Genetic Testing for Inherited Thrombophilia

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

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

Background/Overview
Inherited thrombophilias are a group of disorders that predispose to thrombosis. Genetic testing is available for some of these disorders and could potentially assist in the diagnosis and/or management of patients with thrombosis.

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 5%, accounting for 100,000 deaths annually. 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. These figures do not separate patients who had known predisposing conditions from those who do not.

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 with 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

Treatment of thrombosis involves anticoagulation for a minimum of 3 to 6 months. Following 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 in reducing the subsequent risk of thrombosis, but has its own risks of bleeding.
Pregnancy is often considered a special condition because of its frequency and the unique considerations of preventing and treating VTE in this setting. Pregnancy is associated with a 5-10-fold increase in the risk for VTE, and the absolute risk of VTE in pregnancy has been estimated to be 1-2 per 1,000 deliveries. In women with a previous history of pregnancy-related VTE, the risk of recurrent VTE with subsequent pregnancies is increased greatly at approximately 100-fold.

Inherited Thrombophilia
Inherited thrombophilias are a group of clinical conditions in which there is a genetic variant defect associated with a predisposition to thrombosis. However, not all patients 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 risk of VTE.

There are a number of conditions that fall under the classification of inherited thrombophilias, which arise from genetic variants in the genes involved in defects in the coagulation cascade. Inherited thrombophilias include the following abnormalities:

- Activated protein C resistance (FVL mutations)
- Prothrombin gene mutation
- Protein C deficiency
- Protein S deficiency
- Prothrombin deficiency
- Hyper-homocysteinemia (MTHFR mutations)

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

Genetic testing for gene variants associated with thrombophilias is available for factor V Leiden, the prothrombin gene mutation, and the MTHFR gene. The use of genetic testing for inherited thrombophilia can be considered in several clinical situations. The clinical situations that will be addressed in this policy include the following:

- Assessment of the risk for thrombosis in asymptomatic patients (screening for inherited thrombophilia)
- Evaluation of a patient with established thrombosis, in 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 that is consistent with an inherited thrombophilia
- Evaluation of patients in other situations that are considered high risk for thrombosis, e.g. pregnancy, planned major surgery, or oral contraceptive use.
FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
More than a dozen commercial laboratories currently offer a wide variety of diagnostic procedures for F2 (prothrombin, coagulation factor II), F5 (coagulation factor V), and MTHFR (5, 10-methylenetetrahydrofolate reductase) genetic testing. These tests are available as laboratory developed procedures under the U.S. FDA enforcement discretion policy for laboratory developed tests.

Rationale/Source
Methylenetetrahydrofolate Reductase Mutation Testing
Mutations in the MTHFR gene are associated with hyperhomocysteinemia, which is in turn associated with an increased risk for VTE. However, the clinical utility of testing for homocysteine levels has not been established. There is a large literature base on the association of homocysteine levels with coronary artery disease (CAD), and clinical trials on the impact of lowering homocysteine levels. This body of evidence indicates that testing or treating for homocysteinemia is not associated with improved outcomes.

For the association of MTHFR with VTE, the evidence is not definitive. Some studies have shown an association, but others have not. In one of the larger studies, the MEGA study, there was no association of the MTHFR mutation with recurrent VTE. A randomized controlled trial (RCT) published in abstract form reported that there was no reduction in VTE associated with treatment of hyperhomocysteinemia.

Conclusions
There is limited published evidence on the utility of testing for MTHFR mutations in patients with VTE or at risk for VTE. Given the available literature, and the lack of clinical utility for serum homocysteine testing in general, it is unlikely that testing for the MTHFR gene will improve outcomes.

Factor V Leiden and Prothrombin Mutation Testing
Analytic Validity
Analytic validity refers to the accuracy of detecting a specific mutation when it is present, and excluding it when absent.

For an evidence review reported by the Agency for Healthcare Research and Quality (AHRQ) in 2009, the authors performed a comprehensive literature review of studies of analytic validity. There were 41 studies that compared genetic testing for FVL with a reference standard. The concordance between the tests was high, ranging from 93-100%, and was 100% in the majority of studies. This evidence report also reviewed 23 studies on the concordance of prothrombin gene mutations with a reference standard and found that nearly all of the studies reported a 100% concordance. There were 12 studies that reported multiplex methods to test simultaneously for both FVL and the prothrombin gene mutation, and all of these studies reported a 100% concordance with reference standards.

Bradley et al. evaluated the analytic validity in individual studies and meta-analyses in the setting of pregnancy-related testing. For studies performed in the U.S., the combined analytic sensitivity and specificity for FVL testing was greater than 99%. For the prothrombin mutation, the analytic sensitivity was 98.4% and the analytic specificity was 99.7%.
Conclusions
The analytic validity of genetic testing for inherited thrombophilia is high. Published literature reports that the analytic sensitivity and specificity for FVL testing is greater than 99% and that the analytic sensitivity and specificity for the prothrombin gene mutation is greater than 98%.

Clinical Validity
The clinical validity, and clinical utility, will be discussed for 4 distinct patient populations. These are:
- Individuals without a personal history of VTE
- Individuals with a personal history of VTE
- Family members of individuals with thrombophilia
- Pregnant women

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

Individuals without a Personal History of Venous Thromboembolism
Individuals with both FVL and prothrombin mutations have an elevated risk of thrombosis compared to the general population. For individuals with the FVL mutation, the risk may be 2-5-fold higher than the general population. In one study of asymptomatic individuals, those with a FVL mutation had an annual incidence of VTE of 0.45%, compared with an incidence of 0.1% in those without the mutation.

For the prothrombin mutation, the risk has also been estimated to be 2-5 times greater than the general population. In a meta-analysis of 79 studies, the combined risk ratio was 3.0. Heterozygosity for prothrombin mutation is also associated with an elevated risk of upper extremity thrombosis, estimated to be 5 times that of the general population.

Individuals with a Personal History of Venous Thromboembolism
Factor V Leiden
The 2009 AHRQ evidence report reviewed the evidence on the risk of recurrence for patients with a history of VTE and the FVL mutation. For individuals with a heterozygous FVL mutation, there were a total of 13 studies that compared the risk of recurrence with a mutation to the risk of recurrence with no mutation. Pooled analysis of these 13 studies yielded an odds ratio (OR) of 1.56 (95% confidence interval [CI]: 1.14-2.12) for recurrent VTE in patients with the FVL mutation. For patients with a homozygous mutation, there were 7 studies that evaluated risk. The pooled OR for recurrent VTE in these studies was 2.65 (95% CI: 1.18-5.97).

Not all studies are consistent in reporting an increased risk of recurrent VTE in patients with inherited thrombophilia. For example, the 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 FVL mutation and 6% with a prothrombin mutation. There was not an
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increased recurrence rate for either patients with a FVL mutation or for patients with a prothrombin mutation. For FVL, there was a mild increase in the risk of recurrence that did not reach statistical significance on multivariate analysis (hazard ratio [HR]: 1.3, 95% CI: 0.8-2.1). For the prothrombin mutation, there was no increased risk of recurrence (HR: 0.7, 95% CI: 0.3-2.0). Factors that did predict recurrence were mainly clinical variables, such as a provoked versus an unprovoked VTE, gender, and oral contraceptive use.

One of the larger RCTs that was included in the AHRQ review was the ELATE study, which was an RCT of 738 patients from 16 clinical centers who were randomized to low-intensity versus conventional-intensity treatment with anticoagulation. All patients were tested for inherited thrombophilias, and the risk of recurrence was calculated in patients with and without inherited thrombophilia. For patients with an FVL mutation, there was not an increased risk of recurrence over a mean follow-up of 2.3 years (HR: 0.7, 95% CI: 0.2-2.6).

Prothrombin Gene Mutation
The AHRQ evidence report identified 18 studies that evaluated the risk of recurrence in patients heterozygous for the G20210A prothrombin mutation. Some of these studies included only heterozygotes, while other studies combined both heterozygotes and homozygotes. For the 9 studies that included only heterozygotes, the pooled OR for risk of recurrent VTE was 1.45 (95% CI: 0.96-2.2). There were 7 studies that did not specify whether patients were homozygous or heterozygous, the combined OR for these studies was 0.73 (95% CI: 0.37-1.44).

The prothrombin gene mutation is less common, and therefore, the number of patients evaluated in clinical trials and cohort studies is less than with FVL. In the ELATE trial, the risk of recurrent VTE with the prothrombin mutation could not be calculated because there were no recurrences among 60 patients with the prothrombin mutation. In the LETS study, there were 29 patients with a prothrombin mutation. For patients with a prothrombin mutation, there was no increased risk of recurrence (HR: 0.7, 95% CI: 0.3-2.0). Factors that did predict recurrence were mainly clinical variables, such as a provoked versus an unprovoked VTE, gender, and oral contraceptive use.

Family Members of Individuals with Thrombophilia
Factor V Leiden
The 2009 AHRQ report identified 9 studies that evaluated the risk of VTE in family members of a proband with a heterozygous mutation. The pooled OR for future VTE was 3.49 (95% CI: 2.46-4.96). There were 6 studies that evaluated a total of 48 probands with homozygous FVL mutations. The pooled OR for family members of homozygous individuals was 18 (95% CI: 7.8-40).

In one of the larger, more recent studies of VTE risk in family members, Lijfering et al. pooled results from 5 retrospective family studies of thrombophilia. A total of 2,479 relatives of patients with thrombophilia who were themselves also tested for thrombophilia were included. For relatives with FVL mutations, the annual incidence of thrombosis was 0.49% (95% CI: 0.39-0.60). In relatives without thrombophilia, the incidence of VTE was approximately 0.05%/yr, and the adjusted relative risk for VTE in relatives with a FVL mutation was 7.5 (95% CI: 4.4-12.6). In patients treated with anticoagulation, the annual risk of major bleeding was 0.29% (95% CI: 0.03-1.04).
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Prothrombin Mutation
The evidence on the risk for family members of individuals with a prothrombin mutation is less than for FVL, with 5 studies identified by AHRQ evaluating heterozygotes and only one study evaluating homozygotes. For the heterozygote probands, family members had an OR for future VTE of 1.89 (95% CI: 0.35-10.2).

In the Lijfering family study, relatives with prothrombin mutations had an annual VTE incidence of 0.34% (95% CI: 0.22-0.49). In relatives without thrombophilia, the incidence of VTE was approximately 0.05%/yr, and the adjusted relative risk for VTE in relatives with a prothrombin mutation was 5.2 (95% CI: 2.8-9.7).

Pregnant Patients, and Other High-Risk Situations

Pregnancy
The evidence on the risk of recurrent pregnancy loss in women with FVL or prothrombin gene mutation comes from case-control studies and cohort studies that are primarily retrospective. Several case-control studies have reported a higher prevalence of FVL (OR: 2–5) in women with recurrent, unexplained pregnancy loss compared to controls. Retrospective cohort studies have found a 2- to 3-fold increased risk of pregnancy loss in FVL carriers; homozygous carriers have a 2-fold higher risk than heterozygous carriers. Carriers have the highest risk of pregnancy loss in the second and third trimesters.

A 2012 systematic review by Bradley et al. analyzed the evidence on the association of FVL and prothrombin mutations with pregnancy loss. These authors 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 non-carriers. Four cohort studies met all these criteria; these studies primarily included patients with FVL mutations. Two of the 4 studies reported a significantly increased rate of recurrence for carriers, and 2 studies did not. Combined analysis of these 4 studies yielded a significantly increased OR for recurrence of pregnancy loss in carriers (OR: 1.93, 95% CI: 1.21-3.09).

A number of meta-analyses have concluded that there is also an excess risk of pregnancy loss for patients who are heterozygous for the prothrombin mutation, with an elevated risk in the 2-3 range.

Oral Contraceptives
Oral contraceptive use alone is associated with an approximately 4-fold increase in risk of thrombosis; in combination with FVL risk multiplies 34-fold in heterozygotes and more than 100-fold in homozygotes. However, the absolute incidence in one published study is estimated to be 28 thrombotic events per 10,000 per year, 2% of which are estimated to be fatal.

Hormone Replacement Therapy
Women using hormone replacement therapy have a 2- to 4-fold increase in their risk of thrombosis. Absolute risk is low and may be restricted to the first year of use. Limited data suggest that women using selective estrogen receptor modulators (e.g., tamoxifen) may have a similarly increased risk.

Conclusions
The clinical validity of genetic testing for thrombophilia has been evaluated by assessing the association between thrombophilia status and VTE in a variety of clinical populations. For the populations discussed...
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Here, clinical validity has been reported in numerous case-control and cohort studies. The presence of an FVL or a prothrombin gene mutation is associated with an increased risk for subsequent VTE across a variety of populations studied. However, the magnitude of the association is relatively modest, with ORs most commonly between 1 and 2, except for the case of family members of individuals with inherited thrombophilia, in which the ORs are somewhat higher.

Clinical Utility
The clinical utility of genetic testing depends on the ability of testing results to change management that results in improved outcomes. The clinical utility of genetic testing for thrombophilia is considered in the context of the overall risk of thromboembolism and the risk/benefit ratio of treatment, primarily with anticoagulants. The following factors are part of the decision-making process on whether to test:

- The overall low incidence of thromboembolism in the general population
- The 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.
- The potential risk of prophylactic treatment, especially the bleeding risk with anticoagulation. This risk may outweigh the benefit in patients with a relatively low absolute risk of thrombosis.

Individuals without a Personal History of Venous Thromboembolism
No published studies were identified that directly evaluated the clinical utility of screening asymptomatic individuals for inherited thrombophilia. However, it is unlikely that screening asymptomatic individuals will result in a net health benefit, as prophylactic anticoagulation is likely to have more harms than benefits. The risk of major bleeding with full anticoagulation is in the range of 1%/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 the risk of VTE, such as avoidance of prolonged immobility, but this is unproven.

Individuals with a Personal History of Venous Thromboembolism
The MEGA study was a large, population-based, case-control study that evaluated whether testing for thrombophilia in patients with a first episode of VTE was associated with a decrease in the recurrence rate. The MEGA database consisted of 5,051 patients between the ages of 18-70 years with a first episode of VTE. Researchers identified a total of 197 patients with a recurrence of VTE and matched these patients on age, sex, year of VTE, and geographic region with 324 patients who were free of recurrent VTE. Recurrence rate for VTE was similar in patients who were tested for thrombophilia compared to patients who were not tested (OR: 1.2, 95% CI: 0.9-1.8). The presence of FVL or the prothrombin gene mutation was not associated with an increased recurrence rate, with an OR of 0.8 (95% CI: 0.3-2.6).

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

Family Members of Individuals with Thrombophilia
There are no comparative trials of testing versus no testing in relatives of individuals with thrombophilia. The clinical utility of testing depends on the balance between the benefit of altering management as a result
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of knowledge of mutation status versus the risk of bleeding with intensification of anticoagulation. This risk benefit is unknown, as previously discussed. The absolute risk of VTE remains low even in patients in inherited thrombophilia, and the potential risks of prophylactic treatment with anticoagulants may outweigh the benefit.

Pregnant Patients, and Other High-Risk Situations
No studies directly evaluated clinical utility of thrombophilia testing in pregnant patients. The clinical utility of testing depends on the efficacy of potential treatments in decreasing fetal loss, versus the risks of treatment. Potential treatments in pregnancy include aspirin, low-dose unfractionated or low molecular-weight heparin, and full-dose heparin. The benefits of these treatments in reducing pregnancy loss are questionable. At least two RCTs have reported that there is not a significant reduction in risk with aspirin or heparin therapy. In addition, several meta-analyses also report that there is insufficient evidence to conclude that these interventions reduce recurrent pregnancy loss in patients with FVL or prothrombin mutations. In contrast, the risks of anticoagulation are real, including bleeding, thrombocytopenia, and allergic reactions. There are also additional costs and inconvenience associated with these treatments.

Bradley et al. reviewed the evidence on clinical utility and concluded that the evidence is adequate to conclude that there are no safe and effective treatments to reduce recurrent pregnancy loss in women with inherited thrombophilia. They also concluded that the certainty of the evidence was moderate that treatment resulted in a net harm.

Conclusions
The clinical utility of testing for FVL or prothrombin mutations has not been demonstrated. While 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 risks of major bleeding and other adverse events that may outweigh the reduction in VTE and therefore result in a net harm. The currently available evidence has not defined a role for thrombophilia testing for decisions on the length of anticoagulation treatment.

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, 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, input was received from 4 physician specialty societies (6 reviewers) and 6 academic medical centers, for a total of 12 reviewers, while this policy was under review for July 2012. Overall, input was mixed, and there was not uniform 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 the specific criteria that could be used for testing.

Summary
Genetic testing is available for a number of types of inherited thrombophilia, including mutations in the MTHFR gene, the FVL gene, and the prothrombin gene. For MTHFR testing, the clinical validity and clinical
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The utility of genetic testing is uncertain. Since the 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, and pregnant women. 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 mutation.

The clinical utility of genetic testing for thrombophilia is less certain. Surveys of physicians indicate that a substantial number order thrombophilia testing with the intent of influencing management, but the specific management changes and the impact of those management changes on outcomes is uncertain. According to the existing evidence and recent guidelines, the presence of inherited thrombophilia is not an important factor in determining the optimum length of anticoagulation in patients with VTE. For other clinical situations, given the low absolute risk of VTE, and the defined risks of anticoagulation, it is not possible to define a clinical situation in which the benefit of testing clearly outweighs the risk. Clinical vetting performed in 2012 did not identify consensus for testing in any of the clinical scenarios that were outlined. Because of the lack of documented clinical utility, and the lack of consensus on clinical vetting as to which populations benefit from testing, genetic testing for inherited thrombophilia is considered investigational.

References
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