Genetic Testing for Inherited Thrombophilia

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Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

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

Policy Guidelines

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

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

Table PG1. Nomenclature to Report on Variants Found in DNA

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

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

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

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

GENETIC COUNSELING

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

Background/Overview

VENOUS THROMBOEMBOLISM

The overall U.S. incidence of venous thromboembolism (VTE) is approximately 1 per 1000 person-years, and the lifetime clinical prevalence is approximately 5%, accounting for 100,000 deaths annually. Risk is strongly age-related, with the greatest risk in older populations. VTE also recurs frequently; estimated cumulative incidence of first VTE recurrence is 30% at 10 years. These figures do not separate patients with known predisposing conditions from those without.

Risk factors for thrombosis include a variety of 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 of preventing and treating VTE. Pregnancy is associated with a 5- to 10-fold increase in VTE risk, and absolute VTE risk in pregnancy is estimated to be 1 to 2 per 1000 deliveries. In women with a history of pregnancy-related VTE, risk of recurrent VTE with subsequent pregnancies is increased greatly at approximately 100-fold.

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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 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 (FVL variant),
- Prothrombin (factor II) gene variant (G20210A),
- Protein C deficiency,
- Protein S deficiency,
- Prothrombin deficiency,
- Hyper-homocysteinemia (*MTHFR* variant).

The most common type of inherited thrombophilia is FVL, which accounts for up to 50% of inherited thrombophilia syndromes. In unselected patients with an idiopathic thrombosis, the incidence of FVL is 17% to 24%, compared with a rate of 5% to 6% in normal controls. The prothrombin G20210A variant is found less commonly, in approximately 5% to 8% of unselected patients who have thrombosis compared with 2% to 2.5% of normal controls.

Genetic Testing
Genetic testing for gene variants associated with thrombophilias is available for FVL, the prothrombin G20210A variant, and *MTHFR*. Genetic testing for inherited thrombophilia can be considered in several clinical situations. Clinical situations addressed herein include the following:

- Assessment of thrombosis risk in asymptomatic patients (screening for inherited thrombophilia);
- Evaluation of a patient with established thrombosis, for consideration of change in anticoagulant management based on results;
- Evaluation of close relatives of patients with documented inherited thrombophilia or with a clinical and family history 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).

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FDA or Other Governmental Regulatory Approval

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

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

Table 1. Genetic Tests for Thrombophilia Cleared by FDA

Test	Manufacturer	Location	Date Cleared	510(k) No.
IMPACT Dx™‡ Factor V Leiden and Factor II Genotyping Test	Agena Bioscience[a]	San Diego, CA	06/14	K132978
Invader®‡ Factor II, V, and MTHFR (677, 1298) tests	Hologic	Marlborough, MA	04-06/11	K100943, K100980, K100987, K100496
VeraCode®‡ Genotyping Test for Factor V and Factor II	Illumina	San Diego, CA	04/28/10	K093129
eSensor®‡ Thrombophilia Risk Test, FII-FV, FII, FV and MTHFR (677, 1298) Genotyping Tests	GenMark Dx[b]	Carlsbad, CA	04/22/10	K093974
INFINITI™‡ System Assay for Factor II & Factor V	AutoGenomics	Carlsbad, CA	02/07/07	K060564
Xpert®‡ Factor II and Factor V Genotyping Assay	Cepheid	Sunnyvale, CA	09/18/09	K082118
Verigene®‡ Factor F2, F5, and MTHFR Nucleic Acid Test	Nanosphere	Northbrook, IL	10/11/07	K070597
Factor V Leiden Kit	Roche Diagnostics	Indianapolis, IN	12/17/03	K033607
Factor II (Prothrombin) G20210A Kit	Roche Diagnostics	Indianapolis, IN	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*.

On April 6, 2017, FDA permitted marketing of 23andMe Personal Genome Service Genetic Health Risk (GHR) tests for 10 diseases or conditions. These direct-to-consumer tests are the first authorized by FDA that provide information on an individual's genetic predisposition to certain medical diseases or conditions, which may help to make decisions about lifestyle choices or to inform discussions with a health care professional. The 23andMe GHR tests work by isolating DNA from a saliva sample, which is then tested for more than 500,000 genetic variants. The presence or absence of some of these variants is associated with

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an increased risk for developing any 1 of 10 diseases or conditions. Testing for hereditary thrombophilia (2 variants in the *F5* and *F2* genes; relevant for European descent) is included.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes). The following is a summary of the key literature.

MTHFR VARIANT TESTING

Variants in the *MTHFR* gene are associated with hyperhomocysteinemia, which in turn is considered a weak risk factor for VTE. However, clinical utility of testing for homocysteine levels has not been established. There is a large body of literature on the association of homocysteine levels with 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.

The evidence for the association between *MTHFR* and VTE is not definitive. Some studies have shown an association, while others have not. One larger study (N=9231), the 2007 MEGA study, showed no association between the *MTHFR* 677C>T variant with recurrent VTE. A 2007 randomized controlled trial (RCT) reported no reduction in VTE associated with treatment of hyperhomocysteinemia.

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

Analytic Validity
Analytic validity refers to the accuracy of detecting a specific variant when it is present and excluding it when absent.

For a 2009 evidence review prepared for the Agency for Healthcare Research and Quality (AHRQ), researchers performed a comprehensive evaluation of analytic validity studies. Forty-one studies compared

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genetic testing for FVL with a reference standard. Concordance between the tests was high, ranging from 93% to 100%, and was 100% in most studies. This AHRQ report also reviewed 23 studies on the concordance of prothrombin gene variants with a reference standard and found that nearly all studies reported a 100% concordance. Twelve studies reported multiplex methods to test simultaneously for both FVL and the prothrombin G20210A variant, all of which reported 100% concordance with reference standards.

Bradley et al (2012) reviewed the analytic validity of FVL and prothrombin variant testing in pregnancy as reported in individual studies and meta-analyses. For studies performed in the United States, the combined analytic sensitivity and specificity for FVL testing exceeded 99%. For the prothrombin G20210A variant, the analytic sensitivity was 98.4% and the analytic specificity was 99.7%.

Subsection Summary: Analytic Validity
The analytic validity of genetic testing for inherited thrombophilia is high. The analytic sensitivity and specificity for FVL testing both exceed 99%, and the analytic sensitivity and specificity for the prothrombin G20210A variant both exceed 98%.

Clinical Validity
Clinical validity (and clinical utility) will be discussed for 4 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;
- Pregnancy and other high-risk situations.

The clinical validity of testing for inherited thrombophilias is best determined by the predictive ability of the test for future thromboembolic events, both in patients with and without prior VTE. Highest quality evidence for this question comprises prospective cohort studies in which patients with and without the variant are followed for development of VTE. A few studies are prospective, nested within RCTs, in which patients with and without variants are compared.

Individuals Without a Personal History of VTE
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 1 retrospective study (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.

For the prothrombin G20210A variant, risk also has been estimated to be 2 to 5 times greater than the general population. In a 2009 meta-analysis of 79 studies, combined relative risk was 3.0. 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.

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Individuals With a Personal History of VTE

Factor V Leiden
The 2009 AHRQ report reviewed the evidence on recurrence risk for patients with a history of VTE and the FVL variant. 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 odds ratio (OR) of 1.56 (95% confidence interval [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 OR 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 (LETS) followed 474 patients who had completed a course of anticoagulation for a mean of 7.3 years. 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 a FVL variant or for 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). For the prothrombin G20210A 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.

A larger RCT included in the AHRQ review was the 2008 ELATE trial, which randomized 738 patients from 16 clinical centers to low-intensity versus conventional-intensity anticoagulation. 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 2009 AHRQ evidence report identified 18 studies that evaluated recurrence risk in patients heterozygous for the prothrombin G20210A variant. Some of these studies included only heterozygotes, and others combined both heterozygotes and homozygotes. For 9 studies that included only heterozygotes, pooled OR 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 OR was 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 ELATE trial, 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. In the LETS study, 29 patients had a prothrombin variant. 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.

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Family Members of Individuals With Thrombophilia

Factor V Leiden
The 2009 AHRQ report identified 9 studies that evaluated VTE risk in family members of a proband with a heterozygous variant. The pooled OR 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 OR 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. A total of 2479 relatives of patients with thrombophilia who were themselves also tested for thrombophilia were included. For relatives with FVL variants, annual incidence of thrombosis was 0.49% (95% CI, 0.39% to 0.60%). In relatives without thrombophilia, incidence of VTE was approximately 0.05% per year, and 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, 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 AHRQ evaluating heterozygotes and only 1 study evaluating homozygotes. For heterozygote probands, family members had an OR for future VTE of 1.89 (95% CI, 0.35 to 10.2).

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

Pregnancy and Other High-Risk Conditions

Pregnancy
Evidence of the risk of recurrent pregnancy loss in women with FVL or a prothrombin gene variant comprises primarily retrospective case-control studies 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, 2-5). 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 2012 systematic review by Bradley et al analyzed evidence on the association between FVL and prothrombin variants with pregnancy loss. 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

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carriers and 2 did not. Pooled analysis of these 4 studies yielded a significantly increased OR for recurrent pregnancy loss in carriers (OR=1.93; 95% CI, 1.21 to 3.09).

A number of 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.

Oral Contraceptives
Oral contraceptive use alone is associated with an approximately 4-fold increase in 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 by 1 study published in 1994 was 28 thrombotic events per 10,000 per year, 2% of which were estimated to be fatal.

Hormone Replacement Therapy
Women using hormone replacement therapy have a 2- to 4-fold increased risk of thrombosis. 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.

Subsection Summary: Clinical Validity
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, magnitude of the association is relatively modest, with OR most commonly between 1 and 2, except for family members of individuals with inherited thrombophilia, for whom OR are somewhat higher.

Clinical Utility
The clinical utility of genetic testing depends on the ability of testing results to change management that results in improved outcomes. 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 increased risk of thromboembolism.

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Individuals Without a Personal History of VTE

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

The 2008 MEGA study was a large, population-based, case-control study that evaluated whether testing for thrombophilia in patients with a first episode of VTE was associated with a decrease in recurrence rate. The MEGA database comprised 5051 patients between the ages of 18 and 70 years with a 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 rate for VTE was similar in patients tested for thrombophilia compared with patients who were 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).

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." 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%); of these, testing found positive 37 (12%) positive 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.

A 2009 study surveyed 112 primary care physicians about the impact of FVL testing in patients with VTE. 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

There are no comparative trials of testing versus no testing in relatives of individuals with thrombophilia. 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 intensification of anticoagulation. This risk-benefit is unknown, as previously discussed. Absolute risk of VTE remains low, even in patients with inherited thrombophilia, and potential risks of prophylactic treatment with anticoagulants may outweigh potential benefits.

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Pregnancy and Other High-Risk Conditions

No studies have directly evaluated the clinical utility of thrombophilia testing in pregnant women. 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. 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. In contrast, the real risks of anticoagulation include bleeding, thrombocytopenia, and allergic reactions. There also are costs and inconvenience 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. 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 an increased odds of stillbirth for maternal homozygous FVL variant (2/488 [0.4%] vs 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.

An open-label, international, multicenter randomized trial (2014) of antepartum use of low-molecular weight heparin dalteparin included women with the prothrombin variant. 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 2014) on prothrombin-related thrombophilia in *GeneReviews* concluded: “Although technically possible, prenatal diagnosis and preimplantation genetic diagnosis (PGD) are rarely, if ever, performed because the 20210G>A allele only increases the relative risk for thrombophilia and is not predictive of a thrombotic event.”

Section Summary: Clinical Utility

The clinical utility of testing for FVL or prothrombin variants has not been demonstrated. Although the presence of inherited thrombophilia increases 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 a 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.

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SUMMARY OF EVIDENCE

For individuals who are asymptomatic with or without a personal or family history of VTE or with increased VTE risk (e.g., due to pregnancy) who receive genetic testing for variants in *MTHFR* gene, *F5*, and *F2*, the evidence includes 1 large RCT, prospective cohort analyses, retrospective family studies, case-control studies, and meta-analyses. Relevant outcomes are morbid events and treatment-related morbidity. The analytic validity of genetic testing for inherited thrombophilia is high. The analytic sensitivity and specificity for FVL testing both exceed 99%, and the analytic sensitivity and specificity for the prothrombin G20210A variant both exceed 98%. The clinical validity of genetic testing has been demonstrated by the presence of an FVL or a prothrombin gene variant testing and an association with an increased risk for subsequent VTE across various populations studied. 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 ORs are somewhat higher. The clinical utility of testing for FVL or prothrombin variants has not been demonstrated. Although the presence of inherited thrombophilia increases risk for subsequent VTE events, the increase is modest and the absolute risk of thrombosis remains low. Available prophylactic treatments (e.g., anticoagulation) have defined risks of major bleeding and other adverse events that may outweigh the reduction in VTE and therefore result in a net harm. Currently available evidence has not defined a role for thrombophilia testing for decisions on initiation of prophylactic anticoagulation or on the length of anticoagulation treatment. For *MTHFR* testing, clinical validity and clinical utility of genetic testing is uncertain. Because clinical utility of testing for elevated serum homocysteine itself has not been established, utility of genetic testing also has not been established. The evidence is insufficient to determine the effects of the technology on health outcomes.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, “Genetic Testing for Inherited Thrombophilia”, 2.04.82, 5:2017.
2. Heit JA, Silverstein MD, Mohr DN, et al. The epidemiology of venous thromboembolism in the community. Thromb Haemost. Jul 2001;86(1):452-463. PMID 11487036
3. Baglin T, Gray E, Greaves M, et al. Clinical guidelines for testing for heritable thrombophilia. Br J Haematol. Apr 2010;149(2):209-220. PMID 20128794
4. Bauer KA, Lip GYH. Evaluation of the patient with established venous thrombosis. In: Leung LLK, Landaw SA, eds. Up-To-Date Online, 2011.
5. American College of Obstetricians Gynecologists, Women's Health Care Physicians. ACOG Practice Bulletin No. 138: Inherited thrombophilias in pregnancy. Obstet Gynecol. Sep 2013;122(3):706-717. PMID 23963422
6. Russo PD, Damante G, Pasca S, et al. Thrombophilic mutations as risk factor for retinal vein occlusion: a case-control study. Clin Appl Thromb Hemost. May 2015;21(4):373-377. PMID 24569626
7. Supanc V, Sonicki Z, Vukasovic I, et al. The role of classic risk factors and prothrombotic factor gene mutations in ischemic stroke risk development in young and middle-aged individuals. J Stroke Cerebrovasc Dis. Mar 2014;23(3):e171-176. PMID 24189452
8. Zhou X, Qian W, Li J, et al. Who are at risk for thromboembolism after arthroplasty? A systematic review and meta-analysis. Thromb Res. Nov 2013;132(5):531-536. PMID 24074702
9. Li P, Qin C. Methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms and susceptibility to ischemic stroke: a meta-analysis. Gene. Feb 10 2014;535(2):359-364. PMID 24140489
10. Bezemer ID, Doggen CJ, Vos HL, et al. No association between the common MTHFR 677C->T polymorphism and venous thrombosis: results from the MEGA study. Arch Intern Med. Mar 12 2007;167(5):497-501. PMID 17353498
11. Joachim E, Goldenberg NA, Bernard TJ, et al. The methylenetetrahydrofolate reductase polymorphism (MTHFR c.677C>T) and elevated plasma homocysteine levels in a U.S. pediatric population with incident thromboembolism. Thromb Res. Aug 2013;132(2):170-174. PMID 23866722

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12. Chatterjee T, Gupta N, Choudhry VP, et al. Prediction of ischemic stroke in young Indians: is thrombophilia profiling a way out? Blood Coagul Fibrinolysis. Jun 2013;24(4):449-453. PMID 23337710
13. den Heijer M, Willems HP, Blom HJ, et al. Homocysteine lowering by B vitamins and the secondary prevention of deep vein thrombosis and pulmonary embolism: A randomized, placebo-controlled, double-blind trial. Blood. Jan 1 2007;109(1):139-144. PMID 16960155
14. Segal JB, Brotman DJ, Emadi A, et al. Outcomes of genetic testing in adults with a history of venous thromboembolism. Evid Rep Technol Assess (Full Rep). Jun 2009(180):1-162. PMID 20629476
15. 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
16. Middeldorp S, Henkens CM, Koopman MM, et al. The incidence of venous thromboembolism in family members of patients with factor V Leiden mutation and venous thrombosis. Ann Intern Med. Jan 1 1998;128(1):15-20. PMID 9424976
17. Kujovich JL. Prothrombin-Related Thrombophilia. GeneReviews. 2014. PMID 20301327
18. Gohil R, Peck G, Sharma P. The genetics of venous thromboembolism. A meta-analysis involving approximately 120,000 cases and 180,000 controls. Thromb Haemost. Aug 2009;102(2):360-370. PMID 19652888
19. Christiansen SC, Cannegieter SC, Koster T, et al. Thrombophilia, clinical factors, and recurrent venous thrombotic events. JAMA. May 18 2005;293(19):2352-2361. PMID 15900005
20. Kearon C, Julian JA, Kovacs MJ, et al. Influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin: results from a randomized trial. Blood. Dec 1 2008;112(12):4432-4436. PMID 18791166
21. Lijfering WM, Brouwer JL, Veeger NJ, et al. Selective testing for thrombophilia in patients with first venous thrombosis: results from a retrospective family cohort study on absolute thrombotic risk for currently known thrombophilic defects in 2479 relatives. Blood. May 21 2009;113(21):5314-5322. PMID 19139080
22. Press RD, Bauer KA, Kujovich JL, et al. Clinical utility of factor V leiden (R506Q) testing for the diagnosis and management of thromboembolic disorders. Arch Pathol Lab Med. Nov 2002;126(11):1304-1318. PMID 12421138
23. Vandenbroucke JP, Koster T, Briet E, et al. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. Lancet. Nov 26 1994;344(8935):1453-1457. PMID 7968118
24. Pruller F, Weiss EC, Raggam RB, et al. Activated protein C resistance assay and factor V Leiden. N Engl J Med. Aug 14 2014;371(7):685-686. PMID 25119624
25. Coppens M, Reijnders JH, Middeldorp S, et al. Testing for inherited thrombophilia does not reduce the recurrence of venous thrombosis. J Thromb Haemost. Sep 2008;6(9):1474-1477. PMID 18540999
26. Mahajerin A, Obasaju P, Eckert G, et al. Thrombophilia testing in children: a 7 year experience. Pediatr Blood Cancer. Mar 2014;61(3):523-527. PMID 24249220
27. 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
28. Clark P, Walker ID, Langhorne P, et al. SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage. Blood. May 27 2010;115(21):4162-4167. PMID 20237316
29. Kaandorp SP, Goddijn M, van der Post JA, et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. N Engl J Med. Apr 29 2010;362(17):1586-1596. PMID 20335572
30. Skeith L, Carrier M, Kaaja R, et al. A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia. Blood. Mar 31 2016;127(13):1650-1655. PMID 26837697
31. de Jong PG, Kaandorp S, Di Nisio M, et al. Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia. Cochrane Database Syst Rev. Jul 04 2014(7):CD004734. PMID 24995856
32. Silver RM, Saade GR, Thorsten V, et al. Factor V Leiden, prothrombin G20210A, and methylene tetrahydrofolate reductase mutations and stillbirth: the Stillbirth Collaborative Research Network. Am J Obstet Gynecol. Oct 2016;215(4):468 e461-468 e417. PMID 27131585
33. Rodger MA, Hague WM, Kingdom J, et al. Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial. Lancet. Nov 08 2014;384(9955):1673-1683. PMID 25066248
34. EGAPP Working Group. Recommendations from the EGAPP Working Group: routine testing for Factor V Leiden (R506Q) and prothrombin (20210G>A) mutations in adults with a history of idiopathic venous thromboembolism and their adult family members. Genet Med. Jan 2011;13(1):67-76. PMID 21150787

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35. 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
36. 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
37. 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
38. American Board of Internal Medicine Foundation. Choosing Wisely. 2017; http://www.choosingwisely.org/.

Policy History

Original Effective Date: 12/19/2012
Current Effective Date: 12/20/2017

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

Next Scheduled Review Date: 12/2018

Coding

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Genetic Testing for Inherited Thrombophilia

Policy # 00333
Original Effective Date: 12/19/2012
Current Effective Date: 12/20/2017

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

Code Type	Code
CPT	81240, 81241, 81291, 81401
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

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

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

Appendix Table 1. Categories of Genetic Testing Addressed in Medical Policy 00333

Category	Addressed
1. Testing of an affected individual's germline to benefit the individual	
1a. Diagnostic	X
1b. Prognostic	
1c. Therapeutic	
2. Testing cancer cells from an affected individual to benefit the individual	
2a. Diagnostic	
2b. Prognostic	
2c. Therapeutic	
3. Testing an asymptomatic individual to determine future risk of disease	X
4. Testing of an affected individual's germline to benefit family members	
5. Reproductive testing	
5a. Carrier testing: preconception	

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5b. Carrier testing: prenatal
5c. In utero testing: aneuploidy
5d. In utero testing: familial variants
5e. In utero testing: other
5f. Preimplantation testing with in vitro fertilization

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