



FEP Medical Policy Manual

FEP 2.04.82 Genetic Testing for Inherited Thrombophilia

Effective Policy Date: October 1, 2023

Original Policy Date: September 2013

Related Policies:

None

Genetic Testing for Inherited Thrombophilia

Description

Description

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

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing for 5,10-methylenetetrahydrofolate reductase, *factor V* gene, and prothrombin gene variants improves the net health outcome in individuals with inherited thrombophilias.

POLICY STATEMENT

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

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

Genetic counseling is primarily aimed at individuals 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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA 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	Cleared	510(k) No.
Ancestrydna Factor V Leiden Genetic Health Risk Test	Ancestry Genomics, Inc.	08/13/2020	K192944
cobas Factor II and Factor V Test	Roche Molecular Systems, Inc.	01/12/18	K172913
IMPACT Dx™ Factor V Leiden and Factor II Genotyping Test	Agena Bioscience ^a	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
eSensor Thrombophilia Risk Test, FII-FV, FII, FV and MTHFR (677, 1298) Genotyping Tests	GenMark Dx ^b	04/22/10	K093974
INFINITI™ System Assay for Factor II & Factor V	AutoGenomics	02/07/07	K060564
Xpert Factor II and Factor V Genotyping Assay	Cepheid	09/18/09	K082118
Verigene 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.

^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.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

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 venous thromboembolism (VTE) or who are asymptomatic with increased VTE risk (eg, due to pregnancy) who receive genetic testing for variants in methylenetetrahydrofolate reductase (*MTHFR*), or genetic testing for coagulation *factor V* and coagulation factor II, the evidence includes a large randomized controlled trial (RCT), 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 an factor V Leiden (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 odds ratios most commonly between 1 and 2, except for family members of individuals with inherited thrombophilia, for whom odds ratios are somewhat higher. The clinical utility of testing for FVL or prothrombin variants has not been demonstrated. Although the presence of inherited thrombophilia increases 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 that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Many guidelines and position statements on testing for thrombophilia have been published over the last 2 decades. These guidelines have evolved over time, are 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 (Table 2).³⁵

Table 2. Medical Society Recommendations on Testing for Inherited Thrombophilias

Society	Year	Recommendation
American Society of Hematology	2013	<ul style="list-style-type: none"> "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)."
		<ul style="list-style-type: none"> "Thrombophilia testing is costly and can result in harm to patients if the duration of anticoagulation is inappropriately 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."
Society for Maternal-Fetal Medicine	2014	<ul style="list-style-type: none"> "Don't do an inherited thrombophilia evaluation for women with histories of pregnancy loss, fetal growth restriction (FGR), preeclampsia and abruption."
		<ul style="list-style-type: none"> "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."
	2019	<ul style="list-style-type: none"> "Don't test women for MTHFR mutations."
American Society for Reproductive Medicine	2013	<ul style="list-style-type: none"> "Don't routinely order thrombophilia testing on patients undergoing a routine infertility evaluation."
		<ul style="list-style-type: none"> "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."
American College of Medical Genetics and Genomics	2015	<ul style="list-style-type: none"> "Don't order MTHFR genetic testing for the risk assessment of hereditary thrombophilia."
American Society of Hematology and American Society of Pediatric Hematology/Oncology	2019	<ul style="list-style-type: none"> "Don't order thrombophilia testing on children with venous access (i.e., peripheral or central) associated thrombosis in the absence of a positive family history."

American College of Chest Physicians

Since 2016, the American College of Chest Physicians (2021) guidelines and expert panel report on antithrombotic therapy for venous thromboembolism (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.^{36,37,38} 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.³⁹

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*.⁴⁰ 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).⁴¹

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (2018) published management guidelines for inherited thrombophilias in pregnancy.⁴² 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 if testing will influence management:

- A personal history of VTE, with or without a recurrent risk factor, and no prior thrombophilia testing.
- A first-degree relative (eg, parent, sibling) with a history of high-risk thrombophilia.

Table 3. Guidelines for Managing Inherited Thrombophilias During Pregnancy

Recommendation	GOE	LOE
In women with personal histories of VTE, 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
Testing for inherited thrombophilias in women who have experienced fetal loss or adverse pregnancy outcomes, including placental abruption, preeclampsia, or fetal growth restriction, is not recommended because there is insufficient evidence that 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 2016, Stevens et al. published a guidance document initiated by the Anticoagulation Forum.⁴³ 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 4 summarizes the guidance statements for each question considered in the document.

Table 4. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia (adapted from Stevens et al [2016])

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.	
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, 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.	

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 VTE or for recurrence.⁴⁴ 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.

REFERENCES

1. 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
2. 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
3. Bauer KA, Lip GYH. Evaluating adult patients with established venous thromboembolism for acquired and inherited risk factors In: Leung LLK, Mandel J, eds. *UpToDate.* Waltham, MA: UpToDate; 2022.
4. American College of Obstetricians and Gynecologists Women's Health Care Physicians. ACOG Practice Bulletin No. 138: Inherited thrombophilias in pregnancy. *Obstet Gynecol.* Sep 2013; 122(3): 706-17. PMID 23963422
5. 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
6. 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
7. 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
8. Li P, Qin C. Methylene tetrahydrofolate reductase (MTHFR) gene polymorphisms and susceptibility to ischemic stroke: a meta-analysis. *Gene.* Feb 10 2014; 535(2): 359-64. PMID 24140489
9. 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
10. 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
11. 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
12. 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
13. Gao M, Feng N, Zhang M, et al. Meta-analysis of the relationship between methylenetetrahydrofolate reductase C677T and A1298C polymorphism and venous thromboembolism in the Caucasian and Asian. *Biosci Rep.* Jul 31 2020; 40(7). PMID 32614041
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; 2022.
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
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. Priller 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. 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
25. 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
26. 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
27. Liu X, Chen Y, Ye C, et al. Hereditary thrombophilia and recurrent pregnancy loss: a systematic review and meta-analysis. *Hum Reprod.* Apr 20 2021; 36(5): 1213-1229. PMID 33575779
28. Vandenbroucke JP, Koster T, Brit 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

29. 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
30. 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
31. 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
32. 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; 2014(7): CD004734. PMID 24995856
33. 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
34. 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
35. American Board of Internal Medicine Foundation. *Choosing Wisely*. 2021; <http://www.choosingwisely.org/>. Accessed March 29, 2023.
36. 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
37. 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
38. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. *Chest*. Dec 2021; 160(6): e545-e608. PMID 34352278
39. 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
40. 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
41. 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
42. Metz TD, Silverman NS. ACOG Practice Bulletin No. 197: Inherited Thrombophilias in Pregnancy. *Obstet Gynecol*. Jul 2018; 132(1): e18-e34. PMID 29939939
43. 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
44. 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

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
September 2013	New policy	
September 2014	Replace policy	Policy updated with literature review adding references 5-8, 10-11, 24 and 29, references 4 and 12 were updated. There are no changes to the policy statement.
September 2018	Replace policy	Policy updated with literature review through March 5, 2018; references 16 and 23 added; references 29-32, 34, and 37 updated. The policy is revised with updated genetics nomenclature; "mutations, changed to "variants, throughout policy. Policy statement otherwise unchanged except "not medically necessary, corrected to "investigational, due to 510k FDA clearance.
September 2019	Replace policy	Policy updated with literature review through March 4, 2019; references added. Policy statement unchanged.
September 2020	Replace policy	Policy updated with literature review through March 26, 2020; references added. Policy statement unchanged.
September 2021	Replace policy	Policy updated with literature review through April 7, 2021; references added. Policy statement unchanged.
September 2022	Replace policy	Policy updated with literature review through April 1, 2022; reference added. Policy statement unchanged.
September 2023	Replace policy	Policy updated with literature review through March 29, 2023; no references added. Policy statement unchanged.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.