Genetic Testing for Inherited Thrombophilia

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DESCRIPTION

Thrombophilia is a disorder of blood coagulation that increases the risk for blood clots (thrombosis) in veins or arteries. Thrombophilia can be acquired or inherited. The most common acquired thrombophilias occur because of injury, surgery, or a medical condition. The most common hereditary thrombophilias are Factor V Leiden (FVL), due to a mutation in the F5 gene and prothrombin G20210A, because of a mutation in the F2 gene.

Factor V Leiden (FVL) and Prothrombin G20210A Variant Testing

Clinical Context and Test Purpose

The purpose of genetic testing for variants in coagulation Factor V Leiden (FVL) and prothrombin G20210A (coagulation factor II) is to provide a diagnostic option that is an alternative to or an improvement on existing tests, such as standard clinical management

without testing, in patients who are asymptomatic with or without a personal or family history of venous thromboembolism (VTE)

Factor V Leiden (FVL) variant is the most common heritable prothrombotic risk factor in the United States, with the Leiden variant accounting for 90% to 95% of activated Protein C resistance. Both heterozygotes and homozygotes are at increased risk of occurrence or recurrence of venous thromboembolism (VTE). However, clinical expression of the FVL variant is variable and many individuals with the FVL allele never develop thrombosis. The risk of VTE among pregnant women who are heterozygous for FVL without a personal history of VTE or an affected first-degree relative with a thrombotic episode before age 50 years is less than 0.3%, while this risk increases to at least 10% among pregnant women with a personal or family history of venous thromboembolism.

Prothrombin G20210A is known to be associated with coagulation factor 2 (F2) prothrombin-related thrombophilia. Individuals heterozygous for this variant have an approximately two-to four-fold increased risk of VTE as compared to individuals without the variant. Individuals who are homozygous for the variant may have a more severe thrombophilia and/or an increased risk for thrombosis; however, the number of individuals who are homozygous for the variant is small and it is difficult to determine the risk of VTE in this population.

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

Interventions
The test being considered is genetic testing for variants in coagulation Factor V Leiden (FVL) and prothrombin G20210A (coagulation factor II).

Patients who are asymptomatic with or without a personal or family history of VTE are actively managed in an outpatient clinical setting.

Comparators
Comparators of interest include standard clinical management without testing.

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

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

The harmful outcome of a false-positive result is having unnecessary treatment for VTE.

The harmful outcome of a false-negative result is a potential delay in diagnosis and treatment.

There is consensus by several professional societies/organizations that testing for Factor V Leiden (FVL) and Prothrombin G20210A (F2) is appropriate in selected individuals as an option to inform treatment. The decision to test should be based on clinical utility, that is, the likelihood that test results will impact clinical management (ACOG, ACMG, ACCP). Testing allows for prophylactic and/or ongoing clinical management including thromboprophylaxis and/or modification of risk factors. Persons for whom there is professional consensus regarding clinical utility for testing are:

- Pregnant woman who has a personal history of venous thromboembolism (VTE)
- In an individual with an unprovoked VTE (e.g., not associated with fracture, surgery, prolonged immobilization, cancer) when test results will impact long term medication management and at least one of the following:
    - Concern for homozygous F2 or F5 or compound heterozygous F2/F5
    - Annual risk of recurrent VTE is estimated to be between 5% and 10%
- Individual who has a first-degree relative (i.e., parent, full-sibling, child) with Factor V Leiden thrombophilia or F2 G2021A (prothrombin) thrombophilia and ONE of the following:
    - Surgery is planned
    - pregnant
    - Female who is considering estrogen contraception or hormone replacement therapy if results would influence decision to use estrogen

Potential consequences of identifying a thrombophilic defect in a patient with venous thromboembolism (VTE) include prolonging the anticoagulant therapy beyond three-six months or prescribing a more aggressive thromboprophylaxis in at-risk situations such as surgery, pregnancy, or prolonged immobility.

Summary of Evidence
Targeted genetic testing to confirm diagnosis of coagulation Factor V Leiden (FVL), and Prothrombin G20210A (F2) is appropriate in selected populations. Professional society support for testing is available in the form of published guidelines. The evidence is sufficient to determine the technology results in meaningful improvement in net health outcomes in a select population, see *Policy* section below.

Recurrent Pregnancy Loss

Clinical Context and Test Purpose
The purpose of genetic testing for variants in coagulation Factor V Leiden (FVL), and Prothrombin G20210A (F2, coagulation factor II) is to provide a diagnostic option that is an alternative to or an improvement on existing tests, such as standard clinical management without testing, in patients who are asymptomatic with increased VTE risk (e.g., recurrent pregnancy loss).

Miscarriage is defined as spontaneous loss of pregnancy before the fetus reaches viability (i.e., 24 weeks gestation). Early pregnancy loss generally occurs prior to 20 weeks

gestation. Sporadic pregnancy loss is nonconsecutive pregnancy loss that occurs randomly during a woman's reproductive years. Recurrent pregnancy loss, also referred to as recurrent spontaneous abortion (RSA) or recurrent miscarriage, is defined as two or more failed pregnancies and may affect as many as 1–3% of childbearing women.

The need for formal assessment and testing for recurrent pregnancy loss varies among individuals depending on age and personal choice, although traditionally couples are offered evaluation after three losses. Infertile couples who are in their fourth decade (i.e., age ≥40) may elect to be evaluated after two losses.

Potential Causes of Recurrent Pregnancy Loss
Recurrent pregnancy loss is a heterogeneous condition and may result from several underlying factors, such as anatomic, hormonal, thrombotic, autoimmune, alloimmune, genetic, infectious, or other unknown causes. The following conditions may be associated with recurrent pregnancy loss:

- Parental chromosomal anomalies and genetic disorders
- Autoimmune disorders (e.g., antiphospholipid syndrome, systemic lupus erythematosus)
- Alloimmune disorders
- Structural uterine anomalies (e.g., bicornuate uterus, uterine septum, fibroids, intrauterine adhesions)
- Cervical incompetence
- endocrine disorders (e.g., polycystic ovarian disease, luteal phase defect, thyroid disease)
- Prothrombotic states (e.g., antithrombin III deficiency, protein C or protein S deficiency/resistance, thrombocythemia, factor V Leiden)
- Infectious diseases
- Embryotoxicity

Populations
The relevant population of interest is individuals who are asymptomatic with increased VTE Risk (e.g., recurrent pregnancy loss).

Interventions
The test being considered is genetic testing for variants in coagulation Factor V Leiden (FVL) and Prothrombin G20210A (coagulation factor II).

Comparators
Comparators of interest are morbid events and treatment related morbidity.

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

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

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

Inherited thrombophilic disorders are well-established causes of systemic thrombosis and may be associated with an increased risk of pregnancy loss. Research shows that thrombophilic disorders are also found in 20% of women with normal pregnancies suggesting that additional risk factors may be required for complications to develop. The most common inherited thrombotic disorders are factor V Leiden and prothrombin G20210A mutation. Other, less common deficiencies include anticoagulant protein C, protein S, antithrombin III and methylene tetrahydrofolate reductase (MTHFR) gene. The scientific literature reports inconsistent findings for supporting any association with inherited thrombophilic disorders and recurrent early pregnancy loss, although some studies have shown a relationship with late pregnancy complications. A combination of thrombophilias may further increase the risk for recurrent fetal loss, and identification of one or more of the more common thrombophilias in a woman with RSA may warrant further investigation for other risk factors. However, the probability of having a successful pregnancy outcome remains high despite the presence of thrombophilic disorders. Routine screening of all pregnant women is not recommended. Decisions on testing and prophylactic treatment for thrombophilic disorders are based on a risk/benefit assessment.

ACOG does not recommend testing for inherited thrombophilias for women with recurrent fetal loss. According to a ACOG Practice Bulletin (2018) although there may be an association in these cases, the evidence is insufficient to support that antepartal prophylaxis with unfractionated heparin or LMWH prevent recurrence. ACOG specifically notes for concerning inherited thrombophilias in pregnancy, there is no definitive causal link between inherited thrombophilias and adverse pregnancy outcomes. Most of the available studies are small case-control and cohort studies assembled in heterogeneous populations, are frequently contradictory, and display potential reporting biases. Furthermore, ACOG does not recommend screening with fasting homocysteine levels because there is a lack of association between testing results and negative pregnancy outcomes.

Society for Maternal-Fetal Medicine

The Choosing Wisely® initiative aims to promote conversations between providers and patients by helping patients choose care that is:

- Supported by evidence
- Not duplicative of other tests or procedures already received
- Free from harm
- Truly necessary

The Choosing Wisely list created by the Society for Maternal-Fetal Medicine includes Five things physicians and patients should question. The following information is included in this list:

- Do not do an inherited thrombophilia evaluation for women with:
    - Histories of pregnancy loss
    - Intrauterine growth restriction (IUGR)
    - Preeclampsia and abruption.

A Cochrane review reported that the evidence for safety and efficacy of thromboprophylaxis with aspirin and heparin for women with a history of at least two spontaneous miscarriages without apparent causes other than inherited thrombophilia. is too limited to recommend the use of anticoagulants in this setting. There is a paucity of studies evaluating efficacy and safety of aspirin and heparin in women with a history of at least two miscarriages without apparent causes other than inherited thrombophilia. The two trials reviewed evaluated different treatments and only one study was placebo controlled. Neither of the studies showed a benefit of one treatment over the other. The Cochrane group indicated that further randomized clinical trials are needed.

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

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

Evidence of the risk of recurrent pregnancy loss in women with Factor V Leiden (FVL) or Prothrombin G20210A (F2, coagulation factor II) comprises primarily retrospective case-control and cohort studies.

In a Hayes, Clinical Utility Evaluation September 2021 regarding the clinical utility of Factor V Leiden (FVL) in women with unexplained recurrent pregnancy loss, based on the peer reviewed studies there were no studies identified that supported the clinical utility of genetic testing for Factor V Leiden (FVL) in individuals with unexplained recurrent pregnancy loss. Additional studies are needed that demonstrates this genetic testing for Factor V Leiden (FVL) results in improved outcomes.

In review of the available peer reviewed medical literature there were no studies identified that supported the clinical utility of genetic testing for Prothrombin G20210A (F2, coagulation factor II) in individuals with unexplained recurrent pregnancy loss. Additional studies are needed that demonstrates this genetic testing for Prothrombin G20210A (F2, coagulation factor II) results in improved outcomes.

Summary of Evidence
Based on evidence in the published, peer-reviewed scientific literature, a practice bulletin from ACOG, and other professional specialty organizations, the clinical utility of testing for inherited thrombophilia disorders utilizing Factor V Leiden (FVL) or Prothrombin G20210A (F2, coagulation factor II) is not recommended for unexplained early recurrent

pregnancy loss. Although there may be an association with pregnancy loss that occurs after the first trimester, the clinical utility of screening in this population and benefit of treatment remains unclear. The evidence is insufficient in determining the technology improves net health outcomes.

Methylenetetrahydrofolate Reductase (MTHFR) Variant Testing:

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

The MTHFR gene provides instructions for making an enzyme called methylenetetrahydrofolate reductase. This enzyme plays a role in processing amino acids, the building blocks of proteins. Methylenetetrahydrofolate reductase is important for a chemical reaction involving the vitamin folate (also called vitamin B9). Specifically, this enzyme converts a form of folate called 5,10-methylenetetrahydrofolate to a different form of folate called 5-methyltetrahydrofolate. This is the primary form of folate found in blood and is necessary for the multistep process that converts the amino acid homocysteine to another amino acid, methionine. The body uses methionine to make proteins and other important compounds.

At least 40 variations in the MTHFR gene have been identified in individuals with homocystinuria. Some variations cause the enzyme to be inactivated, while others lead to the production of an abnormally small, nonfunctional version of the enzyme. Other gene variations associated with homocystinuria, include CBS, MTR, MTRR, and MMADHC. In the case of MTHFR variations, homocysteine builds up in the bloodstream, and the amount of methionine is reduced. Researchers have not determined how altered levels of homocysteine and methionine lead to the health problems associated with homocystinuria Increased levels of homocysteine have been associated with an increased risk of thromboembolism. Although MTHFR has been associated with increased risk of homocystinuria; genetic testing is not indicated because these variants are not associated with thromboembolism.

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

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

Patients who are asymptomatic with or without a personal or family history of VTE are actively managed by cardiologists and primary care providers in an outpatient clinical setting.

Comparators
Comparators of interest include standard clinical management without testing.

Outcomes
The general outcomes of interest are morbid events and treatment related morbidity. The beneficial outcomes of a true-positive test result are an appropriate treatment for VTE. The beneficial outcome of a true-negative test result is potentially avoiding unnecessary treatment.

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

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

Variants in the MTHFR gene are associated with hyperhomocysteinemia, which in turn is considered a weak risk factor for VTE.

Clinically Useful
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs). The clinical utility of testing for homocysteine levels has not been established. There is a large body of literature on the association between homocysteine levels and coronary artery disease, and clinical trials have assessed the impact of lowering homocysteine levels. This body of evidence has indicated that testing or treating for homocysteinemia is not associated with improved outcomes.

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

In a May 2021 Hayes, Inc completed an annual review of Clinical Utility Evaluation for MTHFR genetic testing in common clinical conditions in pediatric and adult individuals, that found the current evidence to be low or very low.

In 2020, Gao et. al. evaluated the association between the MTHFR C677T and MTHFR A1298C polymorphisms and the risk of VTE in a meta-analysis of 32 case-control studies. Pooled results demonstrated an increased susceptibility to VTE with MTHFR C677T homozygotes (odds ratio [OR]=0.73; 95% confidence interval [CI], 0.60 to 0.89) and MTHFR C677T homozygotes/heterozygotes (OR=0.80; 95% CI, 0.71 to 0.90) compared to those without a mutation. When results were stratified by ethnicity, a

significant association was maintained in the Asian population, but results were not significant for the Caucasian population. For the MTHFR A1298C polymorphism, there was no significant association between homozygotes (OR=0.90; 95% CI 0.66 to 1.23) or homozygotes/heterozygotes (OR=0.95; 95% CI, 0.83 to 1.07) compared to those without a mutation for susceptibility to VTE.

Summary of Evidence
Several variants of the MTHFR gene have been associated with increased risk of developing several conditions, however, its role in these conditions has not been established. There is insufficient evidence in the published peer-reviewed scientific literature to determine the clinical utility of MTHFR genetic testing and its impact on net health outcomes. Professional society consensus support for MTHFR genotyping is limited. At this time, the role of genetic testing for MTHFR has not been established. The evidence is insufficient in determining this technology results in net health outcomes.

Newborn Screening
Newborn screening is performed to limit the morbidity and mortality attributable to selected inherited diseases (American Academy of Pediatrics [AAP]). Newborn screening programs are organized through state governments and are generally mandated focusing on conditions on the Recommended Uniform Screening Panel (RUSP) screening for 35 specific conditions. According to the March of Dimes (2020), screening is available for disorders in which accurate diagnosis and early treatment of the disorder can improve health outcomes. Some genetic screening tests are not deoxyribonucleic acid (DNA) or chromosome-based tests but use biochemical markers or phenotypic features.

Conditions screened for include the following:

- Amino Acid Disorders
- Endocrine Disorders
- Fatty Acid Oxidation Disorders
- Hemoglobin Disorders
- Organic Acid Conditions

Currently newborn screening does not include testing for the following genetic testing MTHFR, Factor V Leiden (FVL) or Prothrombin G20210A (F2, coagulation factor II). There is insufficient evidence in the published peer-reviewed scientific literature to determine the clinical utility of this genetic testing and its impact on net health outcomes in newborn screening. The evidence is insufficient in determining this technology results in net health outcomes.

Genetic Testing for Venous Thromboembolism in Children
Most of the available treatment recommendations are from adult data despite the differences in in hemostatic system between children and adults. Venous thromboembolism (VTE) in pediatric populations is gaining awareness, with recently reported systematic reviews on pediatric venous thromboembolism (VTE) showing significant association between thrombosis and the presence of inherited thrombophilia

risk factors. Whether genetic testing can impact the treatment options and patient outcomes for pediatric patients who are genetically diagnosed with a common form of hereditary thrombophilia remains controversial.

In a Hayes, Inc., Clinical Utility Evaluation annual review completed June 2021 based on the peer reviewed medical literature there is insufficient evidence to support the clinical utility of genetic testing for common forms of hereditary thrombophilia in asymptomatic children. Further studies are needed to demonstrate whether genetic testing has clinical utility, including aiding in the diagnosis or impacting management, surveillance, treatment, or outcome pediatric patients with known or suspected diagnosis of hereditary thrombophilia. The evidence is insufficient in determining this technology results in net health outcomes.

Pediatric Patients with Asymptomatic Central Venous Catheter-Related Thrombosis

Asymptomatic central venous catheter (CVC)-related thrombosis in children varies in incidence from 5% to 69%. The rate of acute and long-term complications, such as post thrombotic syndrome (PTS), from asymptomatic CVC-related thrombosis is unknown.

In UpToDate regarding thrombophilia testing in children and adolescents (last updated June 2021) a systematic review and meta-analysis of 16 observational studies found that while overall prevalence of inherited thrombophilia (IT) was low and while IT was associated with increased likelihood of CVC-associated VTE, the association was largely accounted for by a relatively high prevalence of elevated factor VIII, which may represent an inherited disorder or may be acquired (since factor VIII is an acute phase reactant and is often transiently elevated after an acute thrombosis). The prevalence of other IT traits in the meta-analysis was low and the association with CVC-related VTE was relatively weak. Based on the available evidence it is not recommended to perform IT genetic testing because the prevalence of thrombophilia is relatively low in this group, and identification of a thrombophilic defect does not influence the acute management or duration of anticoagulation therapy in such patients.

Practice Guidelines and Position Statements

American College of Chest Physicians (ACCP)

In 2012, the American College of Chest Physicians (ACCP) published The Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines that provides treatment guidelines for the circumstance when a pregnant woman is known to be homozygous for FVL or the prothrombin 20210A variant.

American College of Medical Genetics and Genomics (ACMG)

ACMG Practice Guideline: Lack of Evidence for MTHFR Polymorphism Testing

MTHFR polymorphism testing is frequently ordered by physicians as part of the clinical evaluation for thrombophilia. It was previously hypothesized that reduced enzyme activity of MTHFR led to mild hyperhomocysteinemia which led to an increased risk for venous thromboembolism, coronary heart disease, and recurrent pregnancy loss. Recent meta-analysis has disproven an association between hyperhomocysteinemia and risk for coronary heart disease and between MTHFR polymorphism status and risk for venous thromboembolism. There is growing evidence that MTHFR polymorphism testing has minimal clinical utility and therefore should not be ordered as part of a routine evaluation for thrombophilia.

ACMG Recommendations:

- 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 who 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 provider 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.

In 2018, the ACMG has released guidelines for laboratory testing of venous thromboembolism (VTE). This 2018 edition superseded the 2005 edition. The guidelines are as follows:

Testing for factor V Leiden and factor II c.*97G>A (this mutation is also known as G20210A) is recommended in the following circumstance:

- A first unprovoked VTE, especially <50 years old
- VTE at unusual sites (such as hepatic portal, mesenteric, and cerebral veins)
- Recurrent VTE
- Personal history of VTE with (a) two or more family members with a history of VTE or one first-degree relative with VTE at a young age
- Patients with low activated protein C (APC) resistance activity

Testing may also be considered in following circumstances:

- Females under the age of 50 who smoke tobacco and have a history of acute myocardial infarction
- Siblings of individuals known to be homozygous for factor V Leiden or factor II c. *97G>A, because they have a 1 in 4 chance of being a homozygote

- Asymptomatic pregnant female or female contemplating pregnancy, with a first-degree relative with unprovoked VTE or VTE provoked by pregnancy or contraceptive use
- Pregnant female or female contemplating pregnancy or estrogen use who has a first-degree relative with a history of VTE and is a known carrier for factor V Leiden and/or factor II c.98*G>A variant
- Pregnant female or female contemplating pregnancy with a previous non-estrogen related VTE or VTE provoked by a minor risk factor, because knowledge of the factor V Leiden or factor II c.*97G>A status may alter pregnancy related thrombophylaxis.

Testing is not recommended for the following:

- A general population screens
- A prenatal or newborn test, or as a routine test in asymptomatic children
- A routine initial test in individuals with arterial thrombosis (testing may be considered, however, in selected young individuals [under age 50] with unexplained arterial thrombosis in the absence of other risk factors for atherosclerotic vascular disease)

The American College of Obstetricians and Gynecologist (ACOG)

The American College of Obstetricians and Gynecologists (2013) published management guidelines for inherited thrombophilia's in pregnancy which were reaffirmed in 2014 and in 2018. Screening for inherited thrombophilias is useful only when results will affect management decisions and is not useful in situations where treatment is indicated for other risk factors. Targeted assessment may be considered in the following clinical settings:

- A personal history of VTE associated with a nonrecurrent risk factor (e.g., fracture, surgery, or prolonged immobilization).
- A first-degree relative (e.g., parent, sibling) with a history of high-risk thrombophilia.

Recommendations

- Testing for inherited thrombophilias should include FVL, prothrombin G20210A mutation, and tests for deficiencies in antithrombin, protein S and protein C. Grade of Evidence: C; Level of Evidence: Consensus and expert opinion
- Testing for inherited thrombophilias in women who have experienced recurrent fetal loss or placental abruption is not recommended because it is unclear whether anticoagulation therapy reduces recurrence. Grade of Evidence B; Level of Evidence: Limited or inconsistent scientific evidence
- Because an association between either heterozygosity or homozygosity for the MTHFR C677T polymorphism and any negative pregnancy outcomes, including any increased risk for VTE, has not been shown, screening with either MTHFR mutation analyses or fasting homocysteine levels is not recommended. Grade of Evidence: B; Level of Evidence: Limited or inconsistent scientific evidence.

Recommendations based primarily on consensus and expert opinion note screening for inherited thrombophilias should include FVL mutation; prothrombin G20210A mutation; and antithrombin, protein C, and protein S deficiencies. Additionally, all patients with inherited thrombophilias should undergo individualized risk assessment, which may modify management decisions.

International Society on Thrombosis and Haemostasias

The Prevention of Venous Thromboembolism in Pediatric Cancer

Guidance statement
1. We recommend that a comprehensive risk assessment be performed on each pediatric cancer patient at the initiation of cancer therapy.
2. We recommend against routine primary thromboprophylaxis in pediatric cancer patients without a history of prior thrombosis.
3. We recommend thromboprophylaxis in pediatric cancer patients with prior thrombosis who are continuing to receive intensive therapy, so long as there are no contraindications to anticoagulation.
4. We suggest that thromboprophylaxis should be considered, on a case-by-case basis, for pediatric cancer patients with no history of VTE, but with significant combinatorial risk factors (e.g. CVC, asparaginase therapy, obesity, adolescence, hormonal contraceptives or hospitalization for surgery).

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Commercial thrombophilia genetic tests are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing.

Genetic tests for thrombophilia cleared by the Food and Drug Administration (FDA) for use as an aid in the diagnosis of patients with suspected thrombophilia:

Test	**Manufacturer**
eSensor® Thrombophilia Risk Test, FII-FV, FII, FV and MTHFR (677, 1298) Genotyping Tests	GenMark Dx[b]
Factor II (Prothrombin) G20210A Kit	Roche Diagnostics

Factor V Leiden Kit	Roche Diagnostics
INFINITI™ System Assay for Factor II & Factor V	AutoGenomics
IMPACT Dx™ Factor V Leiden and Factor II Genotyping Test	Agena Bioscience[a]
Invader® Factor II, V, and MTHFR (677, 1298) tests	Hologic
VeraCode® Genotyping Test for Factor V and Factor II	Illumina
Verigene® Factor F2, F5, and MTHFR Nucleic Acid Test	Nanosphere
Xpert® Factor II and Factor V Genotyping Assay	Cepheid

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

PRIOR APPROVAL

Not applicable

POLICY

See Related Medical Policies

- 02.04.04 Cardiovascular Disease Risk Tests
- 02.04.67 Pharmacogenomic and Pharmacogenetic Testing for Drug Metabolism Status
- 02.04.79 Circulating Tumor DNA for Management of Non-Small Cell Lung Cancer (Liquid Biopsy)
- 02.04.78 Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer

MTHFR
Genetic testing for variations in the MTHFR gene for all indications, including testing for thrombophilia or recurrent pregnancy loss is considered **investigational**. The evidence is insufficient in determining the technology improves net health outcomes.

Factor V Leiden (FVL) and Prothrombin G20210A (F2) Gene
Genetic testing with targeted mutation analysis for coagulation Factor V Leiden (FVL) and/or Prothrombin G20210A (F2 Gene) may be considered **medically necessary** for **ANY** of the following indications:

A. An asymptomatic individual who is planning pregnancy or is currently pregnant and not taking anticoagulation therapy and either of the following:

    1. First-degree blood relative (i.e., parent, full-sibling, or child) with a history of high-risk thrombophilia (e.g., antithrombin deficiency, double heterozygosity, or homozygosity for FVL or prothrombin G202010A); **or**
    2. First-degree blood relative (i.e., parent, full-sibling, child) with venous thromboembolism (VTE) before age 50 years; **or**

B. First unprovoked (e.g., from an unknown cause) venous thrombosis (VTE) at any age (especially age less than 50 years); **or**
C. Individual with first venous thrombosis (VTE) **AND** a first-degree blood relative (i.e., parent, full-sibling, child) with a VTE occurring before age 50 years: **or**
D. Individual with history of recurrent venous thrombosis (VTE); **or**
E. Venous thrombosis (VTE) at unusual sites (e.g., cerebral, mesenteric, portal, and hepatic veins); **or**
F. Venous thrombosis (VTE) associated with the use of oral contraceptives or hormone replacement therapy (HRT); **or**
G. Venous thrombosis (VTE) during pregnancy or the puerperium (the period of about six weeks after childbirth).

Genetic testing with targeted mutation analysis for Prothrombin G20210A (F2 Gene) or for coagulation Factor V Leiden (FVL) is considered **investigational** for **ANY** of the following indications, because the effectiveness for indications other than those listed above has not been established:

- Not meeting the above criteria
- General population screening
- Recurrent pregnancy loss
- Newborn testing or routine testing in an asymptomatic child
- Routine initial testing in an individual with arterial thrombosis
- Testing of an asymptomatic first-degree blood relative (parent, full-sibling, or child) of an individual with proven symptomatic venous thrombosis (VTE) and a proven coagulation Factor V Leiden or Prothrombin G20210A (F2 Gene) variant, for the purpose of considering prophylactic anticoagulation (except as noted above)

- Neonate or child with asymptomatic central venous catheter-related thrombosis

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81291 MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants
- 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
- 81400 MOLECULAR PATHOLOGY PROCEDURE LEVEL 1 (includes F2 (coagulation factor 2) (e.g., hereditary hypercoagulability), 1199G>A variant)

SELECTED REFERENCES

- American College of Medical Genetics Practice Guidelines: Lack of Evidence for MTHFR Polymorphism Testing. Scott E. Hickey, M.D., FACMG, Cynthia J. Curry, M.D., FACMG and Helga V. Toriello, PhD, FACMG, Genetics in Medicine 2013:15(2):153-156
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POLICY HISTORY

Date	Reason	Action
May 2022	Annual Review	Policy Revised
May 2021	Annual Review	Policy Revised
May 2020	Annual Review	Policy Revised
May 2019	Annual Review	Policy Revised
May 2018	Annual Review	Policy Revised
May 2017	Annual Review	Policy Revised
May 2016	Annual Review	Policy Revised
June 2015	Annual Review	Policy Revised
July 2014	Annual Review	Policy Revised
September 2013		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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