

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR INHERITED THROMBOPHILIA
POLICY NUMBER	MP 2.253

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☒ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	RETIRED 7/1/2026

POLICY

Genetic testing for Factor V Leiden (FVL) and Factor II c.*97G>A (formerly referred to as prothrombin 20210G>A) may be considered **medically necessary** for any one (1) of the following indications:

- A first unprovoked venous thromboembolism (VTE), especially less than 50 years old; **or**
- VTE at unusual sites (such as hepatic portal, mesenteric, and cerebral veins); **or**
- Recurrent VTE; **or**
- Personal history of VTE with:
 - two or more family members with a history of VTE; **or**
 - one first-degree relative with VTE at a young age; **or**
- Individuals with low activated protein C (APC) resistance activity; **or**
- Individuals assigned female at birth under the age of fifty who smoke tobacco and have a history of acute myocardial infarction; **or**
- Siblings of individuals known to be homozygous for Factor V (Leiden) or Factor II (c.*97G>A) (they have a 1 in 4 chance of being a homozygote); **or**
- Individuals assigned female at birth of reproductive age who have:
 - A first-degree relative with unprovoked VTE or VTE provoked by pregnancy or contraceptive use; **or**
 - 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**
 - Personal history of VTE associated with a transient risk factor (pregnancy, estrogen-progestin contraceptive use, femoral fracture, surgery, or prolonged immobilization).
 - A positive or negative result of the genetic test will impact the clinical management (predictive, diagnostic, prognostic or therapeutic) of the individual.

Testing for protein C deficiency, protein S deficiency and antithrombin III deficiency may be considered **medically necessary** in individuals without recurrent VTE risk factors (for example, surgery, prolonged immobilization, collagen vascular disease, malignancy, certain hematologic disorders) in any of the following situations:

- A venous thromboembolism (VTE) before the age of fifty; **or**
- VTE at unusual sites (such as hepatic, mesenteric, and cerebral veins); **or**
- VTE and a strong family history of thrombotic disease; **or**
- Relatives of individuals with VTE before age 50; **or**

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- Individuals assigned female at birth under the age of fifty who smoke tobacco and have a history of acute myocardial infarction; **or**
- Individuals assigned female at birth who wish to start oral contraceptives with personal or family history of VTE; **or**
- VTE during pregnancy or Individuals assigned female at birth taking oral contraceptives; **or**
- Individuals with warfarin-induced skin necrosis; **or**
- Infants who develop Neonatal Purpura Fulminans; **or**
- Pediatric arterial ischemic stroke

Note: Testing should be performed at least six weeks after acute thrombotic event and while the individual is not taking anticoagulants.

Routine testing for individuals 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 general conclusion concerning the health outcomes or benefits associated with this procedure.

MTHFR (5,10-methylenetetrahydrofolate reductase enzyme) polymorphism testing is considered **investigational**, as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure. **(See Policy Guidelines)**

All other indications of genetic testing for inherited thrombophilia other than those described in the policy section are considered **investigational**, as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

POLICY GUIDELINES

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

American College of Medical Genetics and Genomics (ACMG)

American College of Medical Genetics and Genomics (ACMG) is a nationally recognized interdisciplinary professional organization that is composed of a medical genetics team including clinical geneticists, clinical laboratory geneticists, and genetic counselors. In 2018, ACMG technical standards were updated on Venous thromboembolism laboratory testing (Factor V Leiden and Factor II c.*97G>A).

Testing for factor V Leiden and factor II c.*97G>A is recommended in the following circumstances:

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- A first unprovoked VTE, especially <50 years old.
- VTE at unusual sites (such as hepatic portal, mesenteric, and cerebral veins).
- Recurrent VTE.
- Personal history of VTE with (a) two or more family members with a history of VTE or (b) one first-degree relative with VTE at a young age.
- Patients with low activated protein C (APC) resistance activity.

Testing may be considered in the following circumstances:

- Females under the age of fifty who smoke tobacco and have a history of acute myocardial infarction.
- Siblings of individuals known to be homozygous for factor V Leiden or factor II c.*97G>A because they have a 1 in 4 chance of being a homozygote.
- Asymptomatic pregnant female or female contemplating pregnancy, with a first-degree relative with unprovoked VTE or VTE provoked by pregnancy or contraceptive use.
- Pregnant female or female contemplating pregnancy or estrogen use who has a first-degree relative with a history of VTE and is a known carrier for factor V Leiden and/or factor II c.97*G>A variant.
- Pregnant female or female contemplating pregnancy with a previous non-estrogen-related VTE or VTE provoked by a minor risk factor because knowledge of the factor V Leiden or factor II c.*97G>A status may alter pregnancy-related thrombophylaxis.

Per the American Society of Hematology, thrombophilia testing in patients with transient risk factors (such as surgery, immobility, or trauma) has the potential to cause harm if the duration of anticoagulation is inappropriately prolonged.

MTHFR polymorphism testing

MTHFR (5,10-methylenetetrahydrofolate reductase enzyme) polymorphism testing has been shown to have minimal utility in the routine evaluation of thrombophilia.

Per the Society for Maternal-Fetal Medicine, women should not be tested for MTHFR mutations. Due to the lack of evidence associating genotype independently with thrombosis, recurrent pregnancy loss, or other adverse pregnancy outcomes, MTHFR genotyping should not be ordered as part of a workup for thrombophilia.

In 2021, American Society for Clinical Laboratory Science (ASCLS) published guidelines on Choosing Wisely to suggest against ordering a homocysteine assay as part of the thrombophilia work up. "An elevated homocysteine level is not a clotting disorder and should not be included in thrombophilia testing panels"

Genetics Nomenclature Update

Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the Human Genome Organization (HUGO).

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The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

PRODUCT VARIATIONS

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:

<https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>

DESCRIPTION/BACKGROUND

Inherited thrombophilias are a group of disorders that predispose to thrombosis. Genetic testing is available for some of these disorders and could potentially assist in the diagnosis and/or management of patients with thrombosis. For example, testing is available for types of inherited

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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. Plasma testing is also available for protein C, protein S and antithrombin III deficiencies.

Venous Thromboembolism

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

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

- Malignancy
- Immobility
- Surgery
- Obesity
- Pregnancy
- Hormonal therapy with estrogen/progesterone
- Systemic lupus erythematosus (SLE), 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. Following this initial treatment period, patients deemed to be at a continued high risk for recurrent thrombosis may be continued on anticoagulation for longer periods, sometimes indefinitely. Anticoagulation is effective in reducing the subsequent risk of thrombosis but has its own risks of bleeding.

Inherited Thrombophilia

Inherited thrombophilias are a group of clinical conditions in which there is a genetic variant defect associated with a predisposition to thrombosis. Not all patients 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 risk of VTE.

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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 a factor V Leiden variant, which accounts for up to 50% of the inherited thrombophilia syndromes. In unselected patients with an idiopathic thrombosis, the rate of factor V Leiden positivity is in the range of 17-24%, compared to a rate of 5-6% in normal controls. The prothrombin gene variant is found less commonly, in approximately 5-8% of unselected patients with thrombosis, compared to 2-2.5% of normal controls.

The second most common inherited thrombophilia is the G20210A mutation of prothrombin. This mutation is a gain of function mutation where clotting activity is increased by creating more thrombin and fibrin. The overall prevalence of this mutation is about 2%. Genetic defects of antithrombin (an inhibitor of thrombin) may also occur, but the estimated prevalence of antithrombin defects is only a maximum of 0.2%.

Protein C deficiency is a genetic disorder characterized by a deficiency of protein C, which is a natural anticoagulant. Although very rare, there is a severe form that is present at birth (congenital) and can potentially cause widespread small clots in the body and life-threatening complications in infancy. Protein C deficiency is caused by alterations (mutations) in the *PROC* gene. The common form is caused by an alteration in one *PROC* gene. The severe form is caused by an alteration in both *PROC* genes.

Antithrombin deficiency is a blood disorder characterized by the tendency to form venous thrombosis. Antithrombin limits the blood's ability to clot (coagulation) and the primary inhibitor of thrombin, which is required for the development of blood clots. In people with congenital antithrombin deficiency, there is a reduced amount of this substance in the blood due to a genetic abnormality.

Protein S deficiency is a rare inherited disorder characterized by the formation of recurrent blood clots and emboli. Affected individuals are particularly at risk for developing deep vein thrombosis. In severe cases of protein S deficiency, infants may develop a potentially life-threatening complication called purpura fulminans. Protein S deficiency is caused by alterations in the *PROS1* gene.

Genetic Testing

Genetic testing for gene variants associated with thrombophilias is available for factor V Leiden, the prothrombin gene variant, and the *MTHFR* gene. The use of genetic testing for inherited thrombophilia can be considered in several clinical situations. The clinical situations that will be addressed in this policy include the following:

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- Assessment of the risk for thrombosis in asymptomatic patients (screening for inherited thrombophilia)
- Evaluation of a patient with established thrombosis, in 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 that is consistent with an inherited thrombophilia
- Evaluation of patients in other situations that are considered high risk for thrombosis (e.g., pregnancy, planned major surgery, or oral contraceptive use).

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Commercial thrombophilia genetic tests are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

The FDA has cleared several genetic tests for thrombophilia for marketing through the 510(k) process for use as an aid in the diagnosis of patients with suspected thrombophilia. Some of these tests are listed in Table 1.

Table 1. Genetic Tests for Thrombophilia Cleared by FDA

Test	Manufacturer	Location	Date Cleared	510(k) No.
IMPACT Dx™ Factor V Leiden and Factor II Genotyping Test	Agena Bioscience ^a	San Diego, CA	06/14	K132978
Invader® Factor II, V, and MTHFR (677, 1298) tests	Hologic	Marlborough, MA	04-06/11	K100943, K100980, K100987, K100496
VeraCode® Genotyping Test for Factor V and Factor II	Illumina	San Diego, CA	04/28/10	K093129
eSensor® Thrombophilia Risk Test, FII-FV, FII, FV and MTHFR (677, 1298) Genotyping Tests	GenMark Dx ^b	Carlsbad, CA	04/22/10	K093974
INFINITI™ System Assay for Factor II & Factor V	AutoGenomics	Carlsbad, CA	02/07/07	K060564
Xpert® Factor II and Factor V Genotyping Assay	Cepheid	Sunnyvale, CA	09/18/09	K082118
Verigene® Factor F2, F5, and MTHFR Nucleic Acid Test	Nanosphere	Northbrook, IL	10/11/07	K070597
Factor V Leiden Kit	Roche Diagnostics	Indianapolis, IN	12/17/03	K033607

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Factor II (Prothrombin) G20210A Kit	Roche Diagnostics	Indianapolis, IN	12/20/03	K033612
AncestryDNA Factor V Leiden Genetic Health Risk Test	Ancestry Genomics, Inc.	San Francisco, CA	08/13/2020	K192944
cobas® Factor II and Factor V Test	Roche Molecular Systems, Inc.	Pleasanton, CA	01/12/18	K172913

FDA: Food and Drug Administration.

^a FDA marketing clearance was granted to Sequenom Bioscience before it was acquired by Agena Bioscience.

^b FDA marketing clearance was granted to Osmetech Molecular Diagnostics.

Other commercial laboratories may offer a variety of functional assays and genotyping tests for F2 (prothrombin, coagulation factor II) and F5 (coagulation factor V), and single or combined genotyping tests for MTHFR.

In November 2017, the 23andMe Personal Genome Service (PGS) Genetic Health Risk was granted a de novo classification by the FDA (class II with general and special controls, FDA product code: PTA). This is a direct-to-consumer test that has been evaluated by the FDA for accuracy, reliability, and consumer comprehension. This test reports whether an individual has variants associated with a higher risk of developing harmful blood clots. This report is based on a qualitative genetic test for single nucleotide polymorphism detection of Factor V Leiden variant in the F5 gene (rs6025) and Prothrombin G20210A variant in the F2 gene (rs1799963/i3002432). Similarly, in August 2020, Ancestry Genomics, Inc was granted the same de novo classification by the FDA (class II with general and special controls, FDA product code: PTA). This AncestryDNA Factor V Leiden Genetic Health Risk Test reports whether an individual has variants associated with a higher risk of developing harmful blood clots. This report is based on a qualitative genetic test for single nucleotide polymorphism detection of Factor V Leiden variant in the F5 gene (rs6025).

RATIONALE

Summary of Evidence

For individuals who are asymptomatic with or without a personal or family history of VTE or who are asymptomatic with increased VTE risk (e.g., 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, 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 a factor V Leiden 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

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ratios are somewhat higher. The clinical utility of testing for factor V Leiden 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 (e.g., 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 the effects of the technology on health outcomes.

MTHFR [5,10-methylenetetrahydrofolate reductase enzyme] polymorphism testing is frequently ordered by physicians as part of the clinical evaluation for thrombophilia. It was previously hypothesized that reduced enzyme activity of *MTHFR* led to mild hyperhomocysteinemia which led to an increased risk for venous thromboembolism, coronary heart disease, and recurrent pregnancy loss. Recent meta-analyses have disproven an association between hyperhomocysteinemia and risk for coronary heart disease and between *MTHFR* polymorphism status and risk for venous thromboembolism. There is growing evidence that *MTHFR* polymorphism testing has minimal clinical utility and therefore should not be ordered as a part of a routine evaluation for thrombophilia.

DEFINITIONS

N/A

DISCLAIMER

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined

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by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered:

Procedure Codes								
81291								

Covered when medically necessary:

Procedure Codes								
81240	81241	81400	85300	85301	85302	85303	85305	85306
85307								

ICD-10-CM Diagnosis Code*	Description
D68.51	Activated protein C resistance
D68.52	Prothrombin gene mutation
D68.59	Other primary thrombophilia
D68.62	Lupus anticoagulant syndrome
D68.61	Antiphospholipid syndrome
D68.69	Other thrombophilia

REFERENCES

1. American Board of Internal Medicine Foundation. *Choosing Wisely*. July 2021
2. American College of Obstetricians Gynecologists, Women's Health Care Physicians. ACOG Practice Bulletin No. 138: Inherited thrombophilias in pregnancy. *Obstet Gynecol*. Sep 2013;122(3):706-717. PMID 23963422
3. Baglin T, Gray E, Greaves M, et al. Clinical guidelines for testing for heritable thrombophilia. *Br J Haematol*. Apr 2010;149(2):209-220. PMID 20128794
4. Bezemer ID, Doggen CJ, Vos HL, et al. No association between the common MTHFR 677C->T polymorphism and venous thrombosis: results from the MEGA study. *Arch Intern Med*. Mar 12, 2007;167(5):497-501. PMID 17353498
5. Bradley LA, Palomaki GE, Bienstock J, et al. Can Factor V Leiden and prothrombin G20210A testing in women with recurrent pregnancy loss result in improved pregnancy outcomes? Results from a targeted evidence-based review. *Genet Med*. Jan 2012;14(1):39-50. PMID 22237430
6. Chatterjee T, Gupta N, Choudhry VP, et al. Prediction of ischemic stroke in young Indians: is thrombophilia profiling a way out? *Blood Coagul Fibrinolysis*. Jun 2013;24(4):449-453. PMID 23337710
7. Christiansen SC, Cannegieter SC, Koster T, et al. Thrombophilia, clinical factors, and recurrent venous thrombotic events. *JAMA*. May 18, 2005;293(19):2352-2361. PMID 15900005

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8. Clark P, Walker ID, Langhorne P, et al. SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage. *Blood*. May 27, 2010;115(21):4162-4167. PMID 20237316
9. Coppens M, Reijnders JH, Middeldorp S, et al. Testing for inherited thrombophilia does not reduce the recurrence of venous thrombosis. *J Thromb Haemost. Sep* 2008;6(9):1474-1477. PMID 18540999
10. de Jong PG, Kaandorp S, Di Nisio M, et al. Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia. *Cochrane Database Syst Rev*. Jul 04 2014(7):CD004734. PMID 24995856
11. den Heijer M, Willems HP, Blom HJ, et al. Homocysteine lowering by B vitamins and the secondary prevention of deep vein thrombosis and pulmonary embolism: A randomized, placebo-controlled, double-blind trial. *Blood*. Jan 1, 2007;109(1):139-144. PMID 16960155
12. 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. PMID 21150787
13. Gohil R, Peck G, Sharma P. The genetics of venous thromboembolism. A meta-analysis involving approximately 120,000 cases and 180,000 controls. *Thromb Haemost. Aug* 2009;102(2):360-370. PMID 19652888
14. Guyatt GH, Akl EA, Crowther M, et al. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. Feb 2012;141(2 Suppl):7S-47S. PMID 22315257
15. Heit JA, Silverstein MD, Mohr DN, et al. The epidemiology of venous thromboembolism in the community. *Thromb Haemost. Jul* 2001;86(1):452-463. PMID 11487036
16. Hickey, S. E., Curry, C. J., & Toriello, H. V. (2013). ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing. *Genetics in medicine : official journal of the American College of Medical Genetics*, 15(2), 153–156.
17. Hindorff LA, Burke W, Laberge AM, et al. Motivating factors for physician ordering of factor V Leiden genetic tests. *Arch Intern Med*. Jan 12, 2009;169(1):68-74. PMID 19139326
18. Hirsh J, Guyatt G, Albers GW, et al. Antithrombotic and thrombolytic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. Jun 2008;133(6 Suppl):110S-112S. PMID 18574260
19. Joachim E, Goldenberg NA, Bernard TJ, et al. The methylenetetrahydrofolate reductase polymorphism (MTHFR c.677C>T) and elevated plasma homocysteine levels in a U.S. pediatric population with incident thromboembolism. *Thromb Res*. Aug 2013;132(2):170-174. PMID 23866722
20. Kaandorp SP, Goddijn M, van der Post JA, et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. *N Engl J Med*. Apr 29, 2010;362(17):1586-1596. PMID 20335572
21. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest*. Feb 2016;149(2):315-352. PMID 26867832

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22. Kearon C, Julian JA, Kovacs MJ, et al. Influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin: results from a randomized trial. *Blood*. Dec 1, 2008;112(12):4432-4436. PMID 18791166
23. Kujovich JL. Prothrombin-Related Thrombophilia. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews*. Seattle, WA: University of Washington; 2014.
24. 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. PMID 24140489
25. Lijfering WM, Brouwer JL, Veeger NJ, et al. Selective testing for thrombophilia in patients with first venous thrombosis: results from a retrospective family cohort study on absolute thrombotic risk for currently known thrombophilic defects in 2479 relatives. *Blood*. May 21, 2009;113(21):5314-5322. PMID 19139080
26. Lockwood, C. & Bauer, K. Inherited thrombophilias in pregnancy. In: *UpToDate Online Journal* [serial online]. Waltham, MA: UpToDate; updated 03/31/2020
27. Mahajerin A, Obasaju P, Eckert G, et al. Thrombophilia testing in children: a 7-year experience. *Pediatr Blood Cancer*. Mar 2014;61(3):523-527. PMID 24249220
28. Middeldorp S, Henkens CM, Koopman MM, et al. The incidence of venous thromboembolism in family members of patients with factor V Leiden mutation and venous thrombosis. *Ann Intern Med*. Jan 1, 1998;128(1):15-20. PMID 9424976
29. Press RD, Bauer KA, Kujovich JL, et al. Clinical utility of factor V Leiden (R506Q) testing for the diagnosis and management of thromboembolic disorders. *Arch Pathol Lab Med*. Nov 2002;126(11):1304-1318. PMID 12421138
30. Pruller F, Weiss EC, Raggam RB, et al. Activated protein C resistance assay and factor V Leiden. *N Engl J Med*. Aug 14, 2014;371(7):685-686. PMID 25119624
31. 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*. Nov 08, 2014;384(9955):1673-1683. PMID 25066248
32. Russo PD, Damante G, Pasca S, et al. Thrombophilic mutations as risk factor for retinal vein occlusion: a case-control study. *Clin Appl Thromb Hemost*. May 2015;21(4):373-377. PMID 24569626
33. Segal JB, Brotman DJ, Emadi A, et al. Outcomes of genetic testing in adults with a history of venous thromboembolism (Evidence Reports/Technology Assessment, No. 180). Rockville, MD: Agency for Healthcare Research and Quality; 2009.
34. 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*. Oct 2016;215(4):468 e461-468 e417. PMID 27131585
35. Skeith L, Carrier M, Kaaja R, et al. A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia. *Blood*. Mar 31, 2016;127(13):1650-1655. PMID 26837697
36. 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. PMID 24189452

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37. Vandenbroucke JP, Koster T, Briet E, et al. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. *Lancet*. Nov 26, 1994;344(8935):1453-1457. PMID 7968118
38. Zhang, S., Taylor, A.K., Huang, X. et al. 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). *Genet Med* 20, 1489–1498 (2018)., Qian W, Li J, et al. Who are at risk for thromboembolism after arthroplasty? A systematic review and meta-analysis. *Thromb Res*. Nov 2013;132(5):531-536. PMID 24074702
39. Society for Maternal-Fetal Medicine Publications Committee. American Board of Internal Medicine (ABIM) Foundation Choosing Wisely Campaign. December 2022.
40. Ashraf N, Visweshwar N, Jaglal M, Sokol L, Laber D. Evolving paradigm in thrombophilia screening. *Blood Coagul Fibrinolysis*. 2019;30(5):249-252. doi:10.1097/MBC.0000000000000809
41. American Society for Clinical Laboratory Science. American Board of Internal Medicine (ABIM) Foundation Choosing Wisely Campaign. September 2021
42. Bauer, K. Protein C Deficiency. In: UpToDate Online Journal [serial online]. Waltham, MA: UpToDate; updated 11/16/2021
43. Bauer, K. Prothrombin G20210A mutation. In: UpToDate Online Journal [serial online]. Waltham, MA: UpToDate; updated 12/20/2021
44. Bauer, K. Screening for Inherited Thrombophilia in Asymptomatic Adults. In: UpToDate Online Journal [serial online]. Waltham, MA: UpToDate; Feb 2023. Last updated: Aug 16, 2021
45. Bauer, K. Evaluating Adult Patients with Established Venous Thromboembolism for Acquired and Inherited Risk Factors. In: UpToDate Online Journal [serial online]. Waltham, MA: UpToDate; Literature review current through: Feb 2023. Last updated: Oct 25, 2022
46. National Organization for Rare Disorders. Antithrombin Deficiency. 2018
47. National Organization for Rare Disorders. Protein S Deficiency. 2019
48. National Organization for Rare Disorders. Protein C Deficiency. 2018
49. National Institute for Health Care Excellence Guidelines. Venous Thromboembolic Disease: Diagnosis, Management, and Thrombophilia Testing. March 26, 2020
50. American College of Obstetricians Gynecologists. Screening and Management of Bleeding Disorders in Adolescents With Heavy Menstrual Bleeding. Committee Opinion, Number 785, September 2019.
51. Case Report: Managing Menorrhagia in a Familial Case of Factor V Deficiency. Department of Obstetrics and Gynecology, University of Medicine-Jacksonville, Jacksonville, FL. *Journal of Pediatric Adolescent Gynecology* 28(2015) e9-e12.
52. Roy DC, Wang T, Lun R, et al. Inherited thrombophilia gene mutations and risk of venous thromboembolism in patients with cancer: A systematic review and meta-analysis. *American Journal of Hematology*. Published online January 30, 2024. Doi:10.1002/ajh.27222
53. Malod-Dognin N, Ceddia G, Gvozdenov M, et al. A phenotype driven integrative framework uncovers molecular mechanisms of a rare hereditary thrombophilia. *PloS One*. 2023;18(4):e0284084. doi:10.1371/journal.pone.0284084

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54. Badescu MC, Butnariu LI, Costache AD, Gheorghe L, Seritean Isac PN, Chetran A, Leancă SA, Afrăsânie I, Duca Ş-T, Gorduza EV, et al. Acute Myocardial Infarction in Patients with Hereditary Thrombophilia—A Focus on Factor V Leiden and Prothrombin G20210A. *Life*. 2023; 13(6):1371.

POLICY HISTORY

MP 2.253	01/24/2020 Minor Review. Adding medically necessary indications per American College of Medical Genetics. References updated. Coding reviewed.
	08/19/2020 Minor Review. Medically necessary indications for Factor II and Factor V expanded to address additional indications. Investigational statement for routine testing and MTHFR clarified. Policy guideline, product variation, description/background, rationale, benefit variation, disclaimer, and references updated. Coding reviewed.
	08/27/2021 Administrative Update. Spelling correction for necessary.
	11/02/2021 Consensus Review. References updated; coding reviewed
	08/09/2022 Minor Review. Adding MN testing for protein c, protein s and antithrombin III deficiencies. Added codes 85300, 85301, 85302, 85303, 85305, 85306, 85307. Guidelines, background, references, and formatting updated.
	03/23/2023 Consensus Review. No change to policy statements. References updated. No coding changes.
	07/26/2023 Ad Hoc Minor Review. Medically necessary indications expanded to include women of reproductive age who have a positive or negative result of the genetic test will impact the clinical management. References updated.
	05/14/2024 Consensus Review. No change to policy statements. Updated regulatory status and references. No coding changes.
	07/21/2025 Consensus review. No change to policy statements and no coding changes.
	03/03/2026 Retirement Review. Service to be managed by vendor Evicore

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