical Directors
B. Medical Management

**IV. Required Definitions**

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

**V. Additional Definitions**

Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
c. in accordance with current standards of good medical treatment practiced by the general medical community.
d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and
e. the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient.

**Medicaid Business Segment**

Medically Necessary — A service, item, procedure, or level of care that is necessary for the proper treatment or management of an illness, injury, or disability is one that:

- Will, or is reasonably expected to, prevent the onset of an illness, condition, injury or disability.
- Will, or is reasonably expected to, reduce or ameliorate the physical, mental or developmental effects of an

illness, condition, injury or disability.
- Will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for Members of the same age

**DESCRIPTION:**
Inherited thrombophilia is a genetic predisposition to develop a group of clinical conditions caused by associated well-described genetic variants and defects. Common causes include Factor V Leiden (F5), prothrombin thrombophilia (F2), and deficiencies in protein S, protein C, and antithrombin. Venous thromboembolism manifest as deep vein thrombosis (DVT) or pulmonary embolism (PE).

Factor V Leiden thrombophilia is characterized by a poor anticoagulant response to activated protein C (APC) and an increased risk for venous thromboembolism. The diagnosis of factor V Leiden thrombophilia is established in an individual by identification of a heterozygous or homozygous c.1691G>A variant (referred to as the factor V Leiden variant in F5) in conjunction with coagulation tests, such as the APC resistance assay. The growing consensus is that factor V Leiden variant testing should not be performed on a routine basis and should only be considered when the results will affect clinical management.

Among individuals with F2, c.20210G>A heterozygotes had a significantly higher rate of pulmonary embolism (PE) at 32% than those with the factor V Leiden variant (19%) or those without thrombophilia (17%). F2, c.20210G>A heterozygotes are also at increased risk of developing isolated PE and may develop VTE at a younger age than individuals without the variant.

The range of plasma concentrations of prothrombin in heterozygotes overlaps with the normal range. Therefore, plasma prothrombin concentration is not reliable for diagnosis. Genotyping of F2, c.20210G>A is preferred.

Asymptomatic healthy children heterozygous or homozygous for F2, c.20210G>A are at low risk for thrombosis**.**

**INDICATIONS:**

## COMMERCIAL AND MEDICAID BUSINESS SEGMENT:

Genetic testing for Factor V and/or Factor II Blood Clotting Protein mutations may be considered medically necessary for any of the following conditions in members without recurrent VTE risk factors (e.g., recent surgery, prolonged immobilization, collagen vascular disease, malignancy, certain hematologic disorders):

Personal History of venous thrombosis (VTE) and:
- Age less than 50; or
- Recurrent venous thrombosis; or
- Myocardial infarction in female smokers less than age of 50; or
- A first or second degree relative with venous thrombosis at any age; or
- The event occurred during pregnancy or within 6 weeks of delivery; or
- The event occurred in an unusual site (hepatic, mesenteric and cerebral veins); or
- Event occurred associated with the use of estrogen-containing oral contraceptives or hormone replacement therapy (HRT); or:
- Preeclampsia or hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome; or
- History of VTE considering discontinuation of anticoagulation

Family History only:
- One first or second degree relative with venous thrombosis less than age of 50; or
- Two or more first or second degree relatives with VTE at any age; or.
- Relative with confirmed Factor V or Factor II mutation; or
- Prior to the administration of estrogen-containing oral contraceptives when there is a family history of VTE in a first or second degree relative.

Genetic Testing via hereditary thrombosis panel may be considered medically necessary, as more expansive testing may detect variants not assessed in genotyping assays, when:
1. FV and F2 testing is negative or indeterminate, and
2. The member meets the above listed personal or family history-based criteria, and
3. Coagulation studies are suggestive of a clotting disorder

## MEDICARE BUSINESS SEGMENT

MolDx issued a non-coverage LCD (L36089) for genetic testing for thrombophilia testing for the Factor V Leiden (FVL) variant in the F5 gene, the G20210G>A (G20210A) variant in the F2 gene, and the MTHFR gene which encodes the 5,10-methylenetetrahydrofolate reductase enzyme. Genetic testing for these genes for all risk factors, signs, symptoms, diseases, or conditions, including cardiovascular risk assessment, are non-covered except for pregnant patients. However, Medicare will not add coverage of thrombophilia testing for pregnant women because they likely represent a very small group of potential Medicare (disabled) patients. Claims submitted on this limited Medicare population will deny per the policy but should be appealed for coverage with submission of medical records supporting the necessity for testing and specify how testing changed anticoagulant prophylaxis management for the patient.

**EXCLUSIONS:**
The Plan considers the use of genetic testing for hereditary thrombophilia for ANY of the following indications to be **experimental, investigational or unproven** and **NOT COVERED**:

- General population screening
- Routine initial testing in an individual with arterial thrombosis
- Routine screening of asymptomatic women during pregnancy or in women with unexplained recurrent pregnancy loss.
- Routine screening of asymptomatic women 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
- Prenatal or preimplantation testing

The Plan considers the use of genetic testing for Factor V and Factor II mutations for all other indications not listed above to be considered **experimental, investigational or unproven** and **NOT COVERED**.

The Plan considers the use of genetic testing for MTHFR for diagnosis or management of all indications, including but not limited to, inherited thrombophilia, infertility, recurrent pregnancy loss, coronary artery disease, vascular disease, congenital heart defects, hepatitis, stroke, Parkinson's, peripheral neuropathy, cancer, migraine headache, Alzheimer's disease, dementia, autism spectrum disorder, depression, or schizophrenia to be considered **experimental, investigational or unproven** and **NOT COVERED.**

## Medicaid Business Segment:

Any requests for services, that do not meet criteria set in the PARP, may be evaluated on a case by case basis.

**Note: A complete description of the process by which a given technology or service is evaluated and determined to be experimental, investigational or unproven is outlined in MP 15 - Experimental Investigational or Unproven Services or Treatment.**

**CODING ASSOCIATED WITH:** Genetic Testing For Inherited Thrombophilia/ Hypercoagulability
***The following codes are included below for informational purposes and may not be all inclusive. Inclusion of a procedure or device code(s) does not constitute or imply coverage nor does it imply or guarantee provider reimbursement. Coverage is determined by the member specific benefit plan document and any applicable laws regarding coverage of specific services. Please note that per Medicare coverage rules, only specific CPT/HCPCS Codes may be covered for the Medicare Business Segment. Please consult the CMS website at www.cms.gov or the local Medicare Administrative Carrier (MAC) for more information on Medicare coverage and coding requirements.***

81291 MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants
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
81400 MOLECULAR PATHOLOGY PROCEDURE LEVEL 1
81401 MOLECULAR PATHOLOGY PROCEDURE LEVEL 2
0268U Hematology (atypical hemolytic uremic syndrome [aHUS]), genomic sequence analysis of 15 genes, blood, buccal swab, or amniotic fluid (Versiti™ aHUS Genetic Evaluation)
0269U Hematology (autosomal dominant congenital thrombocytopenia), genomic sequence analysis of 14 genes, blood, buccal swab, or amniotic fluid (Versiti™ Autosomal Dominant Thrombocytopenia Panel)
0270U Hematology (congenital coagulation disorders), genomic sequence analysis of 20 genes, blood, buccal swab, or amniotic fluid (Versiti™ Coagulation Disorder Panel)

0271U Hematology (congenital neutropenia), genomic sequence analysis of 23 genes, blood, buccal swab, or amniotic fluid (Versiti™ Congenital Neutropenia Panel
0272U Hematology (genetic bleeding disorders), genomic sequence analysis of 51 genes, blood, buccal swab, or amniotic fluid, comprehensive (Versiti™ Comprehensive Bleeding Disorder Panel)
0273U Hematology (genetic hyperfibrinolysis, delayed bleeding), genomic sequence analysis of 8 genes (F13A1, F13B, FGA, FGB, FGG, SERPINA1, SERPINE1, SERPINF2, PLAU), blood, buccal swab, or amniotic fluid (Versiti™ Fibrinolytic Disorder Panel)
0274U Hematology (genetic platelet disorders), genomic sequence analysis of 43 genes, blood, buccal swab, or amniotic fluid (Versiti™ Comprehensive Platelet Disorder Panel)
0275U Hematology (heparin-induced thrombocytopenia), platelet antibody reactivity by flow cytometry, serum (Versiti™ Heparin-Induced Thrombocytopenia Evaluation)
0276U Hematology (inherited thrombocytopenia), genomic sequence analysis of 23 genes, blood, buccal swab, or amniotic fluid (Versiti™ Inherited Thrombocytopenia Panel)
0277U Hematology (genetic platelet function disorder), genomic sequence analysis of 31 genes, blood, buccal swab, or amniotic fluid (Versiti™ Platelet Function Disorder Panel)
0278U Hematology (genetic thrombosis), genomic sequence analysis of ~~12~~ 14 genes, blood, buccal swab, or amniotic fluid (Versiti™ Thrombosis Panel
0279U Hematology (von Willebrand disease [VWD]), von Willebrand factor (VWF) and collagen III binding by enzyme-linked immunosorbent assays (ELISA), plasma, report of collagen III binding (Versiti™ VWF Collagen III Binding)
0280U Hematology (von Willebrand disease [VWD]), von Willebrand factor (VWF) and collagen IV binding by enzyme-linked immunosorbent assays (ELISA), plasma, report of collagen IV binding (Versiti™ VWF Collagen IV Binding)
0281U Hematology (von Willebrand disease [VWD]), von Willebrand propeptide, enzyme-linked immunosorbent assays (ELISA), plasma, diagnostic report of von Willebrand factor (VWF) propeptide antigen level (Versiti™ VWF Propeptide Antigen)
0282U Red blood cell antigen typing, DNA, genotyping of 12 blood group system genes to predict 44 red blood cell antigen phenotypes (Versiti™ Red Cell Genotyping Panel)
0283U von Willebrand factor (VWF), type 2B, platelet-binding evaluation, radioimmunoassay, plasma (Versiti™ VWD Type 2B Evaluation)
0284U von Willebrand factor (VWF), type 2N, factor VIII and VWF binding evaluation, enzyme-linked immunosorbent assays (ELISA), plasma (Versiti™ VWD Type 2N Binding)



**LINE OF BUSINESS:**
**Eligibility and contract specific benefits, limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD's and NCD's will supercede this policy. For PA Medicaid Business segment, this policy applies as written.**

**REFERENCES:**
EGAPP Working Group. Recommendations from the EGAPP Working Group: routine testing for Factor V Leiden (R506Q) and prothrombin (20210G>A) mutations in adults with a history of idiopathic venous thromboembolism and their adult family members. Genet Med. Jan 2011;13(1):67-76.

Silver RM, Saade GR, Thorsten V, et al. Factor V Leiden, prothrombin G20210A, and methylene tetrahydrofolate reductase mutations and stillbirth: The Stillbirth Collaborative Research Network. Am J Obstet Gynecol. 2016;215(4):468 e461-468 e417.

Rodger MA, Hague WM, Kingdom J, et al. Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial. Lancet. 2014;384(9955):1673-1683.

Supanc V, Sonicki Z, Vukasovic I, et al. The role of classic risk factors and prothrombotic factor gene mutations in ischemic stroke risk development in young and middle-aged individuals. J Stroke Cerebrovasc Dis. Mar 2014;23(3):e171-176

Hickey SE, Curry CJ, Toriello HV. ACMG practice guideline: lack of evidence for MTHFR polymorphism testing. Genet Med. 2013 Feb;15(2):153-6.

Li P, Qin C. Methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms and susceptibility to ischemic stroke: a meta-analysis. Gene. Feb 10 2014;535(2):359-364

Local Coverage Determination (LCD):

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

Zhang, Shulin & K. Taylor, Annette & Huang, Xuan & Luo, Biao & Spector, Elaine & Fang, Ping & Sue Richards, C. Venous thromboembolism laboratory testing (factor V Leiden and factor II c.*97G>A), 2018 update: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine. 2018;10.1038/s41436-018-0322-z.

Gupta, A., Sarode, R., Nagella, S. Thrombophilia Testing in Provoked Venous Thromboembolism: A Teachable Moment. JAMA Intern Med 2017;Jun 5

Prosciak MP, Stawicki SP. Hypercoagulable states: A concise review. Int J Acad Med 2017;3, Suppl S1:82-95.

American College of Medical Genetics Practice Guidelines: Lack of Evidence for MTHFR Polymorphism Testing. Scott E. Hickey, M.D., FACMG, Cynthia J. Curry, M.D., FACMG and Helga V. Toriello, PhD, FACMG, Genetics in Medicine 2013:15(2):153-156

Hayes Inc., Genetic Testing for Common Forms of Hereditary Thrombophilia in Adults with Unprovoked Venous Thromboembolism. Clinical Utility Evaluation. Annual Review June 2021

This policy will be revised as necessary and reviewed no less than annually.

**Devised:** 6/20

**Revised:** 9/21 (add Medicare non-coverage). 9/23 (revise criteria)

**Reviewed:** 6/21, 9/22,