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Medical Policy Manual

Topic: Genetic Testing for Inherited Thrombophilia

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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.

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.[1] 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.[1] 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 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.[2] 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.[2]

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 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 factor V Leiden mutation, 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 17-24%,[3] 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.[3]

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. 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. These tests are available as laboratory developed procedures under the U.S. Food and Drug Administration (FDA) enforcement discretion policy for laboratory developed tests.

MEDICAL POLICY CRITERIA

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

SCIENTIFIC EVIDENCE

Validation of the clinical use of any genetic test focuses on 3 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.

MTHFR Mutation Testing

Mutations in the MTHFR gene are associated with hyper-homocysteinemia, which is in turn associated with an increased risk for venous thromboembolism (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. [4] A randomized controlled trial (RCT) published in abstract form reported that there was no reduction in VTE associated with treatment of hyperhomocysteinemia.[5]

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 (FVL) and Prothrombin Mutation Testing

The analytical validity, clinical validity, and clinical utility, will be discussed for 4 distinct patient populations, including individuals without a personal history of VTE, individuals with a personal history of VTE, family members of individuals with thrombophilia, 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

<u>Individuals without a personal history of VTE</u>

Analytic Validity

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.[6] 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.

Clinical Validity

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.[7]

For the prothrombin mutation, the risk has also been estimated to be 2-5 times greater than the general population.[8] In a meta-analysis of 79 studies, the combined risk ratio was 3.0.[9] 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.[8]

Clinical Utility

There are limited studies available that directly evaluated the clinical utility of screening asymptomatic individuals for inherited thrombophilia. Grandone and others conducted a follow-up study on 157 women from an original sample (n=1107) of infertile women.[10] The cohort of women included in the study had at least 1cycle before the thrombophilia test and 1 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.

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.

<u>Individuals with a Personal History of VTE</u>

Clinical Validity

- FVL

  The 2009 AHRQ evidence report reviewed the evidence on the risk of recurrence for patients with a history of VTE and the FVL mutation.[6] 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 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 odds ratio 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)[11] followed 474 patients who had completed a course of anticoagulation for a mean 0f 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.

One of the larger RCTs that was included in the AHRQ review was the ELATE study,[12] 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.[6] 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 odds ratio 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 odds ratio 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,[12] 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,[11] 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.

Clinical Utility

The MEGA study[13] 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 odds ratio 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.[14] 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.

<u>Family Members of Individuals with Thrombophilia</u>

Clinical Validity

- FVL

  The 2009 AHRQ report identified 9 studies that evaluated the risk of VTE in family members of a proband with a heterozygous mutation.[6] The pooled odds ratio 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 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 et al.[15] 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 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 odds ratio for future VTE of 1.89 (95% CI: 0.35-10.2).

  In the Lijfering family study,[15] 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).

  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.

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.

<u>Hormone Replacement Therapy (HRT)</u>

Clinical Utility

Studies that directly evaluate the clinical utility, or how patient management changes, as a result of thrombophilia testing for hormone replacement use in patients are limited. Women using hormone replacement therapy have a 2- to 4-fold increase in their risk of thrombosis.[16] 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.[16]

In the TREATS study by Wu et al., the risk of clinical complications associated with thrombophilia in three high-risk patient groups: women using oral oestrogen preparations, women during pregnancy and patients undergoing major orthopaedic surgery were assessed.[17] The risk of clinical complications associated with thrombophilia, was analyzed using a systematic review of the literature on venous thromboembolism (VTE) and thrombophilia in women using oral oestrogen preparations. Meta-analysis was used to calculate pooled odds ratios (ORs) associated with individual clinical outcomes, stratified by thrombophilia type and were calculated for each patient group. In the review of risk of clinical complications, 81 studies were included, 9 for oral oestrogen preparations. The authors concluded that for hormone replacement therapy (HRT), a significant association 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.

Oral Contraceptives

Clinical Utility

Studies directly evaluate the clinical utility, or how patient management changes, as a result of thrombophilia testing for oral contraceptive use in patients are limited. Oral contraceptive use alone is associated with an approximately 4-fold increase in risk of thrombosis; in combination with factor V Leiden 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,[18], 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.[17] For oral contraceptive use, significant associations of the risk of VTE were found in women with factor V Leiden (FVL); deficiencies of antithrombin, protein C, or protein S, elevated levels of factor VIIIc; and FVL and prothrombin G20210A. In women who are on combined oral contraceptives, the OR of VTE among those who are carriers of the FVL mutation 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 oestrogen 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.

Orthopedic Surgery

Clinical Utility

Studies that directly evaluate the clinical utility, or how patient management changes, as a result 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.[17] In the review of risk of clinical

complications, 81 studies were included, 8 for orthopaedic surgery. Significant associations were found between FVL and high factor VIIIc and postoperative VTE following elective hip or knee replacement surgery. Prothrombin G20210A 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 prothrombin G20210A 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 (LMWH) prophylaxis following hip and knee endoprosthesis surgery was investigated. Authors screened for the presence of lupus anticoagulant, factor V Leiden mutation, and polymorphism of prothrombin G20210A. Authors reported in 33 patients, thromboembolic complications were reported, 18 with thrombophilia (7 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.

Pregnant Patients

Analytic Validity

Preg Bradley et al.[19] 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%.

Clinical Validity

- Pregnancy with or without history of complications

  The evidence on complications associated with pregnancy in women with the FVL and prothrombin gene mutation (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 HELLP syndrome.

  In a prospective, cohort trial, Rodgers et al. investigated whether FVL or the PGM were associated with placenta-mediated pregnancy complications.[20] 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.

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.[21] 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 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 (odds ratio [OR]: 2–5) in women with recurrent, unexplained pregnancy loss compared to controls.[16] 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.,[19] 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 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 the prothrombin mutation, with an elevated risk in the 2-3 range.[8]

  Bradley et al.[19] 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 alleles or genotype frequencies differ between two groups of individuals (usually diseased subjects and healthy controls). Association studies cannot test causality.

Barlik et al. evaluated the frequency of 20210G>A and 19911A>G prothrombin gene polymorphisms in a group of women with 2 or more miscarriages in the first trimester of pregnancy.[22] 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 and others investigated the effects of factor V and factor II 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 the factor V mutation and factor II mutation 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 factor V Leiden (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 evaluate the clinical utility, or how patient management changes, as a result 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.[23,24] 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.[19] 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 et al. VTE and adverse obstetric complications in women with thrombophilia during pregnancy was conducted.[17] 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.

Clinical Practice Guidelines

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 guidelines published in the last 5 years, from the U.S., and developed by major specialty societies.

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group

The EGAPP working group published recommendations in 2011 that addressed genetic testing for Factor V Leiden mutations and Prothrombin mutations.[25] 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 (ACCP)

The ACCP published evidence-based guidelines for the treatment of thromboembolic disease in 2008.[9] These guidelines stated the following concerning genetic testing for thrombophilia:

- The presence of hereditary thrombophilia has not been used as a major factor to guide duration of anticoagulation for VTE in these guidelines because evidence from prospective studies suggests that these factors are not major determinants of the risk of recurrence.

The ACCP published evidence-based clinical practice guidelines titled, "VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy" in 2012 that state the following:[26]

- "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 (ACOG)

ACOG updated clinical management guidelines for inherited thrombophilias in pregnancy in 2013.[27] 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 thromboembolism that was associated with a nonrecurrent risk factor (eg, 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 (eg parent or sibling) with a history of high-risk thrombophilia.

In other situations, thrombophilia testing is not routinely recommended. Testing for inherited thrombophilias in women who have experienced recurrent fetal loss or placental abruption is 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 (LMWH) prevents recurrence in these patients. However, screening for antiphospholipid antibodies may be appropriate in patients experiencing fetal loss (Practice Bulletin No. 132, Antiphospholipid Syndrome, December 2012). 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 following guidelines are based on consensus and expert opinion:

- All patients with inherited thrombophilias should undergo individualized risk assessment, which may modify management decisions."
- "Screening for inherited thrombophilias should include factor V Leiden mutation; prothrombin G20210A mutation; and antithrombin, protein C, and protein S deficiencies."

<u>The American College of Medical Genetics (ACMG)</u>

ACMG published the 2013 clinical practice guideline, "ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing."[28] The ACMG guidelines are based on consensus and expert opinion:

- *MTHFR* polymorphism genotyping should not be ordered as part of the clinical evaluation for thrombophilia or recurrent pregnancy loss.

- *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 *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

- *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

Genetic testing is available for a number of types of inherited thrombophilia, including mutations in the MTHFR gene, the Factor V Leiden (FVL) gene, and the prothrombin gene; however, the clinical utility of testing is uncertain. There is insufficient evidence in the published peer-reviewed scientific literature to determine how testing for mutations in these genes guides decisions in the clinical setting related to disease treatment, management, or prevention. Additionally, it is not known whether health outcomes are improved as a result of clinical decision-making based on these gene tests. 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 venous thromboembolism (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. Therefore, genetic testing for inherited thrombophilias, including testing for the MTHFR gene, the Factor V Leiden (FVL) gene, and the prothrombin gene is considered investigational.

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CROSS REFERENCES

Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

Genetic Testing for Methionine Metabolism Enzymes, including MTHFR, for Indications Other than Thrombophilia, Genetic Testing, Policy No. 65

CODES	NUMBER	DESCRIPTION
CPT	81240	F2 (prothrombin, coagulation factor II)(e.g., hereditary hypercoagulability) gene analysis, 20210G>A variant
	81241	F5 (coagulation Factor V)(e.g., hereditary hypercoagulability) gene analysis, Leiden variant
	81291	MTHFR (5, 10-methylenetetrahydrofolate reductase)(e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)
HCPCS	None	