FEP Medical Policy Manual

FEP 2.04.82 Genetic Testing for Inherited Thrombophilia

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Related Policies:

2.04.23 - Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease and Venous Thromboembolic Disorders

Genetic Testing for Inherited Thrombophilia

Description

Inherited thrombophilias are a group of disorders that predispose individuals to thrombosis. Genetic testing is available for some of these disorders and could assist in the diagnosis and/or management of patients with thrombosis. For example, testing is available for types of inherited thrombophilia, including variants in the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene, the factor V gene (*factor V Leiden* variant), and the prothrombin (*factor II*) gene.

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing for 5,10-methylenetetrahydrofolate reductase, *factor V* gene, and prothrombin gene variants improves the net health outcome in individuals with inherited thrombophilias.

POLICY STATEMENT

Genetic testing for inherited thrombophilia, including testing for the *factor V Leiden* variant, prothrombin gene variants, and variants in the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene, is considered **investigational**.

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POLICY GUIDELINES

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society"s nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient"s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

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

The FDA has cleared several genetic tests for thrombophilia have been cleared for marketing by the FDA through the 510(k) process for use as an aid in the diagnosis of patients with suspected thrombophilia. Some of these tests are listed in Table 1.

Table 1. Genetic Tests for Thrombophilia Cleared by FDA

Test	Manufacturer	Cleared	510(k) No.
IMPACT Dx™ Factor V Leiden and Factor II Genotyping Test	Agena Biosciencea	06/14	K132978
Invader Factor II, V, and MTHFR (677, 1298) tests	Hologic	04/06/11	K100943, K100980, K100987, K100496
VeraCode Genotyping Test for Factor V and Factor II	Illumina	04/28/10	K093129
eSensor Thrombophilia Risk Test, FII-FV, FII, FV and MTHFR (677, 1298) Genotyping Tests	GenMark Dxb	04/22/10	K093974
INFINITI™ System Assay for Factor II & Factor V	AutoGenomics	02/07/07	K060564
Xpert Factor II and Factor V Genotyping Assay	Cepheid	09/18/09	K082118
Verigene Factor F2, F5, and MTHFR Nucleic Acid Test	Nanosphere	10/11/07	K070597
Factor V Leiden Kit	Roche Diagnostics	12/17/03	K033607
Factor II (Prothrombin) G20210A Kit	Roche Diagnostics	12/20/03	K033612

FDA: Food and Drug Administration.

[a] FDA marketing clearance was granted to Sequenom Bioscience before it was acquired by Agena Bioscience.

[b] FDA marketing clearance was granted to Osmetech Molecular Diagnostics.

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*.

On April 6, 2017, the FDA permitted marketing of 23andMe Personal Genome Service Genetic Health Risk tests for 10 diseases or conditions. These direct-to-consumer tests are the first authorized by the FDA that provide information on an individual"s genetic predisposition to certain medical diseases or conditions, which may help to make decisions about lifestyle choices or to inform discussions with a health care professional. The 23andMe Genetic Health Risk tests work by isolating DNA from a saliva sample, which is then tested for more than 500000 genetic variants. The presence or absence of some of these variants is associated with an

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increased riskof developing any one of ten diseases or conditions. Testing for hereditary thrombophilia (two variants in the *F5* and *F2* genes; relevant for European descent) is included.

RATIONALE

Summary of Evidence

For individuals who are asymptomatic with or without a personal or family history of venous thromboembolism (VTE) or who are asymptomatic with increased VTE risk (eg, due to pregnancy) who receive genetic testing for variants in 5,10-methylenetetrahydrofolate reductase (MTHFR), or genetic testing for coagulation factor V and coagulation factor II, the evidence includes a large randomized controlled trial (RCT), prospective cohort analyses, retrospective family studies, case-control studies, and meta-analyses.The relevant outcomes are morbid events and treatment-related morbidity. The clinical validity of genetic testing has been demonstrated by the presence of a *factor V Leiden* [FVL] variant or a prothrombin gene variant, and an association with an increased risk for subsequent VTE across various populations studied. However, the magnitude of the association is relatively modest, with OR most commonly between one and two, except for family members of individuals with inherited thrombophilia, for whom OR are somewhat higher. The clinical utility of testing for FVL or prothrombin variants has not been demonstrated. Although the presence of inherited thrombophilia increases the risk for subsequent VTE events, the increase is modest, and the absolute-risk of thrombosis remains low. Available prophylactic treatments (eg, anticoagulation) have defined risks of major bleeding and other adverse events that may outweigh the reduction in VTE and therefore result in net harm. Currently, available evidence has not defined a role for thrombophilia testing for decisions on initiation of prophylactic anticoagulation or the length of anticoagulation treatment. For *MTHFR* testing, clinical validity and clinical utility of genetic testing are uncertain. Because clinical utility of testing for elevated serum homocysteine itself has not been established, the utility of genetic testing also has not been established. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Many guidelines and position statements on testing for thrombophilia have been published over the last two decades. These guidelines have evolved over time,often inconsistent and do not typically give specific parameters on when to perform genetic testing. The following are examples of U.S. guidelines developed by major specialty societies and published more recently.

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American Board of Internal Medicine Foundation- Choosing Wisely Campaign

Choosing Wisely, an initiative of the American Board of Internal Medicine Foundation seeks to promote discussions between clinicians and patients to choose care that is: supported by evidence, not duplicative of other tests or procedures already received, free from harm, and truly necessary. Medical specialty societies and their national organizations have identified tests or procedures commonly used in their field whose necessity should be questioned and discussed. The following medical specialist groups have contributed recommendations to *Choosing Wisely* lists specifically related to testing for inherited thrombophilias (see Table 2).[32,]

Table 2. Medical Society Recommendations on Testing for Inherited Thrombophilias

Society	Year	Recommendation
American Society of Hematology	2013	• "Don"t test for thrombophilia in adult patients with venous thromboembolism (VTE) occurring in the setting of major transient risk factors (surgery, trauma or prolonged immobility)."
		• "Thrombophilia testing is costly and can result in harm to patients if the duration of anticoagulation is inappropriately prolonged or if patients are incorrectly labeled as thrombophilic. Thrombophilia testing does not change the management of VTEs occurring in the setting of major transient VTE risk factors. When VTE occurs in the setting of pregnancy or hormonal therapy, or when there is a strong family history plus a major transient risk factor, the role of thrombophilia testing is complex and patients and clinicians are advised to seek guidance from an expert in VTE."
Society for Maternal-Fetal Medicine	2014	• "Don"t do an inherited thrombophilia evaluation for women with histories of pregnancy loss, intrauterine growth restriction (IUGR), preeclampsia and abruption."
		• "Scientific data supporting a causal association between either methylenetetrahydrofolate reductase (MTHFR) polymorphisms or other common inherited thrombophilias and adverse pregnancy outcomes, such as recurrent pregnancy loss, severe preeclampsia and IUGR, are lacking. Specific testing for antiphospholipid antibodies, when clinically indicated, should be limited to lupus anticoagulant, anticardiolipin antibodies and beta 2 glycoprotein antibodies."
American Society for Reproductive Medicine	2013	• "Don"t routinely order thrombophilia testing on patients undergoing a routine infertility evaluation."
		• "There is no indication to order these tests, and there is no benefit to be derived in obtaining them in someone that does not have any history of bleeding or abnormal clotting and in the absence of any family history. This testing is not a part of the infertility workup. Furthermore, the testing is costly, and there are risks associated with the proposed treatments, which would also not be indicated in this routine population."

American College of Chest Physicians

The American College of Chest Physicians (2016) guidelines and expert panel report on antithrombotic therapy for VTE disease no longer includes recommendations for pregnant women with known *factor V Leiden* or prothrombin G20210A variants, which had been included in the 2012 edition.[33,34,]Also, there are no guidelines on genetic testing for thrombophilia. The 2008 edition had indicated that the presence of a hereditary thrombophilia was not a major factor to guide duration of anticoagulation for VTE.[35,]

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American College of Medical Genetics and Genomics

In 2018, the American College of Medical Genetics and Genomics (ACMG) published updated technical standards for genetic testing for variants associated with VTE, with a focus on *factor V Leiden* and *factor II*.[36] The standards do not make recommendations on the indications for testing, and the authors note that testing indications from different professional organizations vary, referring to a review of professional society guidelines published by de Stefano et al (2013).[37]

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (2013) published management guidelines for inherited thrombophilias in pregnancy, which were reaffirmed in 2014 and in 2018.[4,38] These guidelines stated that a definitive causal link between inherited thrombophilias and adverse pregnancy outcomes could not be made. Screening for inherited thrombophilias is controversial, but may be considered for pregnant women in the following situations:

- A personal history of VTE associated with a nonrecurrent risk factor (eg, fracture, surgery, or prolonged immobilization).
- A first-degree relative (eg, parent, sibling) with a history of high-risk thrombophilia. Guidelines for Managing Inherited Thrombophilias During Pregnancy

Recommendation	GOE	LOE
Testing for inherited thrombophilias should include FVL, prothrombin G20210A mutation, and tests for deficiencies in antithrombin, protein S and protein C	C	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	B	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	B	Limited or inconsistent scientific evidence

FVL: *factor V Leiden*; GOE: grade of evidence; LOE: level of evidence; VTE: venous thromboembolism.

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Anticoagulation Forum

In 2019, Stevens et al. published a guidance document initiated by the Anticoagulation Forum.[39] The guidance was intended to inform clinical decisions regarding duration of anticoagulation following VTE and primary prevention of VTE in relatives of affected patients. Statements were based on existing guidelines and consensus expert opinion when guidelines were lacking. The authors concluded that, "Thrombophilia testing is performed far more frequently than can be justified based on available evidence; the majority of such testing is not of benefit to the patient and may be harmful." Table 3 summarizes the guidance statements for each question considered in the document.

Table 3. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia (adapted from Stevens et al [2019])

Question	Guidance Statement	Limits/Exceptions
Should thrombophilia testing be performed to help determine duration of anticoagulation following provoked VTE?	Do not perform thrombophilia testing following an episode of provoked VTE.	
Should thrombophilia testing be performed to help determine duration of anticoagulation following unprovoked VTE?	Do not perform thrombophilia testing in patients following an episode of unprovoked VTE.	If a patient with unprovoked VTE and low bleeding risk is planning to stop anticoagulation, test for thrombophilia if test results would change this decision.
Should family members of patients with VTE or hereditary thrombophilia undergo thrombophilia testing?	Do not test for thrombophilia in asymptomatic family members of patients with VTE or hereditary thrombophilia.	
Should female relatives of patients with VTE or hereditary thrombophilia who are considering using estrogen-containing medications be tested for thrombophilia?	Do not test for thrombophilia in asymptomatic family members of patients with VTE or hereditary thrombophilia who are contemplating use of estrogen.	If a woman contemplating estrogen use has a first degree relative with VTE and a known hereditary thrombophilia, test for that thrombophilia if the result would change the decision to use estrogen.
Should female relatives of patients with VTE or hereditary thrombophilia who are contemplating pregnancy be tested for thrombophilia?	Do not test for thrombophilia in asymptomatic family members of patients with VTE or hereditary thrombophilia who are contemplating pregnancy.	If a woman contemplating pregnancy has a first degree relative with VTE and a known hereditary thrombophilia, test for that thrombophilia if the result would change VTE prophylaxis decisions.
When thrombophilia testing is performed, at what point in the patient"s care should this be done?	Do not perform thrombophilia testing at the time of VTE diagnosis or during the initial 3-month course of anticoagulant therapy. When testing for thrombophilias following VTE, use either a 2-stage testing approach or perform testing after a minimum of 3 months of anticoagulant therapy has been completed, and anticoagulants have been held.	

VTE: Venous thromboembolism.

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Evaluation of Genomic Applications in Practice and Prevention

The Evaluation of Genomic Applications in Practice and Prevention (2011) recommendations did not support the clinical utility of genetic testing for *factor V Leiden* and prothrombin variants for prevention of initial episodes of venous thromboembolism (VTE) or for recurrence.[40,] The recommendations have been archived.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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40. Berg AO, Botkin J, Calonge N, et al. Recommendations from the EGAPP Working Group: routine testing for Factor V Leiden (R506Q) and prothrombin (20210G A) mutations in adults with a history of idiopathic venous thromboembolism and their adult family members. Genet Med. Jan 2011; 13(1): 67-76. PMID 21150787

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
September 2013	New policy	
September 2014	Replace policy	Policy updated with literature review adding references 5-8, 10-11, 24 and 29, references 4 and 12 were updated. There are no changes to the policy statement.
September 2018	Replace policy	Policy updated with literature review through March 5, 2018; references 16 and 23 added; references 29-32, 34, and 37 updated. The policy is revised with updated genetics nomenclature; "mutations" changed to "variants" throughout policy. Policy statement otherwise unchanged except "not medically necessary" corrected to "investigational" due to 510k FDA clearance.
September 2019	Replace policy	Policy updated with literature review through March 4, 2019; references added. Policy statement unchanged.
September 2020	Replace policy	Policy updated with literature review through March 26, 2020; references added. Policy statement unchanged.

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