**Genetic Testing for Inherited Thrombophilia**

**Effective:** April 1, 2018

**Next Review:** February 2019  
**Last Review:** March 2018

**IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

**DESCRIPTION**

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.

**MEDICAL POLICY CRITERIA**

Genetic testing for inherited thrombophilia, including testing for factor V Leiden, prothrombin gene mutations, and mutations in the *MTHFR* gene, is considered **investigational**.

**NOTE:** A summary of the supporting rationale for the policy criteria is at the end of the policy.

**CROSS REFERENCES**

1. [Genetic and Molecular Diagnostic Testing](#), Genetic Testing, Policy No. 20  
2. [Genetic Testing for Methionine Metabolism Enzymes, including *MTHFR* for Indications Other than Thrombophilia](#), Genetic Testing, Policy No. 65

**BACKGROUND**

**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 with or without history of complications
- Recurrent pregnancy loss or recurrent early pregnancy loss
- Hormonal therapy with estrogen/progesterones
- Systemic lupus erythematous (SLE), and/or other rheumatologic disorders
- Myeloproliferative disorders
- Liver dysfunction
- Nephrotic syndrome
- Hereditary factors

Treatment of thrombosis involves anticoagulation for a minimum of three to six 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 to 10-fold increase in the risk for VTE, and the absolute risk of VTE in pregnancy has been estimated to be 1 to 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 (factor V Leiden)
- Prothrombin gene mutation
• Protein C deficiency
• Protein S deficiency
• Prothrombin deficiency
• Hyper-homocysteinemia (*MTHFR* mutations)

The most common type of inherited thrombophilia is a coagulation factor V variant known as factor V Leiden (FVL), which accounts for up to 50% of the inherited thrombophilia syndromes. In unselected patients with an idiopathic thrombosis, the rate of factor V Leiden positivity is in the range of 17% to 24%,[3] compared to a rate of 5 to 6% in normal controls. The prothrombin gene mutation (PGM) is found less commonly, in approximately 5% to 8% of unselected patients with thrombosis, compared to 2% to 2.5% of normal controls.[3]

Genetic testing for gene variants associated with thrombophilias are available for FVL, PGM, 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. planned major surgery, or oral contraceptive use.
• Evaluation of pregnancy with or without history of complications, including recurrent pregnancy loss and recurrent early pregnancy loss

**REGULATORY STATUS**

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. 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, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

**EVIDENCE SUMMARY**

Human Genome Variation Society (HGVS) nomenclature[4] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

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

The focus of the following review is on evidence related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

**MTHFR MUTATION TESTING**

Mutations in the *MTHFR* gene are associated with hyper-homocysteinemia, which is in turn considered a weak risk factor 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.

**Section Summary**

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**

The analytical validity, clinical validity, and clinical utility, will be discussed for distinct patient populations, including individuals without a personal history of VTE, individuals with a personal history of VTE, family members of individuals with thrombophilia, those at high risk for VTE due to hormone use or surgery, and pregnant women with or without a history of adverse complications, including recurrent pregnancy loss and early recurrent pregnancy loss.

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.
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: 1) the overall low incidence of thromboembolism in the general population; 2) 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; 3) the potential risk of prophylactic treatment, especially the bleeding risk with anticoagulation; and 4) this risk may outweigh the benefit in patients with a relatively low absolute risk of thrombosis.

Individuals without a Personal History of Venous Thrombosis

Analytic Validity

In 2009, the Agency for Healthcare Research and Quality (AHRQ) published results from a comprehensive literature review of studies of analytic validity. There were 41 studies that compared genetic testing for factor V Leiden (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 PGM, and all of these studies reported a 100% concordance with reference standards.

Clinical Validity

Individuals with both FVL and PGM have an elevated risk of thrombosis compared to the general population. For individuals with FVL, the risk may be 2 to 5-fold higher than the general population. In one study of asymptomatic individuals, those with FVL had an annual incidence of VTE of 0.45%, compared with an incidence of 0.1% in those without FVL. For the PGM, the risk has also been estimated to be two to five times greater than the general population. In a meta-analysis of 79 studies, the combined risk ratio was 3.0. Heterozygosity for PGM is also associated with an elevated risk of upper extremity thrombosis, estimated to be five times that of the general population.

Clinical Utility

There are limited studies available that directly evaluated the clinical utility of screening asymptomatic individuals for inherited thrombophilia. Grandone published results from a follow-up study on 157 women from an original sample (n=1107) of infertile women. The cohort of women included in the study had at least one cycle before the thrombophilia test and one cycle after the test. All underwent thrombophilia screening. Clinical pregnancy and live birth rates were the main clinical objectives. Overall, 15 (9.6%) women carried thrombophilia. Authors concluded that thrombophilia screening before assisted reproductive technologies is not useful to discriminate women with a worse pregnancy prognosis.

Section Summary

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% 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 the risk of VTE, such as avoidance of prolonged immobility, but this is unproven.

Individuals with a Personal History of VTE

Clinical Validity

In 2014, Mahajerin published the results of a single-center, retrospective cohort study of pediatric patients, mostly adolescents, who presented with VTE (88% DVT) “to help clarify the role of thrombophilia testing in pediatric VTE.”[12] Of 392 inpatients and outpatients, thrombophilia tests (FVL; PGM; 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 one 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.

In a similar study, Kovac evaluated the clinical characteristics of initial VTE in women under the age of 45.[13] A total of 447 women younger than 45 and 174 women over 45 with a confirmed VTE were included in the study. Thrombophilia was reported in 48.7% of younger women compared to 28.7% of older women (p=0.03); however, it is unclear how these test results may impact treatment decisions or overall outcomes in either patient group.

Factor V Leiden (FVL)

The 2009 AHRQ evidence report reviewed the evidence on the risk of recurrence for patients with a history of VTE and FVL.[7] For individuals heterozygous for FVL, there were a total of 13 studies that compared the risk of recurrence with a mutation to the risk of recurrence without FVL. Pooled analysis of these 13 studies yielded an odds ratio of 1.56 (95% confidence interval [CI]: 1.14-2.12) for recurrent VTE in patients with FVL. For patients with homozygous FVL, there were seven studies that evaluated risk. The pooled odds ratio for recurrent VTE in these studies was 2.65 (95% CI: 1.18-5.97).

Not all studies were consistent in reporting an increased risk of recurrent VTE in patients with inherited thrombophilia. For example, the Leiden thrombophilia study (LETS)[14] 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 and 6% with PGM. There was not an increased recurrence rate for either patients with FVL or for patients with PGM. 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).

One of the larger RCTs that was included in the AHRQ review was the ELATE study,[15] 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 FVL, 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).

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.[16] 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 PGM was not associated with an increased recurrence rate, with an odds ratio of 0.8 (95% CI: 0.3-2.6).

Tzoran reported on outcomes during the course of anticoagulation after VTE for individuals with FVL or PGM using the Registro Informatizado de Enfermedad TromboEmbolica database.[17] From 2001 to 2015, 10,139 patients were tested for thrombophilic mutations, with 1,384 found to have FVL and 1,115 found to have the PGM. During the course of anticoagulation, 254 patients had a recurrent VTE: 160 had a DVT and 94 had a pulmonary embolism (16 died), 154 patients had an episode of major bleeding (10 died) and 291 patients had nonmajor bleeding. After multivariable analysis, patients with FVL had a similar risk for VTE recurrence as non-FVL carriers had (adjusted hazard ratio [HR], 1.16; 95% CI, 0.82-1.64), but half the risk of major bleeding compared with non-FVL carriers (adjusted HR, 0.50; 95% CI, 0.25-0.99). The authors conclude that this reduced bleeding risk for patients with FVL may aid in anticoagulation duration decision-making.

**Prothrombin Gene Mutation (PGM)**

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

PGM 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,[15] the risk of recurrent VTE with the PGM could not be calculated because there were no recurrences among 60 patients with the mutation. In the LETS study,[14] there were 29 patients with a PGM. For patients with a PGM, 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. In the study by Tzoran described above, PGM carriers had similar rates of recurrent VTE (adjusted HR, 1.00; 95% CI, 0.68-1.48) and major and minor bleeding events as non-carriers (adjusted HRs, 0.75; 95% CI, 0.42-1.34; and 1.10; 95% CI, 0.77-1.57, respectively).

**Clinical Utility**

A study by Kudo assessed the clinical utility of thrombophilia testing for VTE patients in public hospitals in Australia.[18] This retrospective study evaluated data from 152 patients that presented at the hospitals between August 2011 and September 2012. Of these, 49% had thrombophilia testing and 31% had a positive result. The authors noted that 38% of patients with a provoked VTE were tested, contrary to guideline recommendations, and that the proportion of positive results was higher in the unprovoked VTE patients compared with the provoked VTE patients (45% vs. 29%). Only 1.2% of patients had documented changes to the duration of anticoagulation due to positive results. The authors concluded that testing for
thrombophilia in these hospitals was often not consistent with clinical guidelines and that the results of such testing did not significantly influence decision-making.

One study surveyed 112 primary care physicians about the impact of FVL testing in patients with VTE.¹⁹ 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.

Garcia-Horton evaluated the impact of thrombophilia screening on patient management in a single center, retrospective cohort study of patients with unprovoked VTE.²⁰ The study included 1033 patients referred between 1999 and 2011. Of these, 85.2% received thrombophilia testing (n=881), including testing for FVL and PGM, and 271 (30.8%) tested positive for any thrombophilia. There were 169 patients with FVL (19.2%) and 43 with PGM (4.6%). Outcomes were assessed separately for patients referred before and after 2008, as after 2008, anticoagulation duration decisions were based on clinical and biochemical criteria developed in the REVERSE study. The overall VTE recurrence rate was similar between mutation carriers and non-carriers, though among those who did not have extended anticoagulation, the VTE rate was higher in mutation carriers than non-carriers. The authors concluded that thrombophilia screening may only be useful in very specific situations, and that such screening “continues to have little relevance in clinical decision making for anticoagulation.”

Section Summary

The evidence does not support thrombophilia testing in pediatric patients who present with VTE. Furthermore, the study results indicate that there is a similar rate of VTE recurrence for carriers of FVL or PGM and non-carriers. Finally, there is evidence that this testing rarely leads to treatment changes or changes in net health outcomes; therefore, clinical utility has not been demonstrated.

Family Members of Individuals with Thrombophilia

Clinical Validity

FVL

The 2009 AHRQ report identified nine studies that evaluated the risk of VTE in family members of a proband with a heterozygous mutation.⁷ The pooled odds ratio for future VTE was 3.49 (95% CI: 2.46-4.96). There were six studies that evaluated a total of 48 probands with homozygous FVL. The pooled odds ratio 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 pooled the results from five retrospective family studies of thrombophilia.²¹ A total of 2,479 relatives of patients with thrombophilia who were themselves also tested for thrombophilia were included. For relatives with FVL, 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% per year, and the adjusted relative risk for VTE in relatives with FVL 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 Gene Mutation (PGM)
The evidence on the risk for family members of individuals with a PGM is less than for FVL, with five studies identified by AHRQ evaluating heterozygotes and only one study evaluating homozygotes. For the heterozygote probands, family members had an odds ratio for future VTE of 1.89 (95% CI: 0.35-10.2).

In the Lijfering family study,[21] relatives with PGM 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% per year, and the adjusted relative risk for VTE in relatives with a mutation was 5.2 (95% CI: 2.8-9.7).

Clinical Utility

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.

Section Summary

The evidence suggests that the risk for individual with a VTE who have a family member with FVL or PGM remains low. 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; however, this risk benefit is unknown, therefore, clinical utility has not been demonstrated.

Hormone Replacement Therapy

Clinical Utility

Studies that directly evaluate the clinical utility of hormone replacement therapy (HRT) use in patients are limited. Women using HRT have a 2 to 4-fold increase in their risk of thrombosis.[22] 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.[22]

Wu published results of the TREATS study on the risk of clinical complications associated with thrombophilia in three high-risk patient groups: women using oral estrogen preparations, women during pregnancy and patients undergoing major orthopedic surgery were assessed.[23] The risk of clinical complications associated with thrombophilia, was analyzed using a systematic review of the literature on VTE and thrombophilia in women using oral estrogen preparations. Pooled odds ratios associated with individual clinical outcomes, stratified by thrombophilia type, were calculated for each patient group. In the review of risk of clinical complications, 81 studies were included, nine with oral estrogen preparations. The authors concluded that for HRT, a significant association with VTE was found in women with FVL. The authors further concluded, large prospective studies should be undertaken to refine the risks and establish the associations of thrombophilias with VTE among hormone users.

Section Summary
Although evidence on the clinical utility of HRT is limited, evidence suggests that patients with FVL do have a greater risk of VTE; however, more studies are needed to establish this association.

**Oral Contraceptives**

**Clinical Utility**

Studies that directly evaluated the clinical utility of thrombophilia testing for oral contraceptive use is limited. 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,[24] 2% of which are estimated to be fatal.

In the TREATS study described above, the risk of clinical complications associated with thrombophilia in women using oral oestrogen preparations were described.[23] For oral contraceptive use, significant associations of the risk of VTE were found in women with FVL; deficiencies of antithrombin, protein C, or protein S; elevated levels of factor VIIIc; and PGM. In women who are on combined oral contraceptives, the OR of VTE among those who are FVL carriers was 15.62 (95% confidence interval 8.66 to 28.15). However, in view of the prevalence of thrombophilia and the low prevalence of VTE in non-users of combined oral contraceptives, the absolute risk remains low. Authors concluded that universal thrombophilia screening in women prior to prescribing oral estrogen preparations is not supported by current evidence. Again, large prospective studies are necessary to refine the risks and establish the associations of thrombophilias with VTE among hormone users.

**Section Summary**

Although evidence on the clinical utility of thrombophilia testing for patients using oral contraceptives is limited, evidence does suggest that patients with FVL are at greater risk of thrombosis. However, the absolute risk remains low; therefore, the evidence does not support universal screening in women prior to prescribing oral contraceptives.

**Orthopedic Surgery**

**Clinical Utility**

Studies that directly evaluate the clinical utility of thrombophilia testing for complications associated with orthopedic surgery in patients are limited. In the TREATS study described above, a systematic review of the literature on VTE and thrombophilia in women patients undergoing major orthopedic surgery was conducted.[23] In the review of risk of clinical complications, 81 studies were included, eight with orthopaedic surgery. Significant associations were found between FVL and high factor VIIIc and postoperative VTE following elective hip or knee replacement surgery. PGM was significantly associated with postoperative pulmonary embolism. However, antithrombin deficiency, MTHFR, and hyperhomocysteinaemia were not associated with increased risk of postoperative VTE. All the studies on thrombophilia and major elective orthopedic surgery included in the review of risk complications were also used in the review of the effectiveness of thromboprophylaxis. However, there were insufficient data to determine the relative effectiveness of different thromboprophylaxis in preventing VTE in this patient group. Thrombophilic defects including FVL, high plasma factor VIIIc levels, and PGM are associated with the occurrence of postoperative VTE in elective hip or knee
replacement therapy. These associations were observed in patients who were given preoperative thromboprophylaxis. Authors concluded that universal thrombophilia screening in patients undergoing major orthopedic surgery is not supported by current evidence. The authors concluded that large prospective studies should be conducted to refine the risks and establish the associations of thrombophilias with VTE in patients undergoing orthopedic surgery.

In a case series of 86 patients, congenital thrombophilia responsible for thromboembolic complications despite prolonged low-molecular-weight heparin prophylaxis following hip and knee endoprosthesis surgery was investigated. Authors screened for the presence of lupus anticoagulant, FVL, and PGM. Authors reported in 33 patients, thromboembolic complications were reported, 18 with thrombophilia (seven with combined form). Significant differences were found in the incidence (P < or = 0.01) of thrombophilia and the risk score (P < or = 0.02) between symptomatic and asymptomatic patients. Authors recommended preoperative thrombophilia screening for patients with a history or familial prevalence of thromboembolism and/or with a high risk score (> or =15). However, authors concluded in cases of thrombophilia, the form and duration of anticoagulant treatment must be decided individually.

**Section Summary**

Patients with a *MTHFR* mutation were not associated with an increased risk of postoperative VTE, generally. Evidence suggests there is an increased risk of VTE after an orthopedic surgery for patients with FVL, however, there is insufficient data to determine the relative effectiveness of thromboprophylaxis to prevent VTE.

**Pregnant Patients**

**Analytic Validity**

Bradley[25] published results from a study that 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 PGM, the analytic sensitivity was 98.4% and the analytic specificity was 99.7%.

**Clinical Validity**

*Pregnancy with or without history of complications*

The evidence on complications associated with pregnancy in women with the FVL and PGM is limited. Adverse outcomes associated with pregnancy in women with these mutations include fetal loss; preeclampsia, eclampsia; placental abruption; fetal growth restriction; intrauterine fetal death; and hemolysis, elevated liver enzymes, low platelet counts (HELLP) syndrome.

In a prospective cohort trial, Rodgers investigated whether FVL or PGM were associated with placenta-mediated pregnancy complications.[26] Complete primary outcome and genetic data were available for 7,343 women. Authors report there were 507 (6.9%) women with FVL and/or PGM; 11.64% had a placenta-mediated pregnancy complication. Of the remaining 6,836 women, 11.23% experienced a complication. FVL and/or PGM was associated with a relative risk of 1.04 (95% CI 0.81-1.33) for the composite outcome with similar results after adjustment for important covariates. Authors concluded that carriers of FVL or PGM are not at significantly increased risk of these pregnancy complications.
Silver assessed the role of heritable thrombophilia in stillbirth, using data from the Stillbirth Collaborative Research Network, a population-based case-control study.[27] Genetic testing results for FVL, PGM, MTHFR, and/or plasminogen activator inhibitor 1 (PAI-1) were available for 488 stillbirth and 1342 live birth mothers, and 405 stillbirth and 990 live birth fetuses. There was a significant associations between maternal FVL and risk of stillbirth (2/488; 0.4% vs 1/1380; 0.0046%; OR, 87.44; 95% CI, 7.88-970.92), and between fetal PAI-1 4G/4G polymorphism and decreased risk of stillbirth (OR, 0.63; 95% CI, 0.43-0.91), but no other associations were seen.

A case-control study by Lenz evaluated the relationship between thrombophilic risk factors, including FVL, PGM, and MTHFR mutations, and pregnancy complications in Croatian women.[28] The authors reported that pregnant women with VTE were more likely to have FVL (p=0.005).

Several factors impact studies concerning thrombophilia and pregnancy complications, including the heterogeneity of the populations studied, small sample size, rarity of the end point evaluated, number of thrombophilias assayed, detection methods employed, lack of consistent assessment of fetal thrombophilia status, and potential ascertainment biases.[29] Another confounding factor is pregnancy history and the severity of the pregnancy complication, which significantly impact the recurrence and occurrence of pregnancy complications in subsequent pregnancies, without considering thrombophilia.

**Recurrent Pregnancy Loss (>15 weeks)**

The evidence on the risk of recurrent pregnancy loss in women with FVL or PGM comes from case-control studies and cohort studies that are primarily retrospective. Several case-control studies have reported a higher prevalence of FVL (odds ratio [OR]: 2–5) in women with recurrent, unexplained pregnancy loss compared to controls.[22] 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,[25] analyzed the evidence on the association of FVL and PGM 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. Two of the four studies reported a significantly increased rate of recurrence for carriers, and two studies did not. Combined analysis of these four studies yielded a significantly increased odds ratio (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 PGM, with an elevated risk in the 2-3 range.[8]

Bradley[25] 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.

**Recurrent Early Pregnancy Loss (<15 weeks)**
Recurrent early pregnancy loss is defined as two or more consecutive pregnancies that end in demise before 15 weeks gestation. Studies specific to genetic testing for thrombophilia and early pregnancy loss were limited to retrospective association studies, and these studies yielded conflicting results. Studies of genetic associations aim to test whether single-locus allele or genotype frequencies differ between two groups of individuals (usually diseased subjects and healthy controls). Association studies cannot test causality.

Barlik evaluated the frequency of 20210G>A and 19911A>G prothrombin gene polymorphisms in a group of women with two or more miscarriages in the first trimester of pregnancy.[30] The study involved 150 women with two or more miscarriages in the first trimester of pregnancy (mean age 31.5 +/- 4.1 years). The control group consisted of 180 healthy women (mean age 28.7 +/- 4.0 years). The authors reported a lack of correlation of 20210G>A and 19911A>G prothrombin gene polymorphisms with the risk of recurrent miscarriages in the first trimester of pregnancy.

In a retrospective study, Mierla investigated the effects of FVL and PGM involved in reproductive failure. The frequency of polymorphic variations was calculated for 283 patients with unexplained infertility. The control group included 100 women who had one or more children. Heterozygous and normal homozygous for FVL and PGM were equally distributed among patients with recurrent miscarriage and fertile patients with two or more previous births. The combination of the two polymorphisms, prothrombin (A20210G) and FVL (A506G) revealed a significant correlation between them and early fetal loss. Authors concluded the genes involved in thrombophilia could be one reason for fertility complications in some women with unexplained infertility. Retrospective studies are limited by the accuracy of the medical records reviewed, and there is no randomization or blinding, making it difficult to control for bias and confounders.

Clinical Utility

Studies that directly evaluated the clinical utility of thrombophilia testing in pregnant patients are limited. 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.[31,32] 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 PGM.[25] 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.

In a systemic review, described above, by Wu VTE and adverse obstetric complications in women with thrombophilia during pregnancy was conducted.[23] In the review of risk of clinical complications, 81 studies were included, 72 for pregnancy. The highest risk in pregnancy was found for FVL and VTE, in particular, homozygous carriers of this mutation are 34 times more likely to develop VTE in pregnancy than non-carriers. Significant risks for individual thrombophilic defects were also established for early, recurrent and late pregnancy loss; preeclampsia; placental abruption; and intrauterine growth restriction. In the review of the effectiveness of prophylaxis, based on available data from eight studies, low-dose aspirin and heparin was found to be the most effective in preventing pregnancy loss in thrombophilic
women during pregnancy, while aspirin alone was the most effective in preventing minor bleeding. Significant risks for VTE and adverse pregnancy outcomes have been established with individual thrombophilic defects. Universal thrombophilia screening in women during pregnancy is not supported by current evidence. [27]

**Section Summary**

The analytic validity of FVL and PGM testing during pregnancy is high. Studies concluded that, generally, pregnant patients who are FVL or PGM carriers are not at significantly higher risk for complications. Although there does seem to be some risk for patients who have a recurrent pregnancy loss the authors concluded that there are no safe and effective treatments to reduce recurrent pregnancy loss in women with inherited thrombophilia. Therefore, the current evidence does not support universal thrombophilia screening.

**PRACTICE GUIDELINE SUMMARY**

There are many guidelines and position statements on testing for thrombophilia published over the last 20 years. These guidelines have evolved with time, often do not agree with each other, and do not typically give specific parameters for when to perform genetic testing. The following are examples of recently published U.S. guidelines, developed by major specialty societies.

**THE EVALUATION OF GENOMIC APPLICATIONS IN PRACTICE AND PREVENTION WORKING GROUP**

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group published recommendations in 2011 that addressed genetic testing for FVL and prothrombin (PT) mutations.[33] Utilizing a grading system and expert consensus, this publication included the following recommendations on the clinical utility of genetic testing:

- There is no evidence that knowledge of FVL/PT mutation status in patients with VTE affects anticoagulation treatment to avoid recurrence.
- There is convincing evidence that anticoagulation beyond three months reduces recurrence of VTE, regardless of mutation status.
- There is no evidence that knowledge of FVL/PT mutation status among asymptomatic family members of patients with VTE leads to anticoagulation aimed at avoiding initial episodes of VTE.

**THE AMERICAN COLLEGE OF CHEST PHYSICIANS**

In 2012, the American College of Chest Physicians (ACCP) published the ninth edition of their evidence-based guidelines on antithrombotic therapy and the prevention of thrombosis.[34] For pregnant women with no prior history of VTE who are known to be homozygous for FVL or PGM, ACCP made the following recommendations:

- Positive family history for VTE: ACCP suggests antepartum prophylaxis with prophylactic- or intermediate-dose low molecular weight heparin (LMWH) and postpartum prophylaxis for six weeks with prophylactic- or intermediate-dose LMWH or warfarin (international normalized ratio [INR] target, 2.0-3.0) rather than no prophylaxis (Grade 2B [weak] recommendation, based on moderate-quality evidence)
• No family history for VTE: ACCP suggests antepartum clinical vigilance and postpartum prophylaxis for six weeks with prophylactic- or intermediate-dose LMWH or warfarin (INR target, 2.0-3.0) rather than routine care (Grade 2B [weak] recommendation, based on moderate-quality evidence).

Also in 2012, the ACCP published evidence-based clinical practice guidelines titled, “VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy” which state the following:[35]

“Hyperhomocysteinemia is associated with an increased risk of VTE in nonpregnant women. However, it does not appear that homozygosity for MTHFR C667T (the genetic abnormality most commonly associated with hyperhomocysteinemia) alone leads to an increased risk of VTE in pregnant women. As clinical events in homozygotes are likely to reflect the interaction of the genotype with a relative deficiency of vitamins, such as B12 and folic acid, the absence of an association of this genotype with gestational VTE may reflect pregnancy related physiological reduction in homocysteine levels and the effects of folic acid supplements that are now taken widely by women in pregnancy for prevention of neural tube defects.”

AMERICAN CONGRESS OF OBSTETRICIANS AND GYNECOLOGISTS

The American Congress of Obstetrician and Gynecologists (ACOG) updated clinical management guidelines for inherited thrombophilias in pregnancy in 2013.[36] ACOG guidelines are based upon a rating of the evidence and expert consensus.

The following guidelines are based on limited or inconsistent scientific evidence:

“Screening for thrombophilias is controversial. It is useful only when results will affect management decisions, and it is not useful in situations where treatment is indicated for other risk factors. Screening may be considered in the following clinical settings:

• A personal history of venous thrombembolism that was associated with a nonrecurrent risk factor (e.g., fractures, surgery, and prolonged immobilization). The recurrence risk among untreated pregnant women with such a history and a thrombophilia was 16% (odds ratio, 6.5; 95% confidence interval, 0.8-56.3).

• A first-degree relative (e.g., parent or sibling) with a history of high-risk thrombophilia.

The guideline also indicated situations when testing was not recommended:

• Testing for inherited thrombophilias in women who have experienced recurrent fetal loss or placental abruption was not recommended because it is unclear if anticoagulation therapy reduces recurrence. Although there may be an association in these cases, there is insufficient clinical evidence that antepartum prophylaxis with unfractionated heparin or low molecular weight heparin prevents recurrence in these patients.

• 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.
• In addition, there is insufficient evidence to either screen for or treat women with inherited thrombophilia and obstetric histories that include complications such as fetal growth restriction or preeclampsia.

THE AMERICAN COLLEGE OF MEDICAL GENETICS

In 2013, the American College of Medical Genetics (ACMG) published clinical a practice guideline evaluating the evidence for \textit{MTHFR} polymorphism testing.\cite{37} The ACMG guidelines are based on consensus and expert opinion. The following recommendations were made by the group:

• \textit{MTHFR} polymorphism genotyping should not be ordered as part of the clinical evaluation for thrombophilia or recurrent pregnancy loss.

• \textit{MTHFR} polymorphism genotyping should not be ordered for at-risk family members.

• A clinical geneticist who serves as a consultant for a patient in whom an \textit{MTHFR} polymorphism(s) is found should ensure that the patient has received a thorough and appropriate evaluation for his or her symptoms.

• If the patient is homozygous for the “thermolabile” variant c.665C→T, the geneticist may order a fasting total plasma homocysteine, if not previously ordered, to provide more accurate counseling

• \textit{MTHFR} status does not change the recommendation that women of childbearing age should take the standard dose of folic acid supplementation to reduce the risk of neural tube defects as per the general population guidelines.

SUMMARY

There is not enough research to show that testing for genetic mutations that increase the risk of thrombosis, such as prothrombin gene mutations and Factor V Leiden (FVL) can improve health outcomes for people who may be at risk for venous thrombosis. Clinical guidelines based on research are inconsistent on this topic. Therefore, genetic testing for inherited thrombophilias, including testing for the \textit{MTHFR} gene, the prothrombin gene, and FVL, is considered investigational.

REFERENCES


### CODES

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