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

Policy Guidelines

Genetic 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

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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

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

Coding
The following CPT codes are specific for this testing:
2.04.82 Genetic Testing for Inherited Thrombophilia
Page 2 of 18

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

**Related Policies**

- Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease and Venous Thromboembolic Disease

**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. Commercial thrombophilia genetic tests are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

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

**Table 1. Genetic Tests for Thrombophilia Cleared by the FDA**

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Cleared</th>
<th>510(k) No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPACT Dx™ Factor V Leiden and Factor II Genotyping Test</td>
<td>Agena Bioscience*</td>
<td>06/14</td>
<td>K132978</td>
</tr>
<tr>
<td>Invader® Factor II, V, and MTHFR (677, 1298) tests</td>
<td>Hologic</td>
<td>04-06/11</td>
<td>K100943, K100980, K100987, K100496</td>
</tr>
</tbody>
</table>
### 2.04.82 Genetic Testing for Inherited Thrombophilia

#### Table

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Cleared</th>
<th>510(k) No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>VeraCode® Genotyping Test for Factor V and Factor II</td>
<td>Illumina</td>
<td>04/28/10</td>
<td>K093129</td>
</tr>
<tr>
<td>eSensor® Thrombophilia Risk Test, FII-FV, FII, FV and MTHFR (677, 1298) Genotyping Tests</td>
<td>GenMark Dx&lt;sup&gt;b&lt;/sup&gt;</td>
<td>04/22/10</td>
<td>K093974</td>
</tr>
<tr>
<td>INFINITI™ System Assay for Factor II &amp; Factor V</td>
<td>AutoGenomics</td>
<td>02/07/07</td>
<td>K060564</td>
</tr>
<tr>
<td>Xpert&lt;sup&gt;a&lt;/sup&gt; Factor II and Factor V Genotyping Assay</td>
<td>Cepheid</td>
<td>09/18/09</td>
<td>K082118</td>
</tr>
<tr>
<td>Verigene&lt;sup&gt;a&lt;/sup&gt; Factor F2, F5, and MTHFR Nucleic Acid Test</td>
<td>Nanosphere</td>
<td>10/11/09</td>
<td>K070597</td>
</tr>
<tr>
<td>Factor V Leiden Kit</td>
<td>Roche Diagnostics</td>
<td>12/17/03</td>
<td>K033607</td>
</tr>
<tr>
<td>Factor II (Prothrombin) G20210A Kit</td>
<td>Roche Diagnostics</td>
<td>12/20/03</td>
<td>K033612</td>
</tr>
</tbody>
</table>

FDA: Food and Drug Administration.

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

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

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

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

### Rationale

#### Background

**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. The risk is strongly age-related, with the greatest risk in older populations. VTE also recurs frequently; estimated cumulative incidence of first VTE recurrence is 30% at 10 years. These figures do not separate patients with known predisposing conditions from those without.

Risk factors for thrombosis include clinical and demographic variables, and at least 1 risk factor can be identified in approximately 80% of patients with thrombosis. The following list includes the most important risk factors:

- Malignancy
- Immobility
- Surgery
- Obesity
- Pregnancy
- Hormonal therapy such as estrogen/progestin or selective estrogen modulator products
- Systemic lupus erythematosus and/or other rheumatologic disorders
- Myeloproliferative disorders
- Liver dysfunction
- Nephrotic syndrome
- Hereditary factors.
Pregnancy often is considered a special circumstance because of its frequency and unique considerations for preventing and treating VTE. Pregnancy is associated with a 5- to 10-fold increase in VTE risk, and absolute VTE risk in pregnancy is estimated to be 1 to 2 per 1000 deliveries. In women with a history of pregnancy-related VTE, risk of recurrent VTE with subsequent pregnancies is increased greatly at approximately 100-fold.

**Treatment**

Treatment of thrombosis involves anticoagulation for a minimum of 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 (factor V Leiden [FVL] variant)
- Prothrombin (factor II) gene variant (G20210A)
- Protein C deficiency
- Protein S deficiency
- Prothrombin deficiency
- Hyper-homocysteinemia (5,10-methylenetetrahydrofolate reductase [MTHFR] variant).

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

**Genetic Testing**

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

- Assessment of thrombosis risk in asymptomatic patients (screening for inherited thrombophilia)
- 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.

**MTHFR Variant Testing**

**Clinical Context and Test Purpose**

The purpose of genetic testing of patients who are asymptomatic with or without a personal or family history of venous thromboembolism (VTE) is to inform a decision whether to initiate treatment for VTE.

The question addressed in this evidence review is: Does genetic testing of individuals who are asymptomatic with or without a personal or family history of VTE identify variants in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene that is predictive of developing VTE?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest includes asymptomatic individuals with or without a personal or family history of VTE.

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

**Comparators**
The following practice is currently being used: standard clinical management without testing.

**Outcomes**
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.

**Timing**
The time period of interest for measuring the diagnostic performance is time to complications of thrombophilia including deep venous thrombosis or pulmonary embolism. Prospective trials evaluating incidence or recurrence of VTE typically span years to decades.

**Setting**
Asymptomatic individuals would be seen by a cardiologist in the outpatient setting.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**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).

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, 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 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, while others have not. One larger study (N=9231), the 2007 MEGA study, reported by Bezemer et al (2007) showed no association between the MTHFR 677C>T variant with recurrent VTE. An RCT by der Heijer et al (2007) reported no reduction in VTE associated with the 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
Clinical Context and Test Purpose
The purpose of genetic testing of patients who are asymptomatic with or without a family history of VTE or are at increased risk of developing VTE (e.g., due to pregnancy) is to inform a decision whether to initiate treatment for VTE.

The question addressed in this evidence review is: Does genetic testing of individuals who are asymptomatic with or without a family history of VTE or at increased risk of developing VTE (e.g., due to pregnancy) identify variants in coagulation factor V and coagulation factor II that are predictive of developing VTE?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest include asymptomatic individuals with or without a family history of VTE and asymptomatic individuals at increased risk of developing VTE (e.g., due to pregnancy).

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

Comparators
The following practice is currently being used: standard clinical management without testing.
**Outcomes**
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.

**Timing**
The time period of interest for measuring the diagnostic performance is time to complications of thrombophilia including deep venous thrombosis or pulmonary embolism. Prospective trials evaluating incidence or recurrence of VTE typically span years to decades. In certain clinical settings (i.e. pregnancy), patients may be evaluated for months.

**Setting**
Asymptomatic individuals would be seen by a cardiologist in the outpatient setting.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**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 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.

**Individuals without a Personal History of Venous Thromboembolism**
Individuals with factor V Leiden (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.13

For the prothrombin G20210A variant, risk also has been estimated to be 2 to 5 times greater than the general population.14 A meta-analysis by Gohil et al (2009) evaluated 79 studies and reported combined relative risk was 3.0.15 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.14

**Individuals with a Personal History of Venous Thromboembolism**

**Factor V Leiden**
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.16 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 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 (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 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). 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 vs 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 or 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 AHRQ report by Segal et al (2009) identified 18 studies that evaluated recurrence risk in patients heterozygous for the prothrombin G20210A variant. 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 ELATE 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. 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 vs unprovoked VTE, patient sex, and oral contraceptive use.

**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 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, Lilfering 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, 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 evaluating heterozygotes and only 1 study evaluating homozygotes. For heterozygote probands, family members had an odds 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, 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).

**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 systematic review by Bradley et al (2012) 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 carriers and 2 did not. Pooled analysis of these 4 studies yielded a significantly increased odds 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 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.

**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.

**Section Summary: Clinically Valid**
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 OR most commonly between 1 and 2, except for family members of individuals with inherited thrombophilia, for whom odds ratio somewhat higher.

**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.
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.23

**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.

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.24 The MEGA database comprised 5051 patients between the ages of 18 and 70 years with the 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).

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.”25 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%) 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 study by Hindorff et al (2009) 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.

**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.

**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.

**Pregnancy and Other High-Risk Conditions**

**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 vs 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.\(^{21}\) 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, methylenetetrahydrofolate reductase 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\%] 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.\(^{31}\)

An open-label, international, multicenter randomized trial, reported by Rodger et al (2014), evaluated antepartum use of low-molecular-weight heparin dalteparin in women with the prothrombin variant.\(^{32}\) 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 \(\rightarrow\) A allele only increases the relative risk for thrombophilia and is not predictive of a thrombotic event.”\(^{14}\)

**Section Summary: Clinically Useful**

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.

**Summary of Evidence**

For individuals who are asymptomatic with or without a personal or family history of VTE or who are asymptomatic with increased VTE risk (e.g., due to pregnancy) who receive genetic testing for variants in MTHFR, or genetic testing for coagulation factor V and coagulation factor II, the evidence includes a large randomized controlled trial, prospective cohort analyses, retrospective family studies, case-control studies, and meta-analyses. Relevant outcomes are morbid events and treatment-related morbidity. The clinical validity of genetic testing has been demonstrated by the presence of a factor V Leiden variant or a prothrombin gene variant, and an association with an increased risk for subsequent VTE across various populations studied. However, the magnitude of the association is relatively modest, with odds ratios most commonly between 1 and 2, except for family members of individuals with inherited thrombophilia, for whom odds ratios are somewhat higher. The clinical utility of testing for factor V Leiden or prothrombin variants has not been demonstrated. Although the presence of inherited thrombophilia increases the risk for subsequent VTE events, the increase is modest, and the absolute risk of thrombosis remains low. Available prophylactic treatments (e.g., anticoagulation) have defined risks of major bleeding and other adverse events that may outweigh the reduction in VTE and therefore result in net harm. Currently, available evidence has not defined a role for thrombophilia testing for decisions on initiation of prophylactic anticoagulation or the length of anticoagulation treatment. For MTHFR testing, clinical validity and clinical utility of genetic testing are uncertain. Because clinical utility of testing for elevated
serum homocysteine itself has not been established, the utility of genetic testing also has not been established. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Supplemental Information**

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

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

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

**Practice Guidelines and Position Statements**

Many guidelines and position statements on testing for thrombophilia have been published over the last 2 decades. These guidelines have evolved over time, often inconsistent and do not typically give specific parameters on when to perform genetic testing. The following are examples of U.S. guidelines developed by major specialty societies and published more recently.

**Evaluation of Genomic Applications in Practice and Prevention**

The 2011 Evaluation of Genomic Applications in Practice and Prevention recommendations did not support the clinical utility of genetic testing for factor V Leiden and prothrombin variants for prevention of initial episodes of venous thromboembolism (VTE) or for recurrence.33 The recommendations have been archived.

**American College of Chest Physicians**

The 2016 American College of Chest Physicians guidelines and expert panel report on antithrombotic therapy for VTE disease no longer includes recommendations for pregnant women with known factor V Leiden or prothrombin G20210A variants, which had been included in the 2012 edition.34,35 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.36

**American College of Obstetricians and Gynecologists**

The American College of Obstetricians and Gynecologists published management guidelines for inherited thrombophilies in pregnancy in 2013, which were reaffirmed in 2014.4 These guidelines stated that a definitive causal link between inherited thrombophilias and adverse pregnancy outcomes could not be made. Screening for inherited thrombophilias is controversial, but may be considered for pregnant women in the following situations:

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

The guidelines also recommended (as listed in Table 2) the following.

<table>
<thead>
<tr>
<th>Table 2. Guidelines for Managing Inherited Thrombophilias during Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
</tr>
<tr>
<td>Testing for inherited thrombophilias should include FVL, prothrombin G20210A mutation, and tests for deficiencies in antithrombin, protein S and protein C</td>
</tr>
</tbody>
</table>
Testing for inherited thrombophilias in women who have experienced recurrent fetal loss or placental abruption is not recommended because it is unclear whether anticoagulation therapy reduces recurrence.

Because an association between either heterozygosity or homozygosity for the MTHFR C677T polymorphism and any negative pregnancy outcomes, including any increased risk for VTE, has not been shown, screening with either MTHFR mutation analyses or fasting homocysteine levels is not recommended.

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

American Board of Internal Medicine Foundation
Choosing Wisely, an initiative of the American Board of Internal Medicine Foundation seeks to promote discussions between clinicians and patients to choose care that is supported by evidence, not duplicative of other tests or procedures already received, free from harm, and truly necessary. Medical specialty societies and their national organizations have identified tests or procedures commonly used in their field whose necessity should be questioned and discussed. The following medical specialist groups have contributed recommendations to Choosing Wisely lists specifically related to testing for inherited thrombophilias (see Table 3).37

Table 3. Medical Society Recommendations on Testing for Inherited Thrombophilias

<table>
<thead>
<tr>
<th>Society</th>
<th>Year</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| ASH     | 2013 | • “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 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.” |
| SMFM    | 2014 | • “Don’t do an inherited thrombophilia evaluation for women with histories of pregnancy loss, intrauterine growth restriction (IUGR), 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.” |
| ASRM    | 2013 | • “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.” |

U.S. Preventive Services Task Force Recommendations
Not applicable.

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

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 4.
Table 4. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>NCT02385461</td>
<td>Study on Antithrombotic Prevention in Thrombophilia and Pregnancy Loss (OTTILIA)</td>
<td>108</td>
<td>Jun 2017</td>
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<tr>
<td>NCT02841085</td>
<td>New Genetic Mutations in Thromboembolic Venous Disease Idiopathic</td>
<td>450</td>
<td>May 2018</td>
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<tr>
<td>NCT02685800</td>
<td>Recurrent Failures in assisted Reproductive Techniques (The FIRST Registry)</td>
<td>624</td>
<td>Sep 2018</td>
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<tr>
<td>NCT02990403</td>
<td>The Novel Immunomodulatory and Anticoagulant Therapies for Recurrent Pregnancy Loss</td>
<td>500</td>
<td>Dec 2018</td>
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<tr>
<td>NCT02407730</td>
<td>Effects of Thrombophilia on the Outcomes of Assisted Reproduction Technologies</td>
<td>715</td>
<td>Jun 2019</td>
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<tr>
<td>NCT02986594</td>
<td>Diagnosis and Treatment Strategy of Recurrent Spontaneous Abortion Associated With Thrombophilia</td>
<td>600</td>
<td>Oct 2019</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

References

2.04.82 Genetic Testing for Inherited Thrombophilia


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. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**IE**

The following services may be considered investigational.

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

Policy History

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

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**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 (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. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

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.