Test Specific Guidelines

Inherited Thrombophilia Genetic Testing

MOL.TS.370.A
v1.0.2023

Introduction

Inherited thrombophilia genetic testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
F2 (prothrombin, coagulation factor II) gene analysis, 20210G>A variant	81240
F5 (coagulation factor V) gene analysis, Leiden variant	81241
MTHFR (5,10-methylenetetrahydrofolate reductase) gene analysis, common variants	81291

What Is Inherited Thrombophilia?

Definition

Inherited thrombophilia (hypercoagulability) is a genetic disorder that increases an individual's risk for developing abnormal blood clots (venous thromboembolism or VTE) which can lead to pulmonary embolism (PE).[1,2] Variants in the F2 (prothrombin or Factor II), F5 (Factor V), and MTHFR genes have been associated with thrombophilia.

Prevalence

About 1 in 1000 individuals in the United States (US) experiences a first venous thromboembolism (VTE) each year, and about one-third of symptomatic patients will develop pulmonary embolism (PE).[3]

The frequency of the Factor V Leiden (FVL) variant varies by ethnicity with about 5% of Caucasians, 2% of Hispanics, and 1% of African Americans in the US having one FVL variant.[4] Approximately 1 in 1500 Caucasians has two variants.[4]

Approximately 1-3% of the European population have at least one F2 variant.[1,2,5] Approximately 1 in 10,000 individuals has 2 copies of the F2 variant.[1]

In the US, approximately 42% of individuals have one copy of the MTHFR C677T variant and 9% have two copies, while approximately 44% of individuals have one copy and 11% of individuals have two copies of the A1298C variant.[6]

Symptoms

The presence of F2 or F5 variants does not cause any symptoms, but does increase the risk to develop VTE.[7] Symptoms of a VTE vary depending on the location, but may include:[7]

Tenderness, swelling, or warm feeling in the affected area (limb),

Shortness of breath and chest pain (heart or lung), or

Vision or speech problems, weakness, sudden headache (brain).

There has been conflicting evidence about the association of inherited thrombophilias and other pregnancy complications, such as severe preeclampsia, intrauterine growth restriction, and placental abruption.[5]

Cause

VTE is a multifactorial condition, usually arising from a combination of genetic, acquired, and circumstantial events and risk factors. Idiopathic (formerly unprovoked) VTE has no triggering event identified, while secondary (formerly provoked) VTE is triggered by an event such as trauma, stroke, central venous line or pacemaker, or cancer.[3]

Specific variants in the genes F2, F5, and MTHFR have all been linked to increased risk for thrombophilia in the literature. A variant in the F5 gene called factor V Leiden (FVL), is the most common genetic risk factor for thrombophilia among Caucasians. Other less common causes of inherited thrombophilia include antithrombin deficiency, protein C deficiency, and protein S deficiency; however, these conditions are commonly assessed through non-molecular tests such as functional assays.[5]

F2

Inheriting one prothrombin variant (heterozygous) increases one's risk for developing VTE approximately 2-fold to 4-fold compared to non-carriers.[1,4] Inheriting two prothrombin variants (homozygous) is rare. The prevalence among the general population is 0.001-0.012% and 0.2-4% among individuals with VTE. The annual risk of VTE in homozygotes is not clear but has been reported to be approximately 1.1%/year.[8] Inheriting a prothrombin variant with other genetic risk factors such as Factor V Leiden also significantly increases the risk for developing VTE.[1,8]

400 Buckwalter Place Boulevard, Bluffton, SC 29910 (800) 918-8924

FVL

The risk for FVL-related thrombosis depends on whether one or two FVL variants are present and additional risk factors, such as prothrombin gene variants. A single FVL variant increases the risk for initial VTE up to 3-8 fold. Two FVL variants increases the risk more dramatically at 18-80 fold.[4,9] While the risk of subsequent VTE is significantly increased in anyone with a history of VTE, the risk for recurrent VTE attributable to a FVL variant after a first event is much more modest with a pooled odds ratio of 1.56 for single variant and 2.65 for two variants.[4] The increased risk for pregnancy-related VTE is estimated at 8 fold with a single FVL variant and 17-34 fold with two variants.[9] The risk for oral contraceptive-related VTE is estimated at 16 fold with a single FVL variant and over 100 fold with two variants.[9]

MTHFR

Both hyperhomocysteinemia in general, and MTHFR variants specifically, have been reported in association with cardiovascular disease, venous thromboembolism, pregnancy complications, and certain birth defects, such as neural tube defects.[10,11] However, data is inconsistent and associated risks are generally small. The association between MTHFR polymorphism status and risk for venous thromboembolism has been disproven.[12,13]

Inheritance

First degree relatives of an individual with a single copy of the common F2, FVL, or MTHFR variants have a 50% chance of carrying the same variant.[2,9,14]

Diagnosis

Clinical findings that increase the suspicion for an inherited thrombophilia in an individual with a VTE that may prompt molecular testing include:[2,9]

Idiopathic VTE (where no underlying cause or triggering event can be identified) at an early age,

Recurrent VTE,

VTE occurring at unusual sites,

VTE during pregnancy or with the use of estrogen containing medications, or

Family history of VTE.

A phenotypic activated protein C (APC) resistance assay is the preferred first tier test for investigating whether FVL is the cause of a VTE.[15]

400 Buckwalter Place Boulevard, Bluffton, SC 29910 (800) 918-8924

Although individuals with the prothrombin variant often have mildly elevated prothrombin levels, the levels vary among individuals and even overlap significantly with the normal range.[2] Prothrombin levels are therefore not reliable for the diagnosis of prothrombin thrombophilia, and variant analysis remains the best choice for definitive diagnosis.[2]

Definitive diagnosis of inherited thrombophilia relies on both clinical information and genetic testing.[16]

Management

VTE is managed by anticoagulation therapy which may be prescribed for an extended time depending on risk for recurrent VTE.[7] Lifestyle changes such as smoking cessation, regular exercise, maintaining a healthy weight and balanced diet, and avoiding prolonged inactivity may reduce the risk for VTE.[7]

Confirmation of an inherited thrombophilia may aid in:

Treatment decisions for preventing recurrent VTE in an affected individual,

Primary prevention of VTE in at-risk relatives,

Decisions about use of oral contraceptives, hormone replacement therapy, or other estrogen-containing therapies, and

Management decisions for preventing VTE or other possibly associated complications in pregnancy.

Survival

Inherited thrombophilia can be medically managed, but pulmonary embolism is a life-threatening condition.[7] Not everyone with inherited thrombophilia will develop VTE, and survival depends upon whether and where VTE develops, timely treatment, and adoption of lifestyle changes to minimize clot recurrence.[7]

Test Information

Introduction

Genetic testing for inherited thrombophilia consists of targeted mutation analysis.

Targeted Mutation Analysis

Genetic testing for inherited thrombophilia is performed by targeted mutation analysis for specific gene variants.

Factor II/prothrombin: G20210A variant in the F2 gene [2]

Factor V Leiden: 1691G>A (R506Q); the Leiden variant in the F5 gene[8]

MTHFR: C677T and A1298C in the MTHFR gene[11]

400 Buckwalter Place Boulevard, Bluffton, SC 29910 (800) 918-8924

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess for these variants. Determination of variant copy number (heterozygosity or homozygosity) is important to assessing the relative risk of clotting.[2,8,16] Test sensitivity approaches 100%.[2,8]

These variants may be components of panels for thrombophilia, cardiovascular disease risk, psychiatric conditions, pharmacogenomics, or preeclampsia. There is insufficient evidence in the peer-reviewed literature to establish clinical utility for non-thrombophilia related indications.

In addition to factor V Leiden genotyping, the modified APC resistance assay is available to detect factor V Leiden thrombophilia. This assay makes use of the fact that the Leiden variant creates a protein that resists inactivation by activated protein C (APC). The APC resistance assay is effective, but does not determine how many copies of the Leiden variant are present. Therefore, if positive, factor V Leiden genotyping is recommended to confirm the findings and quantify the number of variants present.[7]

Many experts suggest that measuring homocysteine levels directly is more informative than MTHFR variant testing.[6]

Note **Pathogenic variants in the MTHFR gene (not the common benign variants discussed here) are rarely associated with a genetic disorder called homocystinuria.[11] Targeted MTHFR C677T and A1298C variant testing will not find the pathogenic variants that cause homocystinuria.**

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to inherited thrombophilia genetic testing.

Agency for Healthcare Research and Quality

An Agency for Health Care Research and Quality-supported systematic review (AHRQ, 2009) found the following:[17]

While variant analysis is effective at identifying FVL variants, “the incremental value of testing individuals with VTE for these mutations is uncertain. The literature does not conclusively show that testing individuals with VTE or their family members for FVL or prothrombin G20210A confers other harms or

benefits. If testing is done in conjunction with education, it may increase knowledge about risk factors for VTE".

These guidelines add that other factors (such as hereditary thrombophilia) predict risk of recurrence, but not strongly or consistently enough to influence recommendations on duration of therapy once the primary and secondary factors noted previously have been considered.

American Association of Clinical Endocrinologists and American College of Endocrinology

The joint position statement from the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE, 2017) stated that one of the clinical characteristics of appropriate candidates for hormone replacement therapy (HRT) is absence of Factor V Leiden mutations. Recent evidence "suggests that women at high risk for VTE should either avoid systemic HRT or choose a transdermal rather than oral delivery route".[18]

American College of Chest Physicians

Regarding VTE treatment, the American College of Chest Physicians (ACCP, 2012) recommended the same management for unprovoked VTE or VTE associated with a transient (reversible) risk factor (such as estrogen-containing therapies) irrespective of FVL results.[19]

In an ongoing pregnancy or for those with a prior VTE history during pregnancy, ACCP recommended the same management irrespective of FVL results. However, if a higher risk thrombophilia is present, such as two Leiden variants or a combination of a Leiden and prothrombin variant, ACCP recommends some form of treatment and not simply surveillance.[20]

American College of Medical Genetics and Genomics

A technical standard published by the American College of Medical Genetics and Genomics (ACMG, 2018) stated that genotyping of factor II and factor V Leiden may be considered in these clinical scenarios:[14]

"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.97*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"

ACMG (2020) stated the following regarding MTHFR testing:[12,13]

"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-analyses have 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 a part of a routine evaluation for thrombophilia."

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists guideline on thrombophilia in pregnancy (ACOG, 2018) stated:[5]

"Screening for inherited thrombophilias is useful only when results will affect management decisions, and it is not useful in situations in which treatment is indicated for other risk factors." However, testing may be considered for individuals with a "first-degree relative (eg, parent or sibling) with a history of high-risk thrombophilia."

Targeted assessment for inherited thrombophilia may also be considered in the following clinical scenarios: A personal history of VTE, with or without a recurrent risk factor, and no prior thrombophilia testing and a first-degree relative (e.g., parent or sibling) with a history of high-risk inherited thrombophilia. In this setting, targeted testing for the known thrombophilia can be considered if testing will influence management.

"Among women with personal histories of VTE, recommended screening tests for inherited thrombophilias should include factor V Leiden mutation; prothrombin G20210A mutation; and antithrombin, protein S, and protein C deficiencies."

"Screening for inherited thrombophilias is not recommended for women with a history of fetal loss or adverse pregnancy outcomes including abruption, preeclampsia, or fetal growth restriction because there is insufficient clinical evidence that antepartum prophylaxis with unfractionated heparin or low-molecular-weight heparin prevents recurrence in these patients."

"Because of the lack of association between either heterozygosity or homozygosity for the MTHFR C677T polymorphism and any negative pregnancy outcomes, including any increased risk of VTE, screening with either MTHFR mutation analyses or fasting homocysteine levels is not recommended."

The ACOG contraceptive use guideline (2019) stated:[21]

"The estrogenic component of combined hormonal contraceptives increases hepatic production of serum globulins involved in coagulation (including factor VII, factor X, and fibrinogen) and increases the risk of venous thromboembolism (VTE) in users. Although all combined hormonal contraceptives cause an increased risk of VTE, this risk remains half as high as the elevated risk observed in pregnancy. Women with certain conditions associated with VTE should be counseled for non-hormonal or progestin-only contraceptives. For women with a prior VTE, the risk of a recurrent VTE depends on whether the initial thrombosis was associated with a risk factor that is permanent (e.g., factor Leiden) or reversible (e.g., surgery)."

British Society for Haematology

Guidelines from the British Society for Haematology (BSH, 2010) made the following recommendations regarding testing for inherited thrombophilia:[22]

If a first-degree relative has a VTE and has either not been tested or has tested negative, "then suggest woman considers an alternative contraceptive or transdermal HRT. Testing for heritable thrombophilia will provide an uncertain estimate of risk and is not recommended (1C)".

"If a first-degree relative with venous thrombosis has been tested and the result is positive then suggest woman considers an alternative contraceptive or transdermal HRT before offering testing as a negative test result does not exclude an increased risk of venous thrombosis. Testing for heritable thrombophilia may assist counselling of selected women particularly if a high risk thrombophilia has been identified in the symptomatic relative (C)."

"Most women with a previous unprovoked venous thrombosis (1B) or pregnancy or COC-related thrombosis (2C) will qualify for thrombophylaxis on clinical risk alone and so testing for heritable thrombophilia is not required."

Choosing Wisely Campaign

The Choosing Wisely Campaign promotes care that is evidence-based and necessary.[23]

As part of the Choosing Wisely campaign, the American College of Medical Genetics and Genomics (ACMG, 2017) released "Five Things Physicians and Patients Should Question," which stated:[24]

"Don't order MTHFR genetic testing for the risk assessment of hereditary thrombophilia. The common MTHFR gene variants, 677C>T and 1298A>G, are prevalent in the general population. Recent meta-analyses have disproven an association between the presence of these variants and venous thromboembolism."

As part of the Choosing Wisely campaign, the Society for Maternal Fetal Medicine (SMFM, 2021) released "Fifteen Things Physicians and Patients Should Question," which stated:[25]

"Don't do an inherited thrombophilia evaluation for women with histories of pregnancy loss, fetal growth restriction (FGR), 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 FGR, are lacking."

"Don't test women for MTHFR mutations. MTHFR is responsible for the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. Genetic variant C677T and A1286C have been associated with a mild decrease in enzymatic activity, which in the setting of reduced folate levels has been found to be a risk factor for hyperhomocysteinemia. Although hyperhomocysteinemia is a risk factor for cardiovascular disease and venous thrombosis, its cause is multifactorial and independent of the MTHFR genotype, even in homozygotic individuals. Despite earlier (mostly case control) studies that found an association between the MTHFR genotype and adverse outcomes, recent studies of more robust design have not replicated these findings. Due to the lack of evidence associating genotype independently with thrombosis, recurrent pregnancy loss, or other adverse pregnancy outcomes, MTHFR genotyping should not be ordered as part of a workup for thrombophilia."

Also as part of the Choosing Wisely campaign, the American Society for Clinical Laboratory Science released "Five Things Physicians and Patients Should Question," which stated:[15]

"Don't order a factor V Leiden (FVL) mutation assay as the initial test to identify a congenital cause for a thrombotic event. First, order a phenotypic activated protein C resistance (APCR) ratio assay."

"Best practice guidelines recommend testing for APCR using one of several phenotypic clot-based APCR ratio assays as an initial assay and following up positive APCR ratio results with the molecular factor V Leiden assay. Most currently available phenotypic tests are economical, have a greater than 95% concordance with molecular testing and up to 99% clinical sensitivity."

Evaluation of Genomic Applications in Practice and Prevention Working Group

The Evaluation of Genomic Applications in Practice and Prevention Working Group (EGAPP, 2011) stated the following:[4]

There is adequate evidence to recommend against routine testing for Factor V Leiden (FVL) and/or prothrombin 20210G>A (PT) in the following circumstances: (1) adults with idiopathic venous thromboembolism (VTE). In such cases, longer term secondary prophylaxis to avoid recurrence offers similar benefits to patients with and without one or more of these mutations. (2) Asymptomatic adult family members of patients with VTE and an FVL or PT mutation, for the purpose of considering primary prophylactic anticoagulation. Potential benefits are unlikely to exceed potential harms.

Clinical utility evidence of FVL testing is limited to two limited scenarios: determining anticoagulation duration to prevent recurrence in people with

idiopathic VTE, and primary VTE prevention in their at-risk relatives. They specifically exclude individuals with other risk factors for VTE, such as estrogen-containing therapy use.

"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."

"There is no evidence that knowledge of FVL/PT mutation status in patients with VTE affects anticoagulation treatment to avoid recurrence."

"Additionally, there is convincing evidence that anticoagulation beyond 3 months reduces recurrence of VTE, regardless of mutation status and 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."

Because anticoagulation is associated with significant risks and these mutations are associated with relatively low absolute VTE risk, the potential harms of overtreatment in these scenarios appears to outweigh the benefits of testing. However, test results may be used for other treatment decisions, such as anticoagulation in high-risk situations (e.g., surgery, pregnancy, long-distance travel), avoidance of estrogen-containing therapies, or the use of low-risk preventive measures (e.g., compression hose, activity counseling, smoking cessation). The authors noted that the evidence was insufficient to determine if testing might have utility in some situations, such as for influencing patient behavior or identifying those with homozygous mutations or combined thrombophilias. Therefore, these findings have limited application to the broader decision about who should be tested.

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (NICE, 2020) stated in its Venous Thromboembolic Diseases guideline:[26]

"Do not offer testing for hereditary thrombophilia to people who are continuing anticoagulation treatment."

"Consider testing for hereditary thrombophilia in people who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE if it is planned to stop anticoagulation treatment, but be aware that these tests can be affected by anticoagulants and specialist advice may be needed."

Criteria

Introduction

Requests for inherited thrombophilia genetic testing are reviewed using these criteria.

F2 and F5 Leiden Genotyping for Inherited Thrombophilia

Genetic Counseling:

Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Previous Genetic Testing:

No previous genetic testing for the requested genotype(s), AND

Diagnostic Testing for Symptomatic Individuals:

Member has a personal history of at least one of the following clinical factors suggesting a higher likelihood of having inherited thrombophilia:

VTE before the age of 50 years, or

VTE at any age with a first-degree biological relative with VTE before age 50 years, or

VTE at any age that is idiopathic/unprovoked (where no underlying cause or triggering event can be identified), or

Recurrent VTE, or

VTE at an unusual site (e.g., cerebral, mesenteric, hepatic, and portal veins), or

VTE associated with pregnancy (including up to 6 weeks after delivery), or

VTE associated with the use of estrogen-containing therapy (e.g.: oral contraceptives or hormone replacement) or estrogen mimicking therapy (e.g.: selective estrogen receptor modulators (SERMs) such as tamoxifen), or

Activated protein C (APC) resistance assay that is in the positive or borderline range, OR

Predisposition Testing for Presymptomatic/Asymptomatic Individuals:

Member has at least one of the following family history factors suggesting a higher likelihood of having inherited thrombophilia:

Family history of VTE in a first degree biological relative before age 50 years, or

Family history of F2 or FVL mutation in a first degree biological relative, AND

Test results will be used for guiding management decisions beyond simply therapy of a current first venous thrombosis event or related future prophylaxis decisions, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

Exclusions

The following test indications are considered not medically necessary:

Testing for F2 or F5 mutations without clear evidence of an increased likelihood of having at least one copy of the variant. This includes but is not limited to:

Testing performed as part of expanded cardiovascular disease screening, or

Testing performed as part of broad pharmacogenomic screening, or

Testing based on the presence of conditions with unclear evidence associating them with inherited thrombophilia (including stroke, myocardial infarction, pregnancy loss, and pregnancy complications).

Billing and Reimbursement Considerations

Medical necessity of F2 (81240) and F5 (81241) testing is indicated by billing with an ICD code from Table: *ICD Codes Supporting Increased Risk for Inherited Thrombophilia*.

F2 (81240) and F5 (81241) testing will be considered not medically necessary in the following circumstances:

A claim for the billed procedure code has already been paid in the member's history, or

An ICD code is billed with the procedure code from Table: *ICD Codes Associated with Excluded Conditions for Inherited Thrombophilia*, or

The procedure code is billed on the same date of service as any other procedure code associated with pharmacogenomics or expanded cardiovascular disease testing (including, but not limited to, 81225-81227, 81328, 81355, etc.).

MTHFR Genotyping for Hyperhomocysteinemia

This test is considered investigational and/or experimental.

Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.

In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

Table: ICD Codes Supporting Increased Risk for Inherited Thrombophilia

ICD Codes and Descriptions

400 Buckwalter Place Boulevard, Bluffton, SC 29910 (800) 918-8924

ICD10 Code or Range	Description
D68.2	Hereditary deficiency of other clotting factors
D68.5X	Primary thrombophilia
D68.6X	Other thrombophilia
D68.8	Other specified coagulation defects
D68.9	Coagulation defect, unspecified
G08	Intracranial and intraspinal phlebitis and thrombophlebitis
H34.X	Retinal vascular occlusions
I26.X	Pulmonary embolism
I27.24	Chronic thromboembolic pulmonary hypertension
I27.82	Chronic pulmonary embolism
I63.X	Cerebral infarction
I80.X	Phlebitis and thrombophlebitis
I81	Portal vein thrombosis
I82.X	Other venous embolism and thrombosis
I87.0X	Postthrombotic syndrome
O22.2X	Superficial thrombophlebitis in pregnancy
O22.3X	Deep phlebothrombosis in pregnancy
O22.5X	Cerebral venous thrombosis in pregnancy
O87.0	Superficial thrombophlebitis in the puerperium
O87.1	Deep phlebothrombosis in the puerperium
O87.3	Cerebral venous thrombosis in the puerperium
Z83.2	Family history of diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism

400 Buckwalter Place Boulevard, Bluffton, SC 29910 (800) 918-8924

ICD10 Code or Range	Description
Z86.711	Personal history of pulmonary embolism
Z86.718	Personal history of other venous thrombosis and embolism
Z86.72	Personal history of thrombophlebitis

Table: ICD Codes Associated With Excluded Conditions for Inherited Thrombophilia

ICD Codes and Descriptions

ICD10 Code or Range	Description
E78.X	Disorders of lipoprotein metabolism and other lipidemias
N96	Recurrent pregnancy loss
O02.X	Other abnormal products of conception
O03.X	Spontaneous abortion
O09.29X	Supervision of pregnancy with other poor reproductive or obstetric history
O09.9X	Supervision of high risk pregnancy, unspecified
O26.2	Pregnancy care for patient with recurrent pregnancy loss
Z13.220	Encounter for screening for lipoid disorders
Z82.3	Family history of stroke
Z82.4	Family history of ischemic heart disease and other diseases of the circulatory system
Z86.74	Personal history of sudden cardiac arrest
Z86.79	Personal history of other diseases of the circulatory system

References

Introduction

These references are cited in this guideline.

Prothrombin Thrombophilia. (Updated August 2020). In: MedlinePlus Genetics National Library of Medicine (database online). Copyright, National Institutes of Health. 1993-2020. Available at: http://ghr.nlm.nih.gov/condition/prothrombin-thrombophilia

Kujovich J. Prothrombin-Related Thrombophilia. 2006 Jul 25 [Updated 2021 Feb 4]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1148/

White RH. The epidemiology of venous thromboembolism. *Circulation*. 2003;107(23 Suppl 1):I4-8. doi: 10.1161/01.CIR.0000078468.11849.66

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. 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*. 2011;13:67. doi: 10.1097/GIM.0b013e3181fbe46f

ACOG Practice Bulletin No. 197: Inherited Thrombophilias in Pregnancy. *Obset Gynecol*. 2018; 132:e18-e34. doi: 10.1097/AOG.0000000000002703

Online Mendelian Inheritance in Man, OMIM®. Johns Hopkins University, Baltimore, MD. MIM Number: 176930: June 4, 2019. Available at: https://www.omim.org/entry/176930

Healthline. All About Thrombophilia. Updated February 21, 2019. Available at: https://www.healthline.com/health/thrombophilia

Kujovich J. Factor V Leiden Thrombophilia. 1999 May 14 [Updated 2018 Jan 4]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1368/

Varga EA. Genetic counseling for inherited thrombophilias. *J Thromb Thrombolysis*. 2008; 25:6-9. doi:10.1007/s11239-007-0056-2

Gatt A, Makris M. Hyperhomocysteinemia and venous thrombosis. *Semin Hematol*. 2007 Apr;44(2):70-6. doi: 10.1053/j.seminhematol.2007.01.002

MTHFR gene. (Updated August 2020). In: MedlinePlus Genetics National Library of Medicine (database online). Copyright, National Institutes of Health. 1993-2020. Available at: https://medlineplus.gov/genetics/gene/mthfr/#synonyms

Hickey, SE, Curry, CJ, Toriello, HV; American College of Medical Genetics Practice Guidelines: Lack of Evidence for MTHFR Polymorphism Testing. *Genet Med*. 2013:15(2):153-156. doi: 10.1038/gim.2012.165

Bashford MT, Hickey SE, Curry CJ, Toriello HV; Addendum: ACMG Practice Guideline: Lack of evidence for MTHFR polymorphism testing. *Genet Med*. 2020;22:2125. doi: 10.1038/s41436-020-0843-0

400 Buckwalter Place Boulevard, Bluffton, SC 29910 (800) 918-8924

Zhang S, Taylor AK, Huang X, et al. Venous thromboembolism laboratory testing (factor V Leiden and factor II c.*97G>A), 2018 update: a technical standard of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2018;20 (12):1489-1498. doi:10.1038/s41436-018-0322-z

American Society for Clinical Laboratory Science. American Board of Internal Medicine (ABIM) Foundation Choosing Wisely Campaign. Items 1-5 released June 2020, Items 6-10 released September 2021. Available at: https://www.choosingwisely.org/societies/american-society-for-clinical-laboratory-science/

McGlennen RC, Key NS. Clinical and Laboratory Management of the Prothrombin G20210A Mutation. *Arch Pathol Lab Med*. Nov 2002;126:1319-1325. doi: 10.1043/0003-9985(2002)126<1319:CALMOT>2.0.CO;2

Segal JB, Brotman DJ, Necochea AJ, et al. Predictive Value of Factor V Leiden and Prothrombin G20210A in Adults With Venous Thromboembolism and in Family Members of Those With a Mutation: A Systematic Review. *JAMA*. 2009 Jun;301(23):2472-85. doi: 10.1001/jama.2009.853

Cobin RH, Goodman NF. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on menopause –2017 Update. *Endocr Pract*. 2017;23(7):869-880. doi: 10.4158/EP171828.PS

Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [published correction appears in *Chest*. 2012 Dec;142(6):1698-1704]. *Chest*. 2012;141(2 Suppl):e419S–e496S. doi:10.1378/chest.11-2301

Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e691S–e736S. doi:10.1378/chest.11-2300

ACOG Committee on Practice Bulletins-Gynecology. ACOG practice bulletin No. 206: Use of hormonal contraception in women with coexisting medical conditions. *Obstet Gynecol*. 2019;133(2):e128-e150. doi: 10.1097/AOG.0000000000003072

Baglin T, Gray E, Greaves M, et al; British Committee for Standards in Haematology. Clinical guidelines for testing for heritable thrombophilia. *Br J Haematol*. 2010 Apr;149(2):209-20. doi: 10.1111/j.1365-2141.2009.08022.x

ABIM Foundation. Choosing Wisely. Available at: https://www.choosingwisely.org

American College of Medical Genetics and Genomics. American Board of Internal Medicine (ABIM) Foundation Choosing Wisely Campaign. Available at: http://www.choosingwisely.org/societies/american-college-of-medical-genetics-and-genomics/. Released July 10, 2015; Updated July 1, 2021.

Society for Maternal-Fetal Medicine Publications Committee. American Board of Internal Medicine (ABIM) Foundation Choosing Wisely Campaign. Available at: http://www.choosingwisely.org/doctor-patient-lists/society-for-maternal-fetal-medicine/. Released February 3, 2014 (1–5); February 1, 2016 (6–10); May 1, 2019 (11–15); Revised January 14, 2021.

National Institute for Health and Care Excellence (NICE). Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. London (UK): National Institute for Health and Care Excellence (NICE); 2020 Mar. Available at: https://www.nice.org.uk/guidance/ng158/chapter/Recommendations#thrombophilia-testing Myers KC, Bolyard AA, Otto B, et al. Variable clinical presentation of Shwachman-Diamond syndrome: update from the North American Shwachman Diamond Syndrome Registry. *J Pediatr.* 2014;164(4):866-870.

400 Buckwalter Place Boulevard, Bluffton, SC 29910 (800) 918-8924