



# Louisiana

## Genetic Testing for Inherited Thrombophilia

**Policy #** 00333

**Original Effective Date:** 12/19/2012

**Current Effective Date:** 01/11/2021

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### Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers genetic testing for inherited thrombophilia, including testing for factor V Leiden (FVL) variants, prothrombin gene variants, and variants in the 5.10-methylenetetrahydrofolate reductase (MTHFR) gene to be **investigational**.\*

### Policy Guidelines

#### **Genetics Nomenclature Update**

The Human Genome Variation Society 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). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to 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.

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**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.

### Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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## **Background/Overview**

### **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 approximately 5%, accounting for 100,000 deaths annually. [Heit JA, Silverstein MD, Mohr DN, et al. *The epide.*; 86(1): 452-63. PMID 11487036]

The 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 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. 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 three to six months. After this initial treatment period, patients deemed to be at a continued high-risk for recurrent thrombosis may

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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)

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- 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).

## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

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. Commercial thrombophilia genetic tests are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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 have been cleared for marketing by the FDA 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**

<b>Test</b>	<b>Manufacturer</b>	<b>Cleared</b>	<b>510(k) No.</b>
IMPACT Dx™‡ Factor V Leiden and Factor II Genotyping Test	Agena Biosciencea	06/14	K132978
Invader®‡ Factor II, V, and MTHFR (677, 1298) tests	Hologic	04-06/11	K100943, K100980, K100987, K100496
VeraCode®‡ Genotyping Test for Factor V and Factor II	Illumina	04/28/10	K093129

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eSensor <sup>®‡</sup> Thrombophilia Risk Test, FII-FV, FII, FV and MTHFR (677, 1298) Genotyping Tests	GenMark Dxb	04/22/10	K093974
INFINITI <sup>™‡</sup> System Assay for Factor II & Factor V	AutoGenomics	02/07/07	K060564
Xpert <sup>®‡</sup> Factor II and Factor V Genotyping Assay	Cepheid	09/18/09	K082118
Verigene <sup>®‡</sup> Factor F2, F5, and MTHFR Nucleic Acid Test	Nanosphere	10/11/07	K070597
Factor V Leiden Kit	Roche Diagnostics	12/17/03	K033607
Factor II (Prothrombin) G20210A Kit	Roche Diagnostics	12/20/03	K033612

FDA: Food and Drug Administration.

<sup>a</sup> FDA marketing clearance was granted to Sequenom Bioscience before it was acquired by Agena Bioscience.

<sup>b</sup> FDA marketing clearance was granted to Osmetech Molecular Diagnostics.

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

On April 6, 2017, the FDA permitted marketing of 23andMe Personal Genome Service Genetic Health Risk tests for 10 diseases or conditions. These direct-to-consumer tests are the first authorized by the FDA that provide information on an individual’s genetic predisposition to certain medical diseases or conditions, which may help to make decisions about lifestyle choices or to inform discussions with a health care professional. The 23andMe Genetic Health Risk tests work by isolating DNA from a saliva sample, which is then tested for more than 500000 genetic variants. The presence or absence of some of these variants is associated with an increased risk of developing any one of ten diseases or conditions. Testing for hereditary thrombophilia (two variants in the *F5* and *F2* genes; relevant for European descent) is included.

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### **Rationale/Source**

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* variant), and the prothrombin (*factor II*) gene.

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 RCT, prospective cohort analyses, retrospective family studies, case-control studies, and meta-analyses. The relevant outcomes are morbid events and treatment-related morbidity. The clinical validity of genetic testing has been demonstrated by the presence of a 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 OR most commonly between one and two, except for family members of individuals with inherited thrombophilia, for whom OR 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 the effects of the technology on health outcomes.

### **Supplemental Information**

#### **Clinical Input from Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers,

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input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 4 physician specialty societies (6 reviewers) and 6 academic medical centers, for a total of 12 reviewers, while this policy was under review in 2012. Input was mixed, and there was no consensus that genetic testing for thrombophilia was medically necessary for any of the specific clinical situations included. Several reviewers noted that testing could be useful in isolated instances but were unable to define specific criteria for testing.

### Practice Guidelines and Position Statements

Many guidelines and position statements on testing for thrombophilia have been published over the last two decades. These guidelines have evolved over time, often inconsistent and do not typically give specific parameters on when to perform genetic testing. The following are examples of U.S. guidelines developed by major specialty societies and published more recently.

#### American Board of Internal Medicine Foundation- Choosing Wisely Campaign

*Choosing Wisely*, an initiative of the American Board of Internal Medicine Foundation seeks to promote discussions between clinicians and patients to choose care that is: supported by evidence, not duplicative of other tests or procedures already received, free from harm, and truly necessary. Medical specialty societies and their national organizations have identified tests or procedures commonly used in their field whose necessity should be questioned and discussed. The following medical specialist groups have contributed recommendations to *Choosing Wisely* lists specifically related to testing for inherited thrombophilias (see Table 2).

**Table 2. Medical Society Recommendations on Testing for Inherited Thrombophilias**

Society	Year	Recommendation
American Society of Hematology	2013	<ul style="list-style-type: none"> <li>“Don’t test for thrombophilia in adult patients with venous thromboembolism (VTE) occurring in the setting of major transient risk factors (surgery, trauma or prolonged immobility).”</li> </ul>
•		<ul style="list-style-type: none"> <li>“Thrombophilia testing is costly and can result in harm to patients if the duration of anticoagulation is inappropriately</li> </ul>

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		<p>prolonged or if patients are incorrectly labeled as thrombophilic. Thrombophilia testing does not change the management of VTEs occurring in the setting of major transient VTE risk factors. When VTE occurs in the setting of pregnancy or hormonal therapy, or when there is a strong family history plus a major transient risk factor, the role of thrombophilia testing is complex and patients and clinicians are advised to seek guidance from an expert in VTE.”</p>
Society for Maternal-Fetal Medicine	2014	<ul style="list-style-type: none"> <li>• “Don’t do an inherited thrombophilia evaluation for women with histories of pregnancy loss, intrauterine growth restriction (IUGR), preeclampsia and abruption.”</li> </ul>
•		<ul style="list-style-type: none"> <li>• “Scientific data supporting a causal association between either methylenetetrahydrofolate reductase (MTHFR) polymorphisms or other common inherited thrombophilias and adverse pregnancy outcomes, such as recurrent pregnancy loss, severe preeclampsia and IUGR, are lacking. Specific testing for antiphospholipid antibodies, when clinically indicated, should be limited to lupus anticoagulant, anticardiolipin antibodies and beta 2 glycoprotein antibodies.”</li> </ul>
American Society for Reproductive Medicine	2013	<ul style="list-style-type: none"> <li>• “Don’t routinely order thrombophilia testing on patients undergoing a routine infertility evaluation.”</li> </ul>
•		<ul style="list-style-type: none"> <li>• “There is no indication to order these tests, and there is no benefit to be derived in obtaining them in someone that does not have any history of bleeding or abnormal clotting and in the absence of any family history. This testing is not a part of the infertility workup. Furthermore, the testing is costly, and there are risks associated with the proposed treatments, which would also not be indicated in this routine population.”</li> </ul>

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### American College of Chest Physicians

The American College of Chest Physicians (2016) guidelines and expert panel report on antithrombotic therapy for VTE disease no longer includes recommendations for pregnant women with known *factor V Leiden* or prothrombin G20210A variants, which had been included in the 2012 edition. Also, there are no guidelines on genetic testing for thrombophilia. The 2008 edition had indicated that the presence of a hereditary thrombophilia was not a major factor to guide duration of anticoagulation for VTE.

### American College of Medical Genetics and Genomics

In 2018, the American College of Medical Genetics and Genomics (ACMG) published updated technical standards for genetic testing for variants associated with VTE, with a focus on *factor V Leiden* and *factor II*. The standards do not make recommendations on the indications for testing, and the authors note that testing indications from different professional organizations vary, referring to a review of professional society guidelines published by de Stefano et al (2013).

### American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (2013) published management guidelines for inherited thrombophilias in pregnancy, which were reaffirmed in 2014 and in 2018. These guidelines stated that a definitive causal link between inherited thrombophilias and adverse pregnancy outcomes could not be made. Screening for inherited thrombophilias is controversial, but may be considered for pregnant women in the following situations:

- A personal history of VTE associated with a nonrecurrent risk factor (eg, fracture, surgery, or prolonged immobilization).
- A first-degree relative (eg, parent, sibling) with a history of high-risk thrombophilia.

Guidelines for Managing Inherited Thrombophilias During Pregnancy

Recommendation	GOE	LOE
Testing for inherited thrombophilias should include FVL, prothrombin G20210A mutation, and tests for deficiencies in antithrombin, protein S and protein C	C	Consensus and expert opinion

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Testing for inherited thrombophilias in women who have experienced recurrent fetal loss or placental abruption is not recommended because it is unclear whether anticoagulation therapy reduces recurrence	B	Limited or inconsistent scientific evidence
Because an association between either heterozygosity or homozygosity for the <i>MTHFR</i> C677T polymorphism and any negative pregnancy outcomes, including any increased risk for VTE, has not been shown, screening with either <i>MTHFR</i> mutation analyses or fasting homocysteine levels is not recommended	B	Limited or inconsistent scientific evidence

FVL: *factor V Leiden*; GOE: grade of evidence; LOE: level of evidence; VTE: venous thromboembolism.

### Anticoagulation Forum

In 2019, Stevens et al. published a guidance document initiated by the Anticoagulation Forum. The guidance was intended to inform clinical decisions regarding duration of anticoagulation following VTE and primary prevention of VTE in relatives of affected patients. Statements were based on existing guidelines and consensus expert opinion when guidelines were lacking. The authors concluded that, "Thrombophilia testing is performed far more frequently than can be justified based on available evidence; the majority of such testing is not of benefit to the patient and may be harmful." Table 3 summarizes the guidance statements for each question considered in the document.

**Table 3. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia (adapted from Stevens et al [2019])**

Question	Guidance Statement	Limits/Exceptions
Should thrombophilia testing be performed to help determine duration of anticoagulation following provoked VTE?	Do not perform thrombophilia testing following an episode of provoked VTE.	

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Should thrombophilia testing be performed to help determine duration of anticoagulation following unprovoked VTE?	Do not perform thrombophilia testing in patients following an episode of unprovoked VTE.	If a patient with unprovoked VTE and low bleeding risk is planning to stop anticoagulation, test for thrombophilia if test results would change this decision.
Should family members of patients with VTE or hereditary thrombophilia undergo thrombophilia testing?	Do not test for thrombophilia in asymptomatic family members of patients with VTE or hereditary thrombophilia.	
Should female relatives of patients with VTE or hereditary thrombophilia who are considering using estrogen-containing medications be tested for thrombophilia?	Do not test for thrombophilia in asymptomatic family members of patients with VTE or hereditary thrombophilia who are contemplating use of estrogen.	If a woman contemplating estrogen use has a first degree relative with VTE and a known hereditary thrombophilia, test for that thrombophilia if the result would change the decision to use estrogen.
Should female relatives of patients with VTE or hereditary thrombophilia who are contemplating pregnancy be tested for thrombophilia?	Do not test for thrombophilia in asymptomatic family members of patients with VTE or hereditary thrombophilia who are contemplating pregnancy.	If a woman contemplating pregnancy has a first degree relative with VTE and a known hereditary thrombophilia, test for that thrombophilia if the result would change VTE prophylaxis decisions.
When thrombophilia testing is performed, at what point in the patient's care should this be done?	Do not perform thrombophilia testing at the time of VTE diagnosis or during the initial 3-month course of anticoagulant therapy. When testing for thrombophilias following VTE,	

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	use either a 2-stage testing approach or perform testing after a minimum of 3 months of anticoagulant therapy has been completed, and anticoagulants have been held.	
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VTE: Venous thromboembolism.

### Evaluation of Genomic Applications in Practice and Prevention

The Evaluation of Genomic Applications in Practice and Prevention (2011) recommendations did not support the clinical utility of genetic testing for *factor V Leiden* and prothrombin variants for prevention of initial episodes of venous thromboembolism (VTE) or for recurrence. The recommendations have been archived.

### U.S. Preventive Services Task Force Recommendations

Not applicable.

### Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

### Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 4.

**Table 4. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT02385461	Study on Antithrombotic Prevention in Thrombophilia and Pregnancy Loss (OTTILIA)	108	Dec 2020

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NCT02841085	New Genetic Mutations in Thromboembolic Venous Disease Idiopathic	450	May 2021
NCT02685800	A Registry on Outcomes in Women Undergoing Assisted Reproductive Techniques After Recurrent Failures	624	Sep 2020
<i>Unpublished</i>			
NCT02407730	Effects of Thrombophilia on the Outcomes of Assisted Reproduction Technologies	715	Jun 2019
NCT02986594	Diagnosis and Treatment Strategy of Recurrent Spontaneous Abortion Associated With Thrombophilia	600	Oct 2019

NCT: national clinical trial.

## References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, “Genetic Testing for Inherited Thrombophilia”, 2.04.82, June 2020.
2. Heit JA, Silverstein MD, Mohr DN, et al. The epidemiology of venous thromboembolism in the community. *Thromb Haemost.* Jul 2001; 86(1): 452-63. PMID 11487036
3. Baglin T, Gray E, Greaves M, et al. Clinical guidelines for testing for heritable thrombophilia. *Br J Haematol.* Apr 2010; 149(2): 209-20. PMID 20128794
4. Bauer KA. Management of inherited thrombophilia (Topic 1365). In: Leung LLK, ed. *UpToDate.* Waltham, MA: UpToDate; 2013.
5. ACOG Practice Bulletin No. 138: Inherited thrombophilias in pregnancy. *Obstet Gynecol.* Sep 2013; 122(3): 706-17. PMID 23963422
6. 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): 373-7. PMID 24569626
7. 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): e171-6. PMID 24189452

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8. Zhou X, 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): 531-6. PMID 24074702
9. Li P, Qin C. Methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms and susceptibility to ischemic stroke: a meta-analysis. *Gene.* Feb 10 2014; 535(2): 359-64. PMID 24140489
10. 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
11. 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): 170-4. PMID 23866722
12. 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): 449-53. PMID 23337710
13. 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 01 2007; 109(1): 139-44. PMID 16960155
14. 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 01 1998; 128(1): 15-20. PMID 9424976
15. Kujovich JL. Prothrombin-Related Thrombophilia. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews.* Seattle, WA: University of Washington; 2014.
16. 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): 360-70. PMID 19652888
17. 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.
18. Christiansen SC, Cannegieter SC, Koster T, et al. Thrombophilia, clinical factors, and recurrent venous thrombotic events. *JAMA.* May 18 2005; 293(19): 2352-61. PMID 15900005
19. 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 01 2008; 112(12): 4432-6. PMID 18791166

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20. 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): 5314-22. PMID 19139080
21. 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): 685-6. PMID 25119624
22. 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): 1474-7. PMID 18540999
23. Mahajerin A, Obasaju P, Eckert G, et al. Thrombophilia testing in children: a 7 year experience. *Pediatr Blood Cancer*. Mar 2014; 61(3): 523-7. PMID 24249220
24. 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): 1304-18. PMID 12421138
25. 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
26. Vandembroucke 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): 1453-7. PMID 7968118
27. 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): 4162-7. PMID 20237316
28. 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): 1586-96. PMID 20335572
29. 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): 1650-5. PMID 26837697
30. 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
31. 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.e1-468.e17. PMID 27131585

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32. 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): 1673-83. PMID 25066248
33. American Board of Internal Medicine Foundation. *Choosing Wisely*. 2017; <http://www.choosingwisely.org/>.
34. 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
35. 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
36. 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
37. Zhang S, Taylor AK, 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*. Dec 2018; 20(12): 1489-1498. PMID 30297698
38. De Stefano V, Rossi E. Testing for inherited thrombophilia and consequences for antithrombotic prophylaxis in patients with venous thromboembolism and their relatives. A review of the Guidelines from Scientific Societies and Working Groups. *Thromb Haemost*. Oct 2013; 110(4): 697-705. PMID 23846575
39. American College of Obstetricians and Gynecologists (ACOG). Early Pregnancy Loss. Practice Bulletin Number 200. November 2018. <https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/11/early-pregnancy-loss>.
40. Stevens SM, Woller SC, Bauer KA, et al. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. *J Thromb Thrombolysis*. Jan 2016; 41(1): 154-64. PMID 26780744
41. Berg AO, Botkin J, Calonge N, et al. 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

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### **Policy History**

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Current Effective Date: 01/11/2021

12/06/2012	Medical Policy Committee review
12/19/2012	Medical Policy Implementation Committee approval. New policy.
11/07/2013	Medical Policy Committee review
11/20/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/04/2014	Medical Policy Committee review
12/17/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
12/03/2015	Medical Policy Committee review
12/16/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/06/2018	Medical Policy Committee review
12/19/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. The policy is revised with updated genetics nomenclature; “mutations” changed to “variants” throughout policy. Coverage eligibility unchanged.
12/03/2020	Medical Policy Committee review
12/09/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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### **Coding**

*The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81240, 81241, 81291, 81400
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

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\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
  2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  3. Reference to federal regulations.

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**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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