

2.04.82	Genetic Testing for Inherited Thrombophilia		
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Section:	2.0 Medicine	Page:	Page 1 of 24

Policy Statement

- I. 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**.

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Genetics Nomenclature Update

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

The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) 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.

Coding

The following CPT codes are specific for this testing:

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

*The genes above are also found in panel test: 81400 Pathology testing Level 1.

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.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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 the 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.

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

Background

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.¹ The risk is strongly age-related, with the greatest risk in older populations. Venous thromboembolism also recurs frequently; the estimated cumulative incidence of first VTE recurrence is 30% at 10 years.¹ 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.² In women with a history of pregnancy-related VTE, risk of recurrent VTE with subsequent pregnancies is increased greatly at approximately 100-fold.²

Treatment

Treatment of thrombosis involves anticoagulation for a minimum of 3 to 6 months. After this initial treatment period, patients deemed to be at a continued high risk for recurrent thrombosis may continue on anticoagulation therapy for longer periods, sometimes indefinitely. Anticoagulation is effective for reducing the 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. Generally, routine testing for hypercoagulable disorders is not recommended in unselected patients.³ For those considered at risk (e.g., strong family history, recurrent thromboses), the prevalence of identifying an inherited thrombophilia ranges from 5% to 40%; the prevalence is estimated at 12% to 40% for FVL and 6% to 18% for prothrombin G20210A variant in this population.

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)
- 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 (e.g., pregnancy, planned major surgery, exogenous hormone use).

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

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.

MTHFR Variant Testing

Clinical Context and Test Purpose

The purpose of genetic testing for variants in the *MTHFR* gene is to provide a diagnostic option that is an alternative to or an improvement on existing tests, such as standard clinical management without testing, in patients who are asymptomatic with or without a personal or family history of venous thromboembolism (VTE).

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are asymptomatic with or without a personal or family history of VTE.

Interventions

The test being considered is genetic testing for variants in *MTHFR*.

Comparators

Comparators of interest include standard clinical management without testing.

Outcomes

The general outcomes of interest are morbid events and treatment-related morbidity.

The beneficial outcomes of a true-positive test result are an appropriate treatment for VTE. The beneficial outcome of a true-negative test result is potentially avoiding unnecessary treatment.

The harmful outcome of a false-positive result is having unnecessary treatment for VTE. The harmful outcome of a false-negative result is a potential delay in diagnosis and treatment.

Table 2. Outcomes of interest for individuals who are asymptomatic with or without a personal or family history of venous thromboembolism

Outcomes	Details	Timing
Morbid events	Evaluating risk, including relative risk and absolute annual risk for VTE	1-10 years
Treatment-related morbidity	Evaluating risk, such as relative risk, for morbidities associated with the treatment of VTE such as major bleeding	1-10 years

VTE: venous thromboembolism

Study Selection Criteria

Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operating characteristic, area under receiver operating characteristic, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of diagnostic or risk category.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Variants in the *MTHFR* gene are associated with hyperhomocysteinemia, which in turn is considered a weak risk factor for VTE.⁴

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

The clinical utility of testing for homocysteine levels has not been established. There is a large body of literature on the association between homocysteine levels and coronary artery disease, and clinical trials have assessed the impact of lowering homocysteine levels. This body of evidence has indicated that testing or treating for homocysteinemia is not associated with improved outcomes.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The evidence for the association between *MTHFR* and VTE is not definitive. Some studies have shown an association,^{4,5,6,7,8} while others have not.^{9,10,11} One larger study (N=9231), the 2007 MEGA study, reported by Bezemer et al (2007), showed no association between the common *MTHFR* 677C>T variant with recurrent VTE.⁹ An RCT by der Heijer et al (2007) reported no reduction in VTE associated with the treatment of hyperhomocysteinemia.¹²

Gao et al (2020) evaluated the association between the *MTHFR* C677T and *MTHFR* A1298C polymorphisms and the risk of VTE in a meta-analysis of 32 case-control studies.¹³ Pooled results demonstrated an increased susceptibility to VTE with *MTHFR* C677T homozygotes (odds ratio [OR]=0.73; 95% confidence interval [CI], 0.60 to 0.89) and *MTHFR* C677T homozygotes/heterozygotes (OR=0.80; 95% CI, 0.71 to 0.90) compared to those without a mutation. When results were stratified by ethnicity, a significant association was maintained in the Asian population, but results were not significant for the White population. For the *MTHFR* A1298C polymorphism, there was no significant association between homozygotes (OR=0.90; 95% CI 0.66 to 1.23) or homozygotes/heterozygotes (OR=0.95; 95% CI, 0.83 to 1.07) compared to those without a mutation for susceptibility to VTE.

Section Summary: *MTHFR* Variant Testing

Published evidence on the utility of testing for *MTHFR* variants in patients who have or are at risk for VTE is limited. Given the available evidence, and lack of clinical utility for serum homocysteine testing in general, it is unlikely that testing for *MTHFR* will improve outcomes.

Factor V Leiden and Prothrombin Variant Testing

Clinical Context and Test Purpose

The purpose of genetic testing for variants in coagulation factor V and coagulation factor II is to provide a diagnostic option that is an alternative to or an improvement on existing tests, such as standard clinical management without testing, in patients who are asymptomatic with or without a personal or family history of VTE.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are asymptomatic with or without a personal or family history of VTE.

Interventions

The test being considered is genetic testing for variants in coagulation *factor V* and coagulation factor II.

Comparators

Comparators of interest include standard clinical management without testing.

Outcomes

The general outcomes of interest are morbid events and treatment-related morbidity.

The beneficial outcomes of a true-positive test result are an appropriate treatment for VTE. The beneficial outcome of a true-negative test result is potentially avoiding unnecessary treatment.

The harmful outcome of a false-positive result is having unnecessary treatment for VTE. The harmful outcome of a false-negative result is a potential delay in diagnosis and treatment.

Table 3. Outcomes of interest for individuals who are asymptomatic with or without a personal or family history of venous thromboembolism

Outcomes	Details	Timing
Morbid events	Evaluating outcomes such as recurrence risk and odds ratios for recurrent VTE	1–10 years
Treatment-related morbidity	Evaluating outcomes such as recurrence risk and odds ratios for morbidities associated with treatment of VTE, such as major bleeding	1–10 years

VTE: Venous thromboembolism

Study Selection Criteria

Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operating characteristic, area under receiver operating characteristic, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of diagnostic or risk category.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

The clinical validity and clinical utility are discussed for 3 distinct patient populations. They are:

- Individuals without a personal history of VTE
- Individuals with a personal history of VTE
- Family members of individuals with thrombophilia

Review of Evidence

Individuals Without a Personal History of Venous Thromboembolism

Factor V Leiden Variant

Individuals with FVL or prothrombin variants have an elevated risk of thrombosis compared with the general population. For individuals with the FVL variant, the risk may be 2- to 5-fold higher than that in the general population. In a retrospective study by Middeldorp et al (1998) of first-degree relatives of individuals with documented VTE and heterozygosity for FVL, those with an FVL variant had an absolute annual risk for a first VTE episode of 0.45%, compared with an annual incidence of 0.1% in those family members without the variant.¹⁴

Prothrombin G20210A Variant

For the prothrombin G20210A variant, risk also has been estimated to be 2 to 5 times greater than the general population.¹⁵ A meta-analysis by Gohil et al (2009) evaluated 79 studies and reported a combined relative risk of 3.0.¹⁶ Heterozygosity for the prothrombin G20210A variant also is associated

with an increased risk of upper-extremity thrombosis, estimated to be 5 times that of the general population.¹⁵

Individuals With a Personal History of Venous Thromboembolism

Factor V Leiden Variant

An Agency for Healthcare Research and Quality (AHRQ) report by Segal et al (2009) reviewed the evidence on recurrence risk for patients with a history of VTE and the FVL variant.¹⁷ For individuals with a heterozygous FVL variant, 13 studies compared recurrence risk to a variant with recurrence risk without a variant. Pooled analysis of these 13 studies yielded an OR of 1.56 (95% CI, 1.14 to 2.12) for recurrent VTE in patients with the FVL variant. For patients with a homozygous variant, 7 studies evaluated recurrence risk. Pooled odds for recurrent VTE in these studies was 2.65 (95% CI, 1.18 to 5.97).

Not all studies have reported an increased risk of recurrent VTE in patients with inherited thrombophilia. For example, the 2005 Leiden Thrombophilia Study followed 474 patients who had completed a course of anticoagulation for a mean of 7.3 years.¹⁸ All patients were tested for thrombophilia at baseline, with 20% found to have an FVL variant and 6% a prothrombin variant. Recurrence did not increase either for patients with an FVL variant or patients with a prothrombin variant. For FVL, there was a mild increase in recurrence risk that was not statistically significant on multivariate analysis (hazard ratio [HR], 1.3; 95% CI, 0.8 to 2.1).

One of the larger RCTs that was included in the above-mentioned AHRQ review was the 2008 influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin trial. This trial randomized 738 patients from 16 clinical centers to low-intensity or conventional-intensity anticoagulation.¹⁹ All patients were tested for inherited thrombophilias, and recurrence risk was calculated for patients with and without inherited thrombophilia. For patients with an FVL variant, there was no increased risk of recurrence over a mean follow-up of 2.3 years (HR=0.7; 95% CI, 0.2 to 2.6).

Prothrombin *G20210A* Variant

The AHRQ report by Segal et al (2009) identified 18 studies that evaluated recurrence risk in patients heterozygous for the prothrombin *G20210A* variant.¹⁷ Some of these studies included only heterozygotes, while others combined both heterozygotes and homozygotes. For 9 studies that included only heterozygotes, pooled odds for recurrent VTE was 1.45 (95% CI, 0.96 to 2.2). For 7 studies that did not specify homozygous or heterozygous, the combined odds were 0.73 (95% CI, 0.37 to 1.44).

The prothrombin *G20210A* variant is less common and, therefore, the number of patients evaluated in clinical trials and cohort studies is smaller than for FVL. In the 2008 influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin trial, the risk of recurrent VTE in those with the prothrombin *G20210A* variant could not be calculated because there were no recurrences among 60 patients with the variant.¹⁹ In the 2005 Leiden Thrombophilia Study, 29 patients had a prothrombin variant.¹⁸ For patients with a prothrombin variant, there was no increased risk of recurrence (HR=0.7; 95% CI, 0.3 to 2.0). Factors that predicted recurrence were mainly clinical variables, such as provoked versus unprovoked VTE, patient sex, and oral contraceptive use.

Family Members of Individuals with Thrombophilia

Factor V Leiden

The AHRQ (2009) report identified 9 studies that evaluated VTE risk in family members of a proband with a heterozygous variant. The pooled odds for future VTE was 3.49 (95% CI, 2.46 to 4.96). Six studies evaluated a total of 48 probands with homozygous FVL variants. The pooled odds for family members of homozygous individuals was 18 (95% CI, 7.8 to 40).

In a larger study of VTE risk in family members, Lijfering et al (2009) pooled results from 5 retrospective family studies of thrombophilia.²⁰ A total of 2479 relatives of patients with

thrombophilia who were themselves also tested for thrombophilia were included. For relatives with FVL variants, the annual incidence of thrombosis was 0.49% (95% CI, 0.39% to 0.60%). In relatives without thrombophilia, the incidence of VTE was approximately 0.05% per year, and the adjusted relative risk for VTE in relatives with an FVL variant was 7.5 (95% CI, 4.4 to 12.6). In patients treated with anticoagulation, the annual risk of major bleeding was 0.29% (95% CI, 0.03% to 1.04%).

Prothrombin Variants

Evidence on VTE risk for family members of individuals with a prothrombin variant is lower than for FVL, with 5 studies identified by Segal et al (2009) in the AHRQ report evaluating heterozygotes and only 1 study evaluating homozygotes.¹⁷ For heterozygote probands, family members had an odds for future VTE of 1.89 (95% CI, 0.35 to 10.2).

In the Lijfering et al (2009) family study, relatives with prothrombin variants had an annual VTE incidence of 0.34% (95% CI, 0.22% to 0.49%).²⁰ In relatives without thrombophilia, the incidence of VTE was approximately 0.05% per year, and the adjusted relative risk for VTE in relatives with a prothrombin variant was 5.2 (95% CI, 2.8 to 9.7).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

The clinical utility of genetic testing for thrombophilia is considered in the context of overall VTE risk and the risk-benefit ratio of treatment, primarily with anticoagulants. The following factors are part of the decision-making process on whether to test for:

- Overall low incidence of thromboembolism in the general population.
- Modest increased risk associated with most forms of inherited thrombophilia, meaning that the absolute risk of thrombosis in patients with inherited thrombophilia is still relatively low.
- Potential risk of prophylactic treatment, especially bleeding risk with anticoagulation. This risk may outweigh the benefit in patients with a relatively low absolute risk of thrombosis.

Some have suggested that functional testing for activated protein C resistance may be more clinically relevant than genetic testing for FVL in persons with an increased risk of thromboembolism.²¹

Individuals Without a Personal History of Venous Thromboembolism

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No published studies identified have directly evaluated the clinical utility of screening asymptomatic individuals for inherited thrombophilia.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

It is unlikely that screening asymptomatic individuals will result in a net health benefit because prophylactic anticoagulation is likely to do more harm than benefit. Risk of major bleeding with full anticoagulation is approximately 1% per year; therefore, the number of major bleeding episodes may far exceed the number of VTEs prevented. Knowledge of thrombophilia status may lead to behaviors that reduce VTE risk, such as avoidance of prolonged immobility, but this is unproven.

Individuals With a Personal History of Venous Thromboembolism

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Case-Control Studies

The 2008 MEGA study was a large, population-based, case-control study that evaluated whether testing for thrombophilia in patients with the first episode of VTE was associated with a decrease in recurrence rate.²² The MEGA database was comprised of 5051 patients between the ages of 18 and 70 years with their first episode of VTE. Researchers identified 197 patients with a recurrence of VTE and matched these patients by age, sex, year of VTE, and geographic region with 324 patients who were free of recurrent VTE. Recurrence rates for VTE were similar in patients tested for thrombophilia compared with patients not tested (OR=1.2; 95% CI, 0.9 to 1.8). The presence of FVL or the prothrombin *G20210A* variant was not associated with an increased recurrence rate (OR=0.8; 95% CI, 0.3 to 2.6).

Cohort Studies

Mahajerin et al (2014) conducted a single-center, retrospective cohort study of pediatric patients (mostly adolescents) who presented with VTE (88% deep vein thrombosis) "to help clarify the role of thrombophilia testing in pediatric VTE."²³ Of 392 inpatients and outpatients, thrombophilia tests (FVL; prothrombin gene variant; *MTHFR*; protein C, protein S, and antithrombin activity; antiphospholipid antibodies; plasminogen activator inhibitor-1 levels and variant testing) were ordered in 310 (79%) patients. Of these, testing found 37 positive (12%) results. Given that most patients had at least 1 risk factor for VTE and, as noted by the authors, the "presence or absence of thrombophilia rarely influences VTE management," this evidence does not support thrombophilia genetic testing in pediatric patients who present with VTE.

Cross-Sectional Studies

A study by Hindorff et al (2009) surveyed 112 primary care physicians about the impact of FVL testing in patients with VTE.²⁴ Most physicians indicated that they would use results in clinical practice, with 82% reporting that they would use results to counsel patients on risk of recurrence and 67% reporting that they would use results to make treatment changes. However, physician confidence in their decisions was not high, including decisions to order FVL testing.

Family Members of Individuals with Thrombophilia

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

There are no comparative trials assessing testing with no testing in relatives of individuals who have thrombophilia.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The clinical utility of testing depends on the balance between the benefit of altering management as a result of knowledge of variant status and the risk of bleeding with the intensification of anticoagulation. This risk-benefit is unknown, as previously discussed. The absolute risk of VTE remains low, even in patients with inherited thrombophilia, and potential risks of prophylactic treatment with anticoagulants may outweigh potential benefits.

Section Summary: Factor V Leiden and Prothrombin Variant Testing

The clinical validity of genetic testing for thrombophilia has been evaluated by assessing the association between thrombophilia status and VTE in various clinical populations. For populations discussed herein, the clinical validity has been reported in numerous case-control and cohort studies. The presence of an FVL or a prothrombin gene variant is associated with an increased risk for subsequent VTE across a number of populations. However, the magnitude of the association is relatively modest, with ORs most commonly between 1 and 2, except for family members of individuals with inherited thrombophilia, for whom an OR is 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, such as anticoagulation, have defined the 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 in decisions concerning the initiation of prophylactic anticoagulation or the length of anticoagulation treatment.

Pregnancy and Other High-Risk Conditions

Clinical Context and Test Purpose

The purpose of genetic testing for variants in coagulation *factor V* and coagulation *factor II* is to provide a diagnostic option that is an alternative to or an improvement on existing tests, such as standard clinical management without testing, in patients who are asymptomatic with increased VTE risk (e.g., due to pregnancy).

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are asymptomatic with increased VTE risk (e.g., due to pregnancy).

Interventions

The test being considered is genetic testing for variants in coagulation FVL and coagulation factor II.

Comparators

Comparators of interest include standard clinical management without testing.

Outcomes

The general outcomes of interest are morbid events and treatment-related morbidity.

Table 4. Outcomes of interest for individuals who are asymptomatic with increased venous thromboembolism risk (e.g., due to pregnancy)

Outcomes	Details	Timing
Morbid events	Evaluating outcomes such as risk of pregnancy loss or recurrence of VTE	9 months to 10 years
Treatment-related morbidity	Evaluating outcomes such as risk and odds ratios for morbidities associated with treatment of VTE, oral contraceptives, or hormone replacement therapy	9 months to 10 years

VTE: Venous thromboembolism

Study Selection Criteria

Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.

- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operating characteristic, area under receiver operating characteristic, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of diagnostic or risk category.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Pregnancy

Evidence of the risk of recurrent pregnancy loss in women with FVL or a prothrombin gene variant comprises primarily retrospective case-control and cohort studies. Several case-control studies have reported a higher prevalence of FVL in women with recurrent, unexplained pregnancy loss compared with controls (OR range, 2 to 5).²⁵ Retrospective cohort studies have found a 2- to 3-fold increased risk of pregnancy loss in FVL heterozygous carriers; homozygotes have a 2-fold higher risk than heterozygous carriers. Risk of pregnancy loss for heterozygous carriers is highest during the second and third trimesters.

A systematic review by Bradley et al (2012) analyzed evidence on the association between FVL and prothrombin variants with pregnancy loss.²⁶ They identified the highest quality studies, which were cohort studies that: (1) excluded patients with other causes of VTE, (2) tested eligible women for thrombophilia at baseline, (3) reported on subsequent pregnancy outcomes, and (4) compared rates of pregnancy loss between carriers and noncarriers. Four cohort studies met all 4 criteria; these studies primarily included patients with FVL variants. Two of the 4 studies reported a significantly increased rate of recurrence for carriers and 2 did not. Pooled analysis of these 4 studies yielded significantly increased odds for recurrent pregnancy loss in carriers (OR=1.93; 95% CI, 1.21 to 3.09).

A systematic review by Liu et al (2021) evaluated the association between hereditary thrombophilias, including FVL and prothrombin *G20210A*, and recurrent pregnancy loss.²⁷ Observational studies were included if they compared at least 2 groups of patients – 1 with hereditary thrombophilia and 1 without hereditary thrombophilia. There were 89 studies included in the analysis, with 81 evaluating the risk of FVL and 64 evaluating the risk of prothrombin *G20210A* on recurrent pregnancy loss. Pooled analysis of FVL demonstrated an increased risk for recurrent pregnancy loss with the variant (OR=2.44; 95% CI, 1.96 to 3.03). Pooled analysis for prothrombin *G20210A* also demonstrated an increased risk for recurrent pregnancy loss with the variant (OR=2.08; 95% CI, 1.61 to 2.68). Both analyses were limited by high heterogeneity across the included studies.

A number of other meta-analyses have concluded that the risk of pregnancy loss for patients who are heterozygous for the prothrombin *G20210A* variant also is increased, in the 2- to 3-fold range.¹⁵

Oral Contraceptives

Oral contraceptive use alone is associated with an approximately 4-fold increase in the risk of thrombosis; in combination with FVL, risk multiplies 34-fold in heterozygotes and more than 100-fold in homozygotes. However, the absolute incidence estimated in a study by Vanderbroucke et al (1994) was 28 thrombotic events per 10,000 per year, 2% of which were estimated to be fatal.²⁸

Hormone Replacement Therapy

Women using hormone replacement therapy have a 2- to 4-fold increased risk of thrombosis.²⁵ Absolute risk is low and may be restricted to the first year of use. Limited data have suggested that

women using selective estrogen receptor modulators (e.g., tamoxifen) may have a similarly increased risk.²⁵

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No studies have directly evaluated the clinical utility of thrombophilia testing in pregnant women.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The clinical utility of testing depends on the efficacy of potential treatments in decreasing fetal loss versus the risks of treatment. Potential treatments in pregnancy include aspirin, low-dose unfractionated or low-molecular-weight heparin, and full-dose heparin. Benefits of these treatments in reducing pregnancy loss are questionable. At least 2 RCTs (both 2010) have reported that there is no significant reduction in risk with aspirin or heparin therapy.^{29,30} Additionally, several meta-analyses have reported that evidence is insufficient to conclude that these interventions reduce recurrent pregnancy loss in patients with FVL or prothrombin variants.^{26,31,32} In contrast, the real risks of anticoagulation include bleeding, thrombocytopenia, and allergic reactions. There also are costs and inconveniences associated with these treatments.

Bradley et al (2012) reviewed the evidence on the clinical utility of testing for heritable thrombophilias in pregnancy and found it adequate to conclude there are no safe and effective treatments to reduce recurrent pregnancy loss in women with inherited thrombophilia.²⁶ The certainty of the evidence that treatment resulted in net harm was moderate.

The clinical utility of testing for prothrombin-related thrombophilia was evaluated in a secondary analysis of data from the Stillbirth Collaborative Research Network, a population-based case-control study of stillbirth. Testing for FVL, prothrombin *G20210A*, *MTHFR* C677T, and A1298C, and plasminogen activating inhibitor-1 4G/5G variants was done on maternal and fetal (or placental) DNA from singleton pregnancies. There was increased odds of stillbirth for maternal homozygous FVL variant (2/488 [0.4%] versus 1/1380 [0.0046%]; OR=87.44; 95% CI, 7.88 to 970.92). However, there were no significant differences in the odds of stillbirth for any other maternal thrombophilia, even after stratified analyses.³³

An open-label, international, multicenter randomized trial, reported by Rodger et al (2014), evaluated antepartum use of the low-molecular-weight heparin, dalteparin, in women with the prothrombin variant.³⁴ The intervention did not reduce the occurrence of VTE, pregnancy loss, or placenta-mediated pregnancy complications, and was associated with an increased risk of minor bleeding.

The current chapter (updated in 2021) on prothrombin-related thrombophilia in *GeneReviews* concluded: "Once the *F2* 20210G>A variant has been identified in a family member, prenatal testing for a pregnancy at increased risk for prothrombin thrombophilia and preimplantation genetic testing is possible. Differences in perspective may exist among medical professionals and within families

regarding the use of prenatal testing. While most centers would consider the use of prenatal testing to be a personal decision, discussion of these issues may be helpful.¹⁵

Section Summary: Pregnancy and Other High-Risk Conditions

Evidence of the risk of recurrent pregnancy loss in women with FVL or a prothrombin gene variant comprises primarily retrospective case-control and cohort studies. No studies have directly evaluated the clinical utility of thrombophilia testing in pregnant women, and the clinical utility of testing for FVL or prothrombin variants in pregnant women has not been demonstrated.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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

2012 Input

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

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 5).³⁵

Table 5. 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)." "Thrombophilia testing is costly and can result in harm to patients if the duration of anticoagulation is inappropriately prolonged or if patients

Society	Year	Recommendation
		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." "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." "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 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 (e.g., parent, sibling) with a history of high-risk thrombophilia.

Table 6. 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 7 summarizes the guidance statements for each question considered in the document.

Table 7. 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	Do not test for thrombophilia in asymptomatic family members of patients with VTE or hereditary	If a woman contemplating pregnancy has a first degree relative with VTE and a known hereditary thrombophilia, test

Question	Guidance Statement	Limits/Exceptions
contemplating pregnancy be tested for thrombophilia?	thrombophilia who are contemplating pregnancy.	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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 8.

Table 8. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Unpublished</i>			
NCT02841085	Search for New Mutations Genetic Predisposing to an Increased Risk Venous Thromboembolic Disease Idiopathic. Study "FIT GENETIQUE"	613	May 2021
NCT02685800	A Registry on Outcomes in Women Undergoing Assisted Reproductive Techniques After Recurrent Failures	624	Sep 2020
NCT02385461	Study on Antithrombotic Prevention in Thrombophilia and Pregnancy Loss (OTTILIA)	108	Dec 2020
NCT02407730	Effects of Thrombophilia on the Outcomes of Assisted Reproduction Technologies	687	May 2018
NCT02986594	Diagnosis and Treatment Strategy of Recurrent Spontaneous Abortion Associated With Thrombophilia	600	Oct 2019

NCT: national clinical trial.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	81240	F2 (prothrombin, coagulation factor II) (e.g., hereditary hypercoagulability) gene analysis, 20210G>A variant
	81241	F5 (coagulation factor V) (e.g., hereditary hypercoagulability) gene analysis, Leiden variant
	81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)
	81400	Molecular Pathology Procedure Level 1
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
01/11/2013	BCBSA Medical Policy adoption
03/30/2015	Policy revision with position change effective 5/29/2015
05/29/2015	Policy revision with position change
03/01/2017	Policy revision without position change
07/01/2017	Policy revision without position change
07/01/2018	Policy revision without position change
07/01/2019	Policy revision without position change
07/01/2020	Annual review. No change to policy statement. Literature review updated.
07/01/2021	Annual review. No change to policy statement. Literature review updated.
07/01/2022	Annual review. No change to policy statement. Policy guidelines and literature review updated.
07/01/2023	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	AFTER
<p>Genetic Testing for Inherited Thrombophilia 2.04.82</p> <p>Policy Statement:</p> <p>I. Genetic testing for inherited thrombophilia, including testing for the <i>factor V Leiden</i> variant, prothrombin gene variants, and variants in the 5,10-methylenetetrahydrofolate reductase (<i>MTHFR</i>) gene, is considered investigational.</p>	<p>Genetic Testing for Inherited Thrombophilia 2.04.82</p> <p>Policy Statement:</p> <p>I. Genetic testing for inherited thrombophilia, including testing for the <i>factor V Leiden</i> variant, prothrombin gene variants, and variants in the 5,10-methylenetetrahydrofolate reductase (<i>MTHFR</i>) gene, is considered investigational.</p>