Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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(See policy history boxes for previous effective dates)

Title: Genetic Testing for Inherited Thrombophilias

Description/Background

Inherited thrombophilias are a group of disorders that predispose individuals to thrombosis. Genetic testing is available for some of these disorders and could assist in the diagnosis and/or management of patients with thrombosis. For example, testing is available for types of inherited thrombophilia, including variants in the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene, the factor V gene (factor V Leiden [FVL] variant), and the prothrombin (factor II) gene.

VENOUS THROMBOEMBOLISM
The overall U.S. incidence of venous thromboembolism (VTE) is approximately 1 per 1,000 person-years, and the lifetime clinical prevalence is about 8%. (1) After VTE, 1-year survival varies greatly by underlying VTE cause, with lower survival rates seen for cancer-associated VTE (~47%) and higher survival among patients with provoked (84%) or unprovoked (93%) VTE. The risk is strongly age-related, with the greatest risk in older populations. VTE also recurs frequently; the estimated cumulative incidence of first VTE recurrence is 30% at 10 years.(2,1) 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 one risk factor can be identified in approximately 80% of patients who have a thrombosis. The following list includes the most important risk factors:

- Malignancy
- Immobility
- Surgery
- Obesity
- Pregnancy
- Hormonal therapy with estrogen/progesterones
- Systemic lupus erythematosus (SLE), and/or other rheumatologic disorders
- Myeloproliferative disorders

- Liver dysfunction
- Nephrotic syndrome
- Hereditary factors

Pregnancy is often considered a special circumstance because of its frequency and unique considerations of preventing and treating VTE. Pregnancy is associated with a 5-10-fold increase in VTE risk, and the absolute VTE risk in pregnancy has been estimated to be 1-2 per 1,000 deliveries.(3) In women with a history of pregnancy-related VTE, risk of recurrent VTE with subsequent pregnancies is increased greatly at approximately 100-fold.(3)

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 be continued on anticoagulation for longer periods, sometimes indefinitely. Anticoagulation is effective for reducing the subsequent risk of thrombosis but carries its own risk 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 a patient'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 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 the inherited thrombophilia syndromes. Generally, routine testing for hypercoagulable disorders is not recommended in unselected patients.(3)

Genetic Testing
Genetic testing for gene variants associated with thrombophilias is available for factor V Leiden (FVL), the prothrombin (G20210A) variant, and the *MTHFR*. Genetic testing for inherited thrombophilia can be considered in several clinical situations. Clinical situations addressed here 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 high risk for thrombosis (e.g. pregnancy, planned major surgery, or exogenous hormone use).

Regulatory Status:

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 Act (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, FDA has chosen not to require any regulatory review of this test.

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

Table 1. Genetic Tests for Thrombophilia Cleared by FDA

Test	Manufacturer	Cleared	510(k) No.
Ancestrydna Factor V Leiden Genetic Health Risk Test	Ancestry Genomics, Inc.	08/13/2020	K192944
cobas® Factor II and Factor V Test	Roche Molecular Systems, Inc.	01/18/18	K172913
IMPACT Dx™ Factor V Leiden and Factor II Genotyping Test	Agena Bioscience[a]	06/14	K132978
Invader® Factor II, V, and MTHFR (677, 1298) tests	Hologic	04-06/11	K100943, K100980, K100987, K100496
VeraCode® Genotyping Test for Factor V and Factor II	Illumina	04/28/10	K093129
eSensor® Thrombophilia Risk Test, FII-FV, FII, FV and MTHFR (677, 1298) Genotyping Tests	GenMark Dx[b]	04/22/10	K093974
INFINITI™ System Assay for Factor II & Factor V	AutoGenomics	02/07/07	K060564
Xpert® Factor II and Factor V Genotyping Assay	Cepheid	09/18/09	K082118
Verigene® Factor F2, F5, and MTHFR Nucleic Acid Test	Nanosphere	10/11/07	K070597
Factor V Leiden Kit	Roche Diagnostics	12/17/03	K033607
Factor II (Prothrombin) G20210A Kit	Roche Diagnostics	12/20/03	K033612

FDA: Food and Drug Administration.
[a] FDA marketing clearance was granted to Sequenom Bioscience before it was acquired by Agena Bioscience.
[b] FDA marketing clearance was granted to Osmetech Molecular Diagnostics.

Other commercial laboratories may offer a variety of functional assays and genotyping tests for *F2* (prothrombin, coagulation factor II), *F5* (coagulation factor V), and single or combined genotyping tests for 5, 10-methylenetetrahydrofolate reductase (*MTHFR).*

In November 2017, the 23andMe Personal Genome Service (PGS) Genetic Health Risk was granted a de novo classification by the FDA (class II with general and special controls, FDA product code: PTA). This is a direct-to-consumer test that has been evaluated by the FDA for accuracy, reliability, and consumer comprehension. This test reports whether an individual has

variants associated with a higher risk of developing harmful blood clots. This report is based on a qualitative genetic test for single nucleotide polymorphism detection of Factor V Leiden variant in the F5 gene (rs6025) and Prothrombin G20210A variant in the F2 gene (rs1799963/i3002432). Similarly, in August 2020, Ancestry Genomics, Inc was granted the same de novo classification by the FDA (class II with general and special controls, FDA product code: PTA). This AncestryDNA Factor V Leiden Genetic Health Risk Test reports whether an individual has variants associated with a higher risk of developing harmful blood clots. This report is based on a qualitative genetic test for single nucleotide polymorphism detection of Factor V Leiden variant in the F5 gene (rs6025).

Medical Policy Statement

Genetic testing for factor V Leiden variant and prothrombin gene variant for inherited thrombophilia has been established in select patient populations who meet clinical criteria. This testing may be a useful diagnostic option when indicated.

Genetic testing for variant in the *MTHFR* gene is considered experimental/investigational. There is limited published evidence on the utility of testing for *MTHFR* variant for inherited thrombophilia.

Inclusionary and Exclusionary Guidelines

Inclusions:

Genetic testing for factor V Leiden gene variant and prothrombin gene variant for inherited thrombophilia should only be performed if the results are likely to direct or alter medical management in any of the following:

- Patients with VTE occurring at 50 years of age or younger
- Patients with VTE, at any age, who have a first-degree family member with a history of VTE
- Asymptomatic or symptomatic family members (first-degree relatives) of patients with a known familial thrombophilia
- Patients with VTE in unusual sites, such as hepatic, mesenteric, renal or cerebral veins
- Women with recurrent pregnancy loss or unexplained severe preeclampsia, placental abruption, intrauterine growth retardation, or stillbirth when the knowledge of inherited thrombophilia carrier status will influence the management of future pregnancies
- Patients with VTE provoked by pregnancy, the puerperium (post-partum period), oral contraceptive use, or hormone replacement therapy

Exclusions:

- Genetic testing for variant in the *MTHFR* gene
- As a general population screen
- Asymptomatic patients with no personal or familial history of VTE

- As a routine test prior to the use of oral contraceptives, hormone replacement therapy, selective estrogen receptor modulators, or tamoxifen
- As a routine prenatal or newborn test, or as a routine test in asymptomatic children
- As a routine test in individuals with arterial thrombosis

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

81240 81241 81400

Other codes (investigational, not medically necessary, etc.):

81291 0529U

Rationale

MTHFR VARIANT TESTING

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

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

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

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

Comparators
Comparators of interest include standard clinical management without testing.

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

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

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

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

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

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

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

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

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

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

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

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

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

The evidence for the association between *MTHFR* and VTE is not definitive. Some studies have shown an association,(5-9) but others have not.(10-12) 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.(10) A randomized controlled trial (RCT) by den Heijer et al (2007) reported no reduction in VTE associated with treatment of hyperhomocysteinemia.(13)

Gao et al (2020) evaluated the association between the MTHFR C677T and MTHFR A1298C polymorphisms and the risk of VTE in a meta-analysis of 32 case-control studies.(14) Pooled results demonstrated an increased susceptibility to VTE with MTHFR C677T homozygotes (odds ratio [OR]=0.73; 95% confidence interval [CI], 0.60 to 0.89) and MTHFR C677T homozygotes/heterozygotes (OR=0.80; 95% CI, 0.71 to 0.90) compared to those without a mutation. When results were stratified by ethnicity, a significant association was maintained in the Asian population, but results were not significant for the Caucasian population. For the MTHFR A1298C polymorphism, there was no significant association between homozygotes (OR=0.90; 95% CI 0.66 to 1.23) or homozygotes/heterozygotes (OR=0.95; 95% CI, 0.83 to 1.07) compared to those without a mutation for susceptibility to VTE.

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

FACTOR V LEIDEN AND PROTHROMBIN VARIANT TESTING

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

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

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

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

Comparators
Comparators if interest include standard clinical management without testing.

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

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

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

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

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

VTE: venous thromboembolism

Study Selection Criteria

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

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

Clinically Valid

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

The clinical validity and clinical utility are discussed for four 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

Review of Evidence

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 review of analytic validity studies.(18) Forty-one studies compared genetic testing for factor V Leiden (FVL) with a reference standard. Concordance between the tests was high, ranging from 93% to 100%, and was 100% in most studies. This evidence report also reviewed 23 studies on the concordance of prothrombin gene variant 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.(24) For studies performed in the U.S., combined analytic sensitivity and specificity for FVL testing exceeded 99%. For the prothrombin *G20210A* variant, analytic sensitivity was 98.4%, and analytic specificity was 99.7%.

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

Individuals without a Personal History of Venous Thromboembolism (VTE)

Factor V Leiden Variant
Individuals with FVL or prothrombin variants have an elevated risk of thrombosis compared with the general population. For individuals with the FVL variant, the risk may be 2- to 5-fold higher than that in the general population. In a retrospective study by Middledorp 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.(15)

Prothrombin G20210A Variant
For the prothrombin G20210A variant, risk also has been estimated to be 2 to 5 times greater than the general population.(16) A meta-analysis by Gohil et al (2009) evaluated 79 studies and reported a combined relative risk of 3.0.(17) 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.(16)

Individuals with a Personal History of Venous Thromboembolism (VTE)

Factor V Leiden Variant
An Agency for Healthcare Research and Quality (AHRQ) report by Segal et al (2009) reviewed the evidence on recurrence risk for patients with a history of VTE and the FVL variant.(18) 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.(19) 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.
One of the larger RCTs that was included in the above mentioned AHRQ review was the 2008 Influence of Thrombophilia on Risk of Recurrent Venous Thromboembolism while on Wafarin Trial. This trial randomized 738 patients from 16 clinical centers to low-intensity or conventional-intensity anticoagulation.(20) 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.(18) Some of these studies included only heterozygotes, while others combined both heterozygotes and homozygotes. For 9 studies that included only heterozygotes, pooled odds for recurrent VTE was 1.45 (95% CI, 0.96 to 2.2). For 7 studies that did not specify homozygous or heterozygous, the combined odds were 0.73 (95% CI, 0.37 to 1.44).

The prothrombin G20210A variant is less common, and therefore, the number of patients evaluated in clinical trials and cohort studies is smaller than for FVL. In the 2008 influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin trial, the risk of recurrent VTE in those with the prothrombin G20210A variant could not be calculated because there were no recurrences among 60 patients with the variant.(20) In the 2005 Leiden Thrombophilia Study, 29 patients had a prothrombin variant.(19) For patients with a prothrombin variant, there was no increased risk of recurrence (HR=0.7; 95% CI, 0.3 to 2.0). Factors that predicted recurrence were mainly clinical variables, such as provoked versus unprovoked VTE, patient sex, and oral contraceptive use.

Family Members of Individuals with Thrombophilia

Factor V Leiden Variant
The AHRQ (2009) 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 variant. 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.(21) A total of 2479 relatives of patients with thrombophilia who were themselves also tested for thrombophilia were included. For relatives with FVL variants, the annual incidence of thrombosis was 0.49% (95% CI, 0.39 to 0.60). In relatives without thrombophilia, 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).

Simioni et al (2002) assessed the incidence of spontaneous and risk period related venous VTE in asymptomatic family members of patients who experienced VTE and had the FVL mutation.(29) Of 131 probands, a total of 561 asymptomatic family members of patients who experienced VTE and had the factor V Leiden mutation were included. There were 313 carriers (299 heterozygous and 14 homozygous) and 248 non-carriers of FVL. Average follow-up was 4 years. Eight episodes of VTE occurred in heterozygous carriers, resulting in an annual incidence of 0.67%. Two events occurred in the absence of associated risk factors, determining an annual incidence of spontaneous VTE of 0.17%. Only one VTE (risk period–related) occurred in non-carriers, with an annual incidence of 0.1%. Relative risk for VTE in heterozygous carriers compared with non-carriers of the factor V Leiden mutation was 6.6. Risk period related VTE occurred with an incidence of 18% and 5% per risk period in heterozygous carriers and in non-carriers, respectively. Thus, the low rate of VTE in asymptomatic family members carrying the mutation did not justify continuous anticoagulant prophylaxis. The researchers concluded that screening families of symptomatic probands with the factor V Leiden mutation has the potential to identify those asymptomatic carriers who might benefit from thromboprophylaxis during risk periods.

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 report evaluating heterozygotes and only 1 study evaluating homozygotes(18). For heterozygote probands, family members had an OR for future VTE of 1.89 (95% CI, 0.35 to 10.2).

In the Lijfering et al (2009) family study, relatives with prothrombin variants had an annual VTE incidence of 0.34% (95% CI, 0.22 to 0.49).(21) 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).

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
A study by Hindorff et al (2009) surveyed 112 primary care physicians about the impact of FVL testing in patients with VTE.(22) 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.

Section Summary: Factor V Leiden and Prothrombin Variant Testing
The clinical validity of genetic testing for thrombophilia has been evaluated by assessing the association between thrombophilia status and VTE in various clinical populations. For populations discussed herein, the clinical validity has been reported in numerous case-control and cohort studies. The presence of an FVL or a prothrombin gene variant is associated with an increased risk for subsequent VTE across a number of populations. The magnitude of the association is relatively modest, with ORs most commonly between 1 and 2, except for family members of individuals with inherited thrombophilia, for whom an OR is somewhat higher.

Pregnancy and Other High-Risk Conditions

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

<u>Pregnancy</u>
Evidence of the risk of recurrent pregnancy loss in women with FVL or a prothrombin gene variant comprises primarily retrospective case-control and cohort studies. Several case-control studies reported a higher prevalence of FVL in women with recurrent, unexplained pregnancy loss compared with controls (OR range, 2–5).(23) 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 of FVL and prothrombin variant with pregnancy loss.(24) 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 these 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 OR for recurrent pregnancy loss in carriers (OR=1.93; 95% CI, 1.21 to 3.09).

A systematic review by Liu et al (2021) evaluated the association between hereditary thrombophilias, including FVL and prothrombin G20210A, and recurrent pregnancy loss.(25) Observational studies were included if they compared at least 2 groups of patients - 1 with hereditary thrombophilia and 1 without hereditary thrombophilia. There were 89 studies included in the analysis, with 81 evaluating the risk of FVL and 64 evaluating the risk of prothrombin G20210A on recurrent pregnancy loss. Pooled analysis of FVL demonstrated an increased risk for recurrent pregnancy loss with the variant (OR=2.44; 95% CI, 1.96 to 3.03). Pooled analysis for prothrombin G20210A also demonstrated an increased risk for recurrent pregnancy loss with the variant (OR=2.08; 95% CI, 1.61 to 2.68).

A number of other meta-analyses have concluded that risk of pregnancy loss for patients who are heterozygous for the prothrombin G20210A variant also is increased, in the 2- to 3-fold range.(16)

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 (1994) was 28 thrombotic events per 10,000 per year, 2% of which were estimated to be fatal.(26)

Hormone replacement therapy

Women using hormone replacement therapy have a 2- to 4-fold increased risk of thrombosis.(23) Absolute risk is low and may be restricted to the first year of use. Limited data suggested that women using selective estrogen receptor modulators (eg, tamoxifen) may have a similarly increased risk.(23)

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 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).(27)

Routine Testing

Wu et al (2006) conducted a systematic review and meta-analysis to assess the risk of clinical complications associated with thrombophilia in three high-risk patient groups: 1) women using oral estrogen preparations, 2) women during pregnancy, and 3) patients undergoing major orthopaedic surgery.(30) The study, “Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS)”, evaluated the relative cost-effectiveness of universal and selective VTE history-based screening for thrombophilia compared with no screening in the three high-risk patient groups. Eighty-one studies were included: nine for oral estrogen preparations, 72 for pregnancy and eight for orthopaedic surgery. The authors reported the highest risk of VTE in oral contraception and hormone replacement therapy was in women with FVL. The review suggested that during pregnancy, women with FVL were at a significantly

higher risk to develop VTE and also to experience recurrent pregnancy loss or late pregnancy loss. The odds ratio for the association between FVL and postoperative VTE following hip or knee replacement surgery was 1.86. The authors noted that regardless of patient group, selective screening based on the personal or family history of VTE was more cost effective than universal screening in all four screening scenarios. The authors concluded that “Universal thrombophilia screening in women prior to prescribing oral estrogen preparations, in women during pregnancy and in patients undergoing major orthopedic surgery is not supported by the evidence. The findings from this study show that selective screening based on prior VTE history is more cost-effective than universal screening.”

Patients less than 50 years old with first VTE

Raffini et al (2021) discussed thrombophilia testing in children and adolescents. The majority of pediatric VTEs occur in hospitalized children with underlying medical conditions, such as prematurity, cancer, congenital heart disease, and infection. Often multiple VTE risk factors are present, the most common being the presence of a central venous catheter (CVC). Though the incidence of pediatric VTE is highest among hospitalized neonates and infants, there is a second "peak" in adolescence. VTE in adolescence often presents in the setting of oral contraceptive use, or it may be unprovoked. The most common inherited thrombophilia’s identified in pediatric VTE include factor V Leiden, prothrombin *G20210A* mutation, antithrombin deficiency, and proteins S and C deficiencies. Identification of a thrombophilic defect rarely influences the acute management of a patient with VTE, in whom the mainstay of therapy is therapeutic anticoagulation. The exception would be a neonate with severe (homozygous or compound heterozygous) deficiency of proteins C or S who presents with purpura fulminans, which can be life threatening and requires special interventions. Factors that may influence the decision include the specific thrombophilic defect, age of the patient, whether the thrombus was unprovoked or provoked, and the child's risk of bleeding. Recommendations were given for thrombophilia testing of patients (1) who have non-central venous catheter related VTE regardless of other risk factors (identification of strong or combined thrombophilias may impact counseling or treatment duration) (2) with recurrent VTE, including those with recurrent central venous catheter related VTE. (3) who have had an arterial ischemic stroke outside of the neonatal period (except for children with sickle cell disease) and (4) who have a strong family history of VTE or inherited thrombophilia (eg, VTE in a first-degree relative <40 years old), if there are additional risk factors or underlying medical problems that place them at risk for thrombosis (cancer, central venous catheter, trauma, major surgery).(31)

Subsection Summary: Clinical Utility

The presence of inherited thrombophilia provides a modest risk for subsequent VTE events. While the absolute risk of VTE events related to inherited thrombophilia is relatively low, the clinical literature consistently supports genetic testing in select patient populations: young patients (< 50 years) with a first VTE, a VTE at an unusual anatomic site, patients with a strong family history of VTE, a VTE related to pregnancy, oral contraceptive use or hormone replacement therapy, and women with recurrent pregnancy loss and unexplained obstetrical complications.

Summary of Evidence

Genetic testing is available for a number of types of inherited thrombophilia, including variant in the *MTHFR gene*, the FVL gene, and the prothrombin gene. For *MTHFR* testing, the clinical

validity and clinical utility of genetic testing is uncertain. Because clinical utility of testing for elevated serum homocysteine itself has not been established, the utility of genetic testing has also not been established.

For FVL and prothrombin gene testing, clinical validity has been established in a variety of clinical situations, by the association of genetic status with subsequent risk of VTE. Increased risk of VTE has been demonstrated for asymptomatic patients, patients with a personal history of VTE, family members of a patient with established inherited thrombophilia, a VTE at an unusual anatomic site, patients with a strong family history of VTE young patients (< 50 years) with a first VTE, a VTE related to pregnancy, oral contraceptive use or hormone replacement therapy, and women with recurrent pregnancy loss and unexplained obstetrical complications. However, in most reports, the magnitude of this association is modest, resulting in a relatively low absolute rate of VTE even in patients with a genetic variant.

Supplemental Information

CLINICAL INPUT RECEIVED THROUGH SPECIALTY MEDICAL SOCIETIES AND ACADEMIC MEDICAL CENTERS

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

In response to requests, input was received from two specialty society physicians. There was agreement that genetic testing for thrombophilia (FVL and PT 20210) is indicated in selected populations, especially if ordered by a hematologist, vascular medicine or vascular surgery specialist. Thrombophilia testing is also indicated in certain obstetrical scenarios, particularly in the evaluation of recurrent miscarriage and stillbirths where findings might indicate the need for anticoagulation during pregnancy. *MTHFR* variant analysis was noted to not be helpful.

One of the physician specialists referenced the *Chest* guidelines “for treatment and prophylaxis of DVT/PE where decision making on the need for long term anticoagulation is predicated in part on knowing whether a patient carries genetic risk factors for thrombophilia” and that one “can’t fully risk stratify and apply *Chest* guidelines in patients with recurrent thrombosis or pregnancy and thrombosis without genetic testing.” Additional input related that “in the complex cases we see in hemostasis /thrombosis practices, these tests are indeed of value.”

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Society for Reproductive Medicine

The American Society for Reproductive Medicine published guidelines (2013) recommending against routine thrombophilia testing of patients undergoing infertility evaluations. No indication or benefit was found in obtaining thrombophilia testing in someone who does not have a history of bleeding or abnormal clotting in the absence of family history. This testing is not considered 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.(31)

American College of Medical Genetics and Genomics

The American College of Medical Genetics (updated in 2018), recommends FVL mutation testing for the following indications:(32)

- A first unprovoked venous thromboembolism (VTE), especially age under 50
- VTE in unusual sites (such as hepatic portal, mesenteric and cerebral veins)
- Recurrent VTE
- Personal history of VTE with:
  - Two or more family members with a history of VTE **or**
  - One first-degree relative with VTE at a young age
- Patients with low activated protein C (APC) resistance activity

Testing may also be considered in the following situations (2018):

- Females under the age of 50 who smoke tobacco and have a history of acute myocardial infarction
- Siblings of individuals known to be homozygous for factor V Leiden or factor II c.*87G>A, because they have a 1 in 4 chance of being a homozygote
- Asymptomatic pregnant female or female contemplating pregnancy, with a first degree relative with unprovoked VTE or VTE provoked by pregnancy or contraceptive use
- Pregnant female or female contemplating pregnancy or estrogen use who has a first degree relative with a history of VTE and is a known carrier for factor V Leiden and/or factor II c.97*G>A variant
- Pregnant female or female contemplating pregnancy with a previous non-estrogen-related VTE or VTE provoked by a minor risk factor, because knowledge of the factor V Leiden or factor II c.*97G>A status may alter pregnancy-related thrombophylaxis

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (2018, reaffirmed in 2022) published management guidelines for inherited thrombophilias in pregnancy.(27) These guidelines stated that a definitive causal link between inherited thrombophilias and adverse pregnancy outcomes cannot be made. Screening for inherited thrombophilias and adverse pregnancy outcomes could not be made. Screening for inherited thrombophilias is controversial, but may be considered for pregnant women in the following situations if testing will influence management:

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

Table 4. Guidelines for Managing Inherited Thrombophilias During Pregnancy

Recommendation	GOE	LOE
In women with personal history of VTE testing for inherited thrombophilias should include FVL, prothrombin G20210A mutation, and tests for deficiencies in antithrombin, protein S and protein C	C	Consensus and expert opinion
Testing for inherited thrombophilias in women who have experienced fetal loss or adverse pregnancy outcomes, including placental abruption, preeclampsia, or fetal growth restriction, is not recommended because there is insufficient evidence that anticoagulation therapy reduces recurrence	B	Limited or inconsistent scientific evidence
Because an association between either heterozygosity or homozygosity for the *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	B	Limited or inconsistent scientific evidence

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

American Heart Association

The American Heart Association (2003) published a statement supporting the American College of Medical Genetics guidelines. “Patients who develop a DVT or PE and are from a family with a confirmed factor V Leiden diagnosis should be tested. Likewise, even if there is no family history of factor V Leiden, anyone who has had a DVT or PE that is unexplained, recurrent, occurred at a young age (under 50), occurred during pregnancy, was associated with hormone use, or developed in an unusual site (such as the veins of the brain or abdomen) may benefit from testing for factor V Leiden and other causes of hereditary thrombophilia.”(33)

European Genetics Foundation, The Cardiovascular Disease Educational and Research Trust, The International Union of Angiology and The Mediterranean League on Thromboembolism

Under the auspices of the European Genetics Foundation, The Cardiovascular Disease Educational and Research Trust, The International Union of Angiology and The Mediterranean League on Thromboembolism (2005), an International Consensus Statement was developed for thrombophilia and venous thromboembolism.(34)

Screening for thrombophilia should be performed in:

1. All patients with a first episode of spontaneous VTE;
2. Patients with VTE under the age of 50 even with a transient predisposing factor;
3. Patients with VTE whose only risk factor is oral contraceptive therapy, estrogen replacement therapy or pregnancy. However, screening with other than molecular (PCR) tests should be performed at least two months after delivery or hormone therapy cessation;
4. Patient with recurrent VTE irrespective of the presence of risk factors;
5. Patients with recurrent superficial thrombophlebitis without cancer and in the absence of varicose veins;
6. Patients with VTE at unusual site such as cerebral venous sinus, mesenteric or hepatic veins, and retinal vein occlusion under the age of 50;
7. Patients with warfarin-induced skin necrosis and neonates with purpura fulminans not related to sepsis;
8. Asymptomatic first-degree relatives of individuals with proven symptomatic thrombophilia. This is particularly important for females in the childbearing age;
9. Two consecutive or three non-consecutive abortions at any gestational age, or one fetal death after the 20th week;
10. Severe pre-eclampsia
11. Children with VTE.

The guidelines further states “there is no point for screening for thrombophilia for patients in whom the decision has been made for prolonged anti vitamin K therapy, such as cancer and VTE. Also, routine preoperative screening for thrombophylaxis before surgery is not recommended” and “preoperative thrombophilia screening should be reserved only for patients with personal or family history of VTE of unknown etiology who have not been investigated.”

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

U.S. Preventive Services Task Force recommendations for genetic testing for thrombophilia were not identified.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

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

NCT: national clinical trial.

Government Regulations

National:

There is no national coverage determination for these tests.

Local:

Genetic Testing for Hypercoagulability/Thrombophilia (Factor V Leiden, Factor II Prothrombin and MTHFR); L36400**:** Effective for services performed on or after 7/20/23

- This is a non-coverage policy for genetic testing for thrombophilia testing for the Factor V Leiden (FVL) variant in F5 gene, the 20210G>A variant in the F2 gene, and the MTHFR gene which encodes the 5, 10-methylenetetrahydrofolate reductase enzyme. Genetic testing for these genes for all risk factors, signs, symptoms, diseases, or conditions, including cardiovascular risk assessment, are non-covered except for pregnant patients.

- Testing for FVL and F2 G20210A variant is indicated for pregnant patients who have a history of personal venous thromboembolism (VTE) associated with non-recurrent (transient) risk factor who are not otherwise receiving anticoagulant prophylaxis. The results of genetic testing can inform risk stratification for VTE recurrence and subsequent need for antenatal prophylaxis. However, Medicare will not add coverage of thrombophilia testing for pregnant women because they likely represent a very small group of potential Medicare (disabled) patients. Claims submitted on this limited Medicare population will deny per the policy but should be appealed for coverage with submission of medical records supporting the necessity for testing and specify how testing changed anticoagulant prophylaxis management for the patient.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Laboratory Tests-Genetic, Molecular, and Other – Experimental/Investigational Status
- Genetic Testing and Counseling

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 9/23/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/14	101513	10/25/13	Joint policy established
5/1/15	2/17/15	2/27/15	Routine maintenance
5/1/16	2/16/16	2/16/16	Routine maintenance
7/1/16	4/19/16	4/19/16	New LCD added
7/1/17	4/18/17	4/18/17	Routine maintenance
7/1/18	4/17/18	4/17/18	Routine maintenance
7/1/19	4/16/19		Routine maintenance
3/1/20	12/17/19		Routine maintenance
3/1/21	12/15/20		Routine maintenance
3/1/22	12/14/21		Routine maintenance
3/1/23	12/20/22		Routine maintenance (ky)
3/1/23	12/19/23		Routine maintenance Vendor: N/A (ky)
3/2/24	12/17/24		Routine maintenance Vendor: N/A New code 0529U Hematology (venous thromboembolism [VTE]), genome-wide single-nucleotide polymorphism variants, including F2 and F5 gene analysis, and Leiden variant, by microarray analysis, saliva, report as risk score for VTE effective 1/1/25 added to policy as E/I. There is insufficient scientific evidence in the current medical literature to determine whether the test improves health outcomes. (ky)

Next Review Date: 4th Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR INHERITED THROMBOPHILIAS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.