Genetic Testing for Inherited Thrombophilia

Policy # 00333
Original Effective Date: 12/19/2012
Current Effective Date: 12/21/2016

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

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

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

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 1000 person-years, and the lifetime clinical prevalence is approximately 5%, accounting for 100,000 deaths annually. Risk is strongly age-related, with the greatest risk in older populations. Venous thromboembolism also recurs frequently; 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 did not.

Risk factors for thrombosis include a variety of clinical and demographic variables, and at least 1 risk factor can be identified in approximately 80% of patients 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, 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. After this initial treatment period, patients deemed to be at a continued high risk for recurrent thrombosis may be continued on
Genetic Testing for Inherited Thrombophilia

Policy # 00333
Original Effective Date: 12/19/2012
Current Effective Date: 12/21/2016

Anticoagulation for longer periods, sometimes indefinitely. Anticoagulation is effective for reducing subsequent risk of thrombosis but carries its own risk of bleeding.

Pregnancy often is considered a special circumstance because of its frequency and unique considerations of preventing and treating VTE in this setting. 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 previous history of pregnancy-related VTE, risk of recurrent VTE with subsequent pregnancies is increased greatly at approximately 100-fold.

**Inherited Thrombophilia**

Inherited thrombophilias are a group of clinical conditions characterized by genetic variant defects 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 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 (FVL mutations)
- Prothrombin gene mutation (G20210A)
- Protein C deficiency
- Protein S deficiency
- Prothrombin deficiency
- Hyper-homocysteinemia (MTHFR mutations)

The most common type of inherited thrombophilia is FVL mutation, which accounts for up to 50% of inherited thrombophilia syndromes. In unselected patients with an idiopathic thrombosis, the rate of FVL positivity is 17% to 24%, compared with a rate of 5% to 6% in normal controls. The prothrombin G20210A mutation 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 for gene variants associated with thrombophilias is available for FVL, the prothrombin G20210A mutation, and MTHFR. Genetic testing for inherited thrombophilia can be considered in several clinical situations. Clinical situations that will be addressed in this policy 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 that is consistent with an inherited thrombophilia
- Evaluation of patients in other situations that are considered high risk for thrombosis, eg pregnancy, planned major surgery, or oral contraceptive use
Genetic Testing for Inherited Thrombophilia

Policy # 00333
Original Effective Date: 12/19/2012
Current Effective Date: 12/21/2016

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)
Several genetic tests for thrombophilia have received FDA marketing clearance for use as an aid in the diagnosis of patients with suspected thrombophilia. Several of these tests are listed in Table 1.

### Table 1. Genetic Tests for Thrombophilia Cleared by FDA

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Location</th>
<th>Date 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>San Diego, CA</td>
<td>06/14</td>
<td>K132978</td>
</tr>
<tr>
<td>Invader® Factor II, V, and MTHFR tests</td>
<td>Hologic</td>
<td>Marlborough, MA</td>
<td>04-06/11</td>
<td>K100943, K100980, K100987, K100496</td>
</tr>
<tr>
<td>VeraCode® Genotyping Test for Factor V and Factor II</td>
<td>Illumina</td>
<td>San Diego, CA</td>
<td>04/28/10</td>
<td>K093129</td>
</tr>
<tr>
<td>eSensor® Thrombophilia Risk Test</td>
<td>GenMark Dx®</td>
<td>Carlsbad, CA</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>Carlsbad, CA</td>
<td>02/07/07</td>
<td>K060564</td>
</tr>
<tr>
<td>Xpert® Factor II and Factor V Genotyping Assay</td>
<td>Cepheid</td>
<td>Sunnyvale, CA</td>
<td>09/18/09</td>
<td>K082118</td>
</tr>
<tr>
<td>Verigene® Factor F2, F5, and MTHFR Nucleic Acid Test</td>
<td>Nanosphere</td>
<td>Northbrook, IL</td>
<td>10/11/07</td>
<td>K070597</td>
</tr>
<tr>
<td>Factor V Leiden Kit</td>
<td>Roche Diagnostics</td>
<td>Indianapolis, IN</td>
<td>12/17/03</td>
<td>K033607</td>
</tr>
</tbody>
</table>

**FDA**: Food and Drug Administration.

a FDA marketing clearance was granted to Sequenom Bioscience before it was acquired by Agena.
b FDA marketing clearance was granted to Osmetech Molecular Diagnostics.

Other commercial laboratories offer a variety of diagnostic procedures for F2 (prothrombin, coagulation factor II), F5 (coagulation factor V), and MTHFR (5, 10-MTHFR) genetic testing. 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. To date, FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)
There is no National Coverage Determination (NCD).

### Rationale/Source

**MTHFR Mutation Testing**

Mutations in the MTHFR gene are associated with hyperhomocysteinemia, which in turn is considered a weak risk factor for VTE. However, the clinical utility of testing for homocystein levels has not been established. There is a large literature base on the association of homocystein levels with coronary artery disease (CAD), and clinical trials on the impact of lowering homocystein levels. This body of evidence indicates that testing or treating for homocysteinemia is not associated with improved outcomes.
Genetic Testing for Inherited Thrombophilia

Policy # 0033
Original Effective Date: 12/19/2012
Current Effective Date: 12/21/2016

Evidence for the association of MTHFR with VTE is not definitive. Some studies have shown an association, but others have not. One larger study (N=9231), the 2007 MEGA study, showed no association between the MTHFR mutation with recurrent VTE. A randomized controlled trial (RCT) reported no reduction in VTE associated with treatment of hyperhomocysteinemia.

Section Summary
Published evidence on the utility of testing for MTHFR mutations 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 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 a 2009 evidence review prepared for the Agency for Healthcare Research and Quality (AHRQ), researchers performed a comprehensive review of analytic validity studies. Forty-one studies compared genetic testing for FVL with a reference standard. Concordance between the tests was high, ranging from 93% to 100%, and was 100% in most studies. This evidence report also reviewed 23 studies on the concordance of prothrombin gene mutations 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 mutation, all of which reported 100% concordance with reference standards.

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

Section Summary
Analytic validity of genetic testing for inherited thrombophilia is high. Analytic sensitivity and specificity for FVL testing exceeds 99%, and analytic sensitivity and specificity for the prothrombin G20210A mutation exceeds 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
- Pregnancy and other high-risk situations

The clinical validity of testing for inherited thrombophilias is best determined by the predictive ability of the test for future thromboembolic events, both in patients with and without prior thromboembolism. The highest
genetic testing for inherited thrombophilia

policy # 00333
original effective date: 12/19/2012
current effective date: 12/21/2016

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 G20210A 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 G20210A 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

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 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.

A larger RCT included in the AHRQ review was the 2008 ELATE trial, which randomized 738 patients from 16 clinical centers who were randomized to low-intensity versus conventional-intensity anticoagulation. All patients were tested for inherited thrombophilias, and recurrence risk was calculated in patients with and without inherited thrombophilia. For patients with an FVL mutation, 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 Mutation
The 2009 AHRQ evidence report identified 18 studies that evaluated recurrence risk in patients heterozygous for the prothrombin G20210A mutation. Some of these studies included only heterozygotes, and others combined both heterozygotes and homozygotes. For 9 studies that included only heterozygotes, pooled OR for recurrent VTE was 1.45 (95% CI: 0.96 to 2.2). For 7 studies that did not specify whether patients were homozygous or heterozygous, the combined OR was 0.73 (95% CI: 0.37 to 1.44).

The prothrombin G20210A 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).

Prothrombin Mutations
Evidence on VTE 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 1 study evaluating homozygotes. For heterozygote probands, family members had an OR for future VTE of 1.89 (95% CI, 0.35 to 10.2).

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

Pregnancy and other high-risk situations
Pregnancy
Evidence on the risk of recurrent pregnancy loss in women with FVL or a prothrombin gene mutation...
Genetic Testing for Inherited Thrombophilia

Policy # 00333
Original Effective Date: 12/19/2012
Current Effective Date: 12/21/2016

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

A 2012 systematic review by Bradley et al. analyzed 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 G20210A 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.

**Section Summary**
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 populations discussed 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, 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 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:
Genetic Testing for Inherited Thrombophilia

Policy # 00333
Original Effective Date: 12/19/2012
Current Effective Date: 12/21/2016

- 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.

Some authors 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.

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 2008 MEGA study was a large, population-based, case-control study that evaluated whether testing for thrombophilia in patients with a first episode of VTE was associated with a decrease in 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).

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

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

There are no comparative trials of testing versus no testing in relatives of individuals with thrombophilia. The clinical utility of testing depends on the balance between the benefit of altering management as a result of knowledge of 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.

Pregnancy

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.

The current chapter on prothrombin-related thrombophilia in GeneReviews® concluded: “Although technically possible, prenatal diagnosis and preimplantation genetic diagnosis (PGD) are rarely, if ever, performed because the 20210G>A allele only increases the relative risk for thrombophilia and is not predictive of a thrombotic event.”

Section Summary

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.

Ongoing and Unpublished Clinical Trials

One currently unpublished trial that might influence this policy is listed in Table 2.

Table 2. 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>
<td></td>
<td></td>
</tr>
</tbody>
</table>

©2016 Blue Cross and Blue Shield of Louisiana
An independent licensee of the Blue Cross and Blue Shield Association
No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Page 9 of 13
Genetic Testing for Inherited Thrombophilia

Policy # 00333
Original Effective Date: 12/19/2012
Current Effective Date: 12/21/2016

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 of Evidence
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 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.

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 specific management changes and the impact of those management changes on outcomes is uncertain. According to 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 outweights the risk. Because of the lack of documented clinical utility, evidence for genetic testing for inherited thrombophilia is considered insufficient to demonstrate improvement in net health outcome. Studies that show how test results impact treatment decisions and how these modified treatments improve net health outcome compared with no testing are required.

References
Genetic Testing for Inherited Thrombophilia

Policy # 00333
Original Effective Date: 12/19/2012
Current Effective Date: 12/21/2016

Genetic Testing for Inherited Thrombophilia

Policy # 00333
Original Effective Date: 12/19/2012
Current Effective Date: 12/21/2016


Policy History

Original Effective Date: 12/19/2012
Current Effective Date: 12/21/2016
12/06/2012 Medical Policy Committee review
12/19/2012 Medical Policy Implementation Committee approval. New policy.
11/07/2013 Medical Policy Committee review
12/04/2014 Medical Policy Committee review
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
12/03/2015 Medical Policy Committee review
12/16/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/01/2016 Medical Policy Committee review
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

Next Scheduled Review Date: 12/2017

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2015 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.
Genetic Testing for Inherited Thrombophilia

Policy # 00333
Original Effective Date: 12/19/2012
Current Effective Date: 12/21/2016

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

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81240, 81241, 81291, 81401</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
</tbody>
</table>

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

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.