Subject:	RTM Venous and Arterial Thrombosis Risk Testing		
Policy Number:	PO-RE-008v2		
Effective Date:	09/01/2023	**Last Approval Date:**	08/07/2023

I. Policy Description

A thrombosis, also known as a blood clot, occurs within blood vessels in the body. The two main types of thrombosis include venous thrombosis, which is when a vein is blocked due to a blood clot, and arterial thrombosis, which is when an artery is blocked due to a blood clot. Thrombophilias refer to hereditary and/or acquired abnormalities of hemostasis that predispose patients to thrombosis (Stevens et al., 2016). The most common presentations of venous thromboembolism (VTE) are deep vein thrombosis (DVT) and pulmonary embolism (PE) (Bartholomew, 2017).

Terms such as male and female are used when necessary to refer to sex assigned at birth.

Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in Applicable State and Federal Regulations of this policy document.

1. For individuals without recurrent venous thromboembolism (VTE) risk factors (e.g., surgery, prolonged immobilization, collagen vascular disease, malignancy, certain hematologic disorders), plasma testing for protein C deficiency, protein S deficiency, and antithrombin III deficiency (see Note 1 and Note 2) **MEETS COVERAGE CRITERIA** in any of the following situations:
    a. For individuals less than 50 years of age who have experienced any deep venous thrombosis (DVT).
    b. For individuals who have experienced a DVT in unusual sites (e.g., hepatic, mesenteric, or cerebral veins).
    c. For individuals who have experienced a DVT and who have a strong family history of thrombotic disease.

   d. For individuals who are pregnant or taking oral contraceptives and who have experienced a DVT.
   e. For first- and second-degree relatives (see Note 2) of individuals who experienced a deep venous thrombosis before 50 years of age.
   f. For women under the age of 50 who smoke and who have suffered a myocardial infarction.
   g. Before the administration of oral contraceptives, targeted testing of individuals with a personal or family history of DVT.
   h. For pediatric individuals who have suffered from a pediatric arterial ischemic stroke.

2. For individuals with warfarin-induced skin necrosis or for infants who develop neonatal purpura fulminans, plasma testing for protein C deficiency and protein S deficiency (see Note 1) **MEETS COVERAGE CRITERIA**.

3. Venous thrombosis risk testing for superficial venous thrombosis (including superficial thrombophlebitis and varicosities) **DOES NOT MEET COVERAGE CRITERIA**.

4. For all situations, activated protein C (aPC) resistance assay **DOES NOT MEET COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

5. DVT risk testing as part of a pre-transplant evaluation test **DOES NOT MEET COVERAGE CRITERIA**.

NOTES:

Note 1: Plasma testing for protein C deficiency, protein S deficiency, and antithrombin III deficiency should be performed at least six weeks after the acute thrombotic event and while the patient is not taking anticoagulants. Assays for clotting inhibitors amount and function should be performed prior to any molecular testing.

Note 2: In addition to plasma testing (protein C deficiency, protein S deficiency, antithrombin III deficiency), risk factor testing for individuals suspected of having a hereditary and/or acquired thrombophilia should include genetic testing for Factor V Leiden and Prothrombin gene G20210A mutations.

Note 3: First-degree relatives include parents, full siblings, and children of the individual. Second-degree relatives include grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings of the individual.

Scientific Background

A thrombus is “an aggregate of coagulated blood within the vascular system or heart which contains platelets, fibrin, leukocytes, and red blood cells in varying amounts” (Herrmann, 2018). This aggregate of blood can be problematic as it may obstruct normal blood circulation throughout the body and even travel to peripheral areas. The primary manifestations of venous thromboembolisms (VTE) are deep vein thrombosis and pulmonary embolism. These conditions affect an estimated one million individuals in the United States annually (Bartholomew, 2017).

Thrombosis is widely theorized to develop due to Virchow’s Triad, which consists of abnormalities in blood flow, a vascular endothelial injury, and alterations in the blood constituents. Changes in any of these characteristics may cause the clot to form (Bauer & Lip, 2022b). For example, sickle red blood cells may cause increased clumping or decreased adhesion to the vessel walls (Byrnes & Wolberg, 2017). There are two main types of thrombosis: venous thrombosis (when a vein is blocked due to a blood clot) and arterial thrombosis (when an artery is blocked due to a blood clot).

A deep vein thrombosis (DVT) refers to a thrombus in a “deep” vein whereas a pulmonary embolism (PE) refers to an obstruction of the pulmonary artery (or one of its branches) by foreign material (Bauer, 2022; Thompson, 2022). DVT of the lower extremities may cause symptoms, such as swelling or edema in the lower extremities, pain, and warmth in the affected area (Bauer, 2022). This thrombus may travel to the lungs (becoming an embolus) and cause a PE. A PE has similar symptoms to DVT but may include pulmonary issues, such as shortness of breath. The risk factors for VTE, PE, and DVT are similar (Thompson, 2022). The two primary categories of risk factors for VTE are hereditary and acquired, and the genetic tendency toward VTE is referred to as inherited thrombophilia. Hereditary risk factors include genetic mutations such as Factor V Leiden (FVL) mutations. The five most common genetic risk factors for VTE are FVL mutations, prothrombin mutations, protein S defect, protein C defect, and antithrombin defect (Bauer & Lip, 2022b). Approximately 50–60% of the variance in VTE incidence are attributed to genetic effects (Crous-Bou et al., 2016).

A modified activated partial thromboplastin time (aPTT) assay detects the anticoagulant activity of activated protein C (aPC). FVL mutations cause coagulation factor V to be unresponsive to aPC and initially, these changes were termed “aPC resistance” due to the reduced activity of aPC on a modified aPTT assay. A single nucleotide change (G1691A) results in a point mutation of glutamine to arginine at position 506. Approximately 99% of carriers of this mutation are heterozygous, and only 5% of these heterozygotes will experience a VTE in their lifetime. These mutations are often suspected in patients experiencing a VTE at a young age (under 50), a VTE in unusual areas such as a portal vein, or recurrent VTEs (Bauer, 2023). Protein C may also be genetically deficient, but this mutation is only seen in 2-5% of individuals with a VTE (Bauer, 2022). Protein S, a cofactor for the aPC control mechanism, and deficiencies in this protein may also confer additional risk for VTE (K. Bauer, 2021b).

The second most common inherited thrombophilia is the G20210A mutation of prothrombin. This mutation is a gain of function mutation where clotting activity is increased by creating more thrombin and fibrin. The overall prevalence of this mutation is about 2% (K. Bauer, 2021c). Genetic defects of antithrombin (an inhibitor of thrombin) may also occur, but the estimated prevalence of antithrombin defects is only a maximum of 0.2% (K. Bauer, 2021a).

Acquired risk factors or predisposing conditions for thrombosis include a prior thrombotic event, recent major surgery, presence of a central venous catheter, trauma, immobilization, malignancy, pregnancy,

the use of oral contraceptives or heparin, myeloproliferative disorders, antiphospholipid syndrome (APS), and a number of other major medical illnesses (Bauer & Lip, 2022b). Patients with acquired hypercoagulability have an increased risk of venous thrombosis, arterial thrombosis, or both; however, there is a low risk of recurrence, regardless of thrombophilia status (Connors, 2017). A rare complication of warfarin treatment, warfarin-induced skin necrosis is commonly due to protein C deficiency, with rare cases of protein S deficiency or PVL having been reported (Bauer & Lip, 2022a).

Risk factors for arterial thrombosis are lesser known. The relationship between FVL and arterial thrombosis is controversial with studies reporting varying results; overall, FVL is not currently considered a major risk factor for arterial thrombosis (Carroll & Piazza, 2018; Kujovich, 2011). Kujovich (2018) states that FVL testing should not be performed on persons with any type of arterial thrombosis including myocardial infarction and stroke in children or adults. It has also been reported that while inherited antithrombin, protein S and protein C deficiencies are important risk factors for venous thrombosis, “they have little or no effect on arterial thrombosis” (Previtali et al., 2011). Further, prothrombin gene mutation is not consistently shown to increase the risk of an arterial thromboembolism, and “There is no association of antithrombin deficiency with arterial thrombosis” (Carroll & Piazza, 2018).

It has been proposed that venous thrombosis risk testing may be beneficial as a pre-transplant evaluation test. However, no studies have been identified suggesting this. The North American Thrombosis Forum (NAFT) states that even though certain genetic conditions predispose a small proportion of the population to the development of blood clots, “few people with thrombophilias develop symptoms”; further, there is no cost-effective, safe or long-term method to prevent a blood clot from forming even if a genetic predisposition is identified (NATF, 2019).

Thrombotic events such as thrombophilia and stroke have become increasingly documented in hospitalized pediatric patients with underlying medical conditions such as prematurity, cancer, and congenital heart disease, but they are rarely identified in healthy children. Furthermore, in most cases of pediatric venous thromboembolism, there exist other underlying risk factors such as indwelling central venous catheter and inherited thrombophilia that are worthy of further investigation. The incidence of venous thromboembolisms is highest in neonates and infants, but there is a second peak recorded in adolescence, coinciding with the use of oral contraceptives. However, as in the case with adults, little to no evidence suggests that the use of venous thrombosis risk testing in children will affect the acute management of venous thromboembolisms. In a study including a total of 271 children with VTE, it was found that the relative frequencies of individually inherited thrombophilias were low—for example, the highest recorded frequency of IT disorders was of Factor V Leiden, occurring in only 5 to 10 percent of the samples. Moreover, a study of 52 children with thromboembolic events during the acute phase did not urge any changes to acute management, regardless of the result of the test (Raffini et al., 2022).

Venous thrombosis risk testing has also been entertained as a manner of combatting pediatric stroke, which can be characterized in a variety of ways, such as by age and by presentation. Arterial ischemic infarctions are the most common, comprising approximately 80% of all perinatal strokes, and this form of stroke can occur in up to 1 in 3500 of newborns. However, though it would seem reasonable for venous thrombosis risk testing to be employed here, recent prospective case-control studies suggest that routine thrombophilia testing is not warranted. The study showed that conditions associated with thrombophilia rarely coincided with arterial ischemic strokes, and these conditions included, but were not limited to, decreased levels of protein C, protein S, or prothrombin, and genotyping of factor V

Leiden (FVL) and factor II (FII, prothrombin) G20210A. Of the 14 parameters examined, 12 showed no difference, including all common thrombophilias examined, with specific mention that FVL and FII were comparable to population norms (Curtis et al., 2017; Ferriero et al., 2019). Subsequent evaluation deemed thrombophilia evaluation in neonates as having limited clinical utility because "levels of protein C, protein S, antithrombin, and factor XI are normally decreased to 30% of adults levels, and these levels only approach adult levels at various time points during childhood". Therefore, the use of thrombophilia testing for these proteins may be misleading in the neonatal period, and MRIs instead should be used to diagnose the thrombosis (Ferriero et al., 2019). Moreover, studies focusing on the roles of thrombophilia, arteriopathy, and cardiac abnormalities in perinatal ischemic stroke find that these risk factors were at best unclear, weakening what predictive power they were believed to contain for even recurrent events after perinatal stroke and leading researchers to conclude that thrombophilia evaluation should rarely be considered in cases of perinatal stroke (Lehman et al., 2017).

While the initial aPTT assays used unaltered plasma (first-generation assays), some versions were neither sensitive nor specific for FVL. Modifications to this test resulted in second generation functional aPC resistance assays that correlate well with the presence of FVL. However, in rare cases, functional assays for aPC resistance can give misleading results (e.g., the presence of a lupis anticoagulant can cause falsely abnormal results in some assays; therapy with a direct thrombin inhibitor or oral factor Za inhibitor can cause falsely normal results). In addition, while FVL can be detected by genetic testing or a second-generation functional coagulation test for aPC resistance, individuals with a positive aPC resistance assay would still need to receive genetic testing to confirm a diagnosis (Bauer, 2023). Due to difficulty with interpretation, a need for confirmatory genetic testing, and the overall declining cost of genetic testing, aPC resistance assays are performed infrequently. When performed, they are simply reported as positive, borderline, or negative (K. A. Bauer, 2021).

Clinical Utility and Validity

A D-dimer assay is a blood test that is used in clinical practice to assist in identifying if a patient has a DVT or PE; this test may also help patients experiencing unprovoked VTE to determine if anticoagulation treatment should continue or halt after initial treatment is complete (Linkins & Takach Lapner, 2017). A D-dimer assay may vary greatly based on the type of antibody used, the method of capture, calibration, and instrumentation. Currently, 30 different assays as available which use 20 different monoclonal antibodies; various studies have reported a broad sensitivity and specificity range for D-dimer assays from 69-97% and 43-99% respectively (Linkins & Takach Lapner, 2017). Hence, all D-dimer assays differ and need to be validated within the population of interest. Because of this, comparing study results is challenging.

Factor VIII is a blood clotting protein encoded by the F8 gene. A case report by Algahtani and Stuckey (2019) suggests that high factor VIII levels may also assist in risk factor determination for thrombosis or ischemic heart disease. "We conclude that high factor VIII levels are a risk factor for thrombosis, with a greater impact on venous than on arterial thrombosis. However, due to a lack of international consensus on methods for the laboratory testing of factor VIII levels in plasma, we would not currently recommend the measurement of factor VIII levels as part of routine thrombophilia screening (Algahtani & Stuckey, 2019)." This relationship has been shown previously as elevated levels of coagulation factor VIII:C were identified in a retrospective study of 584 first-degree relatives of 177 patients with high coagulation factor VIII:C levels; the researchers found that 40% of first degree relatives also had high VIII:C levels and were at an increased risk for VTE and arterial thrombosis when compared to

other first-degree relatives with normal VIII:C levels (Bank et al., 2005).

Lee et al. (2017) performed whole exome sequencing on 64 patients with VTE to assess the types of mutations of inherited thrombophilias. Of these 64 patients, 39 of them were found to have a pathogenic variant or variant of unknown significance (VUS). Further, eight were found to have a Factor V mutation (6 with FVL and 2 with less common mutations), two were found to have a prothrombin G20210A mutation, six were found to have a protein S mutation, two were found to have a protein C mutation, and three were found to have an antithrombin mutation (Lee et al., 2017).

Segal et al. (2009) reviewed the utility of FVL and prothrombin G20210A testing. The authors reviewed 124 articles and concluded that although genetic testing for these two risk factors is very accurate (valid), the clinical utility is lacking due to lack of evidence demonstrating improvement in clinical outcomes (Segal et al., 2009).

Onda studied the clinical utility of a new diagnostic algorithm based on serum D-dimer levels for VTE after hepatectomy. 742 patients who underwent hepatectomy were enrolled in the study and measured for serum D-dimer levels post-op. CT scan was performed for patients who had a D-dimer level of greater than 20 μg/mL. Based on D-dimer and CT scan, VTE was diagnosed in 26 patients and pulmonary embolism (PE) was diagnosed in 18 patients. Multivariate analysis also showed that a resected liver weight of more than 120 grams is a significant predictor of VTE. Overall, “patients who undergo hepatectomy are at high risk for VTE, especially when the resected liver weight is high. The proposed diagnostic algorithm based on serum D-dimer levels for VTE after hepatectomy can be useful for early diagnosis" (Onda et al., 2021).

Analytical Validity

Murphy and Sabath (2019) have compared the accuracy and reliability of two tests: a genotypic assay which identifies FVL mutations, and a phenotypic aPC resistance assay. Data from 1596 patients was analyzed; each patient had received both types of testing. The authors state that the phenotypic testing exhibited both high sensitivity and specificity compared to genotypic testing. “Phenotypic assays had close to total concordance with genotypic assays over 16 years of testing. Changing ordering practices could result in up to an 80% reduction in testing costs (Murphy & Sabath, 2019).”

A systematic review and meta-analysis by Chiasakul et al. (2019) researched the relationship between inherited thrombophilia and the risk of arterial ischemic stroke in adults. Inherited thrombophilias included FVL, protein C and S deficiency, antithrombin deficiency and prothrombin G20210A mutation. For this study, 11,916 stroke patients and 96,057 controls were identified. The authors concluded that “Compared with controls, patients with arterial ischemic stroke were significantly more likely to have the following inherited thrombophilias: factor V Leiden (OR, 1.25; 95% CI, 1.08-1.44; I2=0%), prothrombin G20210A mutation (OR, 1.48; 95% CI, 1.22-1.80; I2=0%), protein C deficiency (OR, 2.13; 95% CI, 1.16-3.90; I2=0%), and protein S deficiency (OR, 2.26; 95% CI, 1.34-3.80; I2=8.8%)” (Chiasakul et al., 2019). Antithrombin deficiency did not reach statistical significance in this study. Hence, in this review, inherited thrombophilias were found to be associated with an increased risk of arterial ischemic stroke in adults.

In a systematic review, Ortega studied the predictive value of D-dimer testing for venous thrombosis diagnosis in unusual locations. 3378 patients from 23 articles with thrombosis in unusual sites, such as upper extremity deep vein thrombosis (DVT), cerebral vein thrombosis (CVT) and splanchnic vein thrombosis (SVT), were studied. 12 articles on CVT concluded that timing of D-dimer testing is important and patients with short duration of symptoms displayed higher D-dimer levels. Sensitivity

and specificity in these patients ranged from 58% to 97% and from 77% to 97.5%, respectively. The authors conclude that "D-dimer testing should not be currently recommended for the diagnosis of thrombosis in unusual sites as a first line diagnostic tool. The development of algorithms combining biomarkers such as D-dimer and clinical decision tools could improve the diagnosis" (Ordieres-Ortega et al., 2020).

Guidelines and Recommendations:

American Heart Association/American Stroke Association (AHA/ASA)

The AHA/ASA has issued a scientific statement for the management of stroke in neonates and children, wherein testing for thrombophilic abnormalities are discussed. The AHA/ASA admits that due to the lack of “an adequately powered study to detect the impact of genetic thrombophilia on recurrence risk in pediatric AIS [arterial ischemic stroke], definite recommendations about evaluation remain challenging”, but acknowledges that “laboratory testing outside of clinical studies may provide guidance for long-term management of the patient”. For cases of thrombophilia the AHA/ASA provides an algorithm for the “Targeted Evaluation of a Child With AIS for Rare Causes or Causes Requiring Additional Evaluation” that includes the examination of Factor VIII level Lipoprotein(a), *MTHFR* mutation, and homocysteine levels, and it is suggested that “non-DNA testing may need to be repeated when the child is older to ensure that adult levels of proteins have been attained” and “measurement of proteins or homocysteine levels in the acute phase of stroke may not be accurate and should be repeated after the acute event”. Finally, for the evaluation of a child with AIS, it is believed that “A thrombophilia evaluation is helpful in every case of childhood stroke, especially if there is no identifiable cause, medical history of thrombosis, or a first-degree relative with thrombosis history” (Ferriero et al., 2019).

In 2021, the AHA released guidelines on stroke prevention. The AHA brushes on testing for hematologic traits in the context of secondary stroke prevention. "If in certain clinical scenarios (eg, paradoxical emboli caused by venous thrombosis or recurrent venous thrombosis) testing for thrombophilic states is considered, testing for protein C, protein S, or antithrombin levels should be deferred or repeated at least 4 to 6 weeks (or up to 6 months for factor VIII609) after the acute stroke given that these protein levels may be altered during the acute stroke phase” (Kleindorfer et al., 2021).

American College of Medical Genetics and Genomics (ACMG)

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 circumstances:

- 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 (b) one first-degree relative with VTE at a young age

- Patients with low aPC resistance activity
- Testing may be considered in the 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.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 (Zhang et al., 2018).

The ACMG found several clinical scenarios requiring special considerations worth mentioning, involving different populations. One involved the testing of asymptomatic versus symptomatic individuals, in which they assert that “It is generally not recommended to test asymptomatic minors as VTE rarely occurs before young adulthood even in the homozygous state.” For prenatal testing and population screening, the ACMG suggests that “prenatal testing and population screening are not indicated due to the low penetrance of these variants, later age of onset, and lack of genotype-directed prophylaxis”. Lastly, in women considering taking estrogen-containing oral contraceptives (OC) or hormone replacement therapy (HRT), the ACMG indicates that “A family and personal history of thrombosis should be carefully evaluated for all women before initiating HRT and a positive history may warrant thrombophilia screening” (Zhang et al., 2018).

ACMG does not support testing for *MTHFR* variants in thrombophilia assessment due to the lack of correlation with negative pregnancy outcomes (Hickey et al., 2013). This statement was reaffirmed in 2020 (Bashford et al., 2020).

American Society of Hematology (ASH)

The 2013 ASH recommends against testing “for thrombophilia in adult patients with venous thromboembolism (VTE) occurring in the setting of major transient risk factors (surgery, trauma or prolonged immobility)’ (ASH, 2013).

In 2018, ASH released their guidelines for management of venous thromboembolism, which included the following recommendations (Lim et al., 2018):

- “*Recommends* using a strategy starting with D-dimer for excluding PE in a population with low prevalence/PTP (≤5%), followed by ventilation-perfusion (VQ) scan or computed tomography pulmonary angiography (CTPA) for patients requiring additional testing.
- *Recommends against* using a positive D-dimer alone to diagnose PE, and against additional testing following negative CTPA or normal VQ scan in a population with low prevalence/PTP (≤5%).
- S*uggests* using a strategy starting with D-dimer for excluding PE in a population with

intermediate prevalence/PTP (~20%), followed by VQ scan or CTPA for patients requiring additional testing.
- *Recommends against* using a positive D-dimer alone to diagnose PE, and against additional testing following negative CTPA or normal VQ scan in a population with intermediate prevalence/PTP (~20%).
- *Recommends against* using a positive D-dimer alone to diagnose PE, and against using D-dimer as a subsequent test following a negative CT scan in a population with high prevalence/PTP (≥50%).
- *Suggests* using a strategy starting with D-dimer for excluding recurrent PE in a population with unlikely PTP.
- *Recommends* using a strategy starting with D-dimer for excluding DVT in a population with low prevalence/PTP (≤10%), followed by proximal lower extremity ultrasound or whole-leg ultrasound for patients requiring additional testing.
- *Recommends against* using a positive D-dimer alone to diagnose DVT, and against additional testing following negative proximal or whole-leg ultrasound in a population with low prevalence/PTP (≤10%).
- *Recommends against* using a positive D-dimer alone to diagnose DVT in a population with intermediate prevalence/PTP (~25%).
- *Recommends against* using a positive D-dimer alone to diagnose DVT in a population with high prevalence/PTP (≥50%).
- *Suggests* using a strategy starting with D-dimer for excluding recurrent DVT in a population with unlikely PTP.
- *Suggests* a strategy starting with D-dimer for excluding upper extremity DVT in a population with low prevalence/unlikely PTP (10%), followed by duplex ultrasound if D-dimer is positive.
- *Recommends against* using a positive D-dimer alone to diagnose upper extremity DVT in a population with low prevalence/unlikely PTP (10%).
- *Suggests* a strategy of either D-dimer followed by duplex ultrasound/serial duplex ultrasound, or duplex ultrasound/serial duplex ultrasound alone for assessing patients suspected of having upper extremity DVT in a population with high prevalence/likely PTP (40%).
- *Recommends against* using a positive D-dimer alone to diagnose upper extremity DVT in a population with high prevalence/likely PTP (40%) (Lim et al., 2018)."

In 2020, The ASH guidelines released guidelines on management of venous thromboembolism. ASH suggest "against the routine use of prognostic scores, D-dimer testing, or venous ultrasound to guide the duration of anticoagulation" (Ortel et al., 2020).

Society for Vascular Medicine

This society recommends against workup for clotting disorders for patients with DVT as treatment will not change based on any abnormalities (SVM, 2013).

American College of Obstetricians and Gynecologists

The 2013 ACOG clinical management guidelines recommend that screening for inherited thrombophilia "may be considered in the following clinical settings:

1. "A personal history of venous thromboembolism that was associated with a non-recurrent risk factor

2. A first degree relative (parent or sibling) with a history of high-risk thrombophilia (ACOG, 2013)."

The 2018 ACOG Practice Bulletin Summary Number 197 supersedes the above 2013 guidelines (Practice Bulletin Number 138). In this update, the ACOG makes the following recommendations regarding screening based on "limited or inconsistent scientific evidence":

"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 2018 ACOG recommends the following screening guideline based on "consensus and expert opinion":

"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" (ACOG, 2018).

Evaluation of Genomic Applications in Practice and Prevention

"The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group found adequate evidence to recommend against *routine* testing for Factor V Leiden (FVL) and/or prothrombin 20210G>A (Gupta et al.) 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. The evidence was insufficient to determine whether FVL/PT testing might have clinical utility in some circumstances, such as for identifying FVL homozygosity among asymptomatic family members of adults with idiopathic VTE or counseling patients about the risks and benefits of antithrombotic therapy. The recommendations do not extend to patients with other risk factors for thrombosis, such as contraceptive use, as the evidence review that serves as the basis for the recommendations focused primarily on idiopathic VTE" (EGAPP, 2011).

The Anticoagulation Forum

The Anticoagulation Forum published guidance in the Journal of Thrombosis and Thrombolysis on (Stevens et al., 2016):

- "Do not perform thrombophilia testing following an episode of provoked VTE. A positive thrombophilia evaluation is not a sufficient basis to offer extended anticoagulation following

an episode of provoked 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. A negative thrombophilia evaluation is not a sufficient basis to stop anticoagulants following an episode of unprovoked VTE in a patient with low bleeding risk and willingness to continue therapy. Heterozygosity for FVL or PGM does not increase the predicted risk of recurrence after unprovoked VTE to a clinically significant degree.
- Do not test for thrombophilia in asymptomatic family members of patients with VTE or hereditary thrombophilia. As a family history of VTE confers an excess risk of thrombosis, relatives should be counseled regarding use of prophylaxis in high risk situations.
- 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.
- 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.
- 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" (Stevens et al., 2016).

American College of Cardiology (ACC)

In 2017, guidance published in the New England Journal of Medicine by Gupta was summarized by Barnes for the American College of Cardiology:

1. "Venous thromboembolism (VTE) affects an estimated 300,000-600,000 patients annually in the United States.
2. The risk of VTE recurrence is best predicted by whether the initial VTE episode was provoked or unprovoked, not the results of inherited thrombophilia testing.
3. Most patients with a provoked VTE have recently undergone surgery, immobility, trauma, or have a concurrent cancer diagnosis. Concurrent use of hormones (e.g., estrogen-containing contraceptive pills) is also frequently considered a provoking factor for VTE development.
4. For patients with a first provoked VTE event, guidelines recommend anticoagulation for only 3 months (not longer). Prolonged anticoagulation is associated with an increased risk of bleeding that outweighs the risk of VTE recurrence for these patients.
5. Patients with an unprovoked VTE (none of the provoking risk factors listed above) require longer anticoagulation due to a higher risk of recurrence that outweighs the risk of bleeding associated with long-term anticoagulation therapy.
6. Thrombophilia testing performed in the setting of an acute clot or ongoing anticoagulation therapy will often result in spurious results (usually false positive). For example, natural anticoagulants (e.g., protein C and S, antithrombin) are consumed during an acute thrombotic event and the levels can be reduced by ongoing anticoagulant therapy.
7. A recent study identified that up to 55% of Medicare patients with provoked VTE had

undergone inappropriate thrombophilia testing, associated with significant cost to the healthcare system.
8. While thrombophilia testing rarely impacts management decisions about anticoagulation therapy, it may be beneficial for genetic testing purposes in patients presenting with a first unprovoked VTE at a young age (e.g., <45 years) or at an unusual site.
9. For patients with unprovoked VTE at a young age, VTE at an unusual site, arterial thrombosis, or pregnancy morbidity, testing for antiphospholipid antibodies, JAK2 mutation, and paroxysmal nocturnal hemoglobinuria may be beneficial.
10. There is no role for extensive cancer screening (e.g., computed tomography scanning) in patients with VTE. Only routine, age-appropriate cancer screening is recommended" (G. Barnes, 2017; Gupta et al., 2017).

Again in 2017, key points—inclusive of guiding points—published in the New England Journal of Medicine by Connors were captured by Barnes for the American College of Cardiology:

1. "The majority of patients with venous thromboembolism (VTE) should not be tested for thrombophilia. Data supporting clinical usefulness and benefits are limited or nonexistent.
2. Most patients with inherited thrombophilia can be identified by coagulation experts based on the patient's personal and family history of VTE. Thrombophilia testing is usually not required.
3. Factors associated with an inherited thrombophilia include VTE at a young age (<40-50 years), a strong family history of VTE, VTE in conjunction with weak provoking factors at a young age, recurrent VTE, and VTE in an unusual site (e.g., cerebral or splanchnic veins).
4. Do not perform thrombophilia testing at the time of a VTE event, as it can be inaccurate (often false positive). Perform testing (when indicated) after completion of initial therapy and if it might change management strategies.
5. Do not perform thrombophilia testing while a patient is receiving anticoagulation. Instead, wait until 2 weeks after discontinuing warfarin, or 2 days for direct oral anticoagulants and heparin.
6. The goal of thrombophilia testing should be to aid decision making regarding future VTE prophylaxis, to guide testing of family members, and to determine the cause in severe or fatal VTE. Test results alone should not be used to decide on the duration of anticoagulation therapy.
7. Most VTE recurrence risk tools do not incorporate thrombophilia test results into their risk stratification schemes.
8. For patients with provoked VTE, even if they have homozygous factor V Leiden, prothrombin gene mutations, or deficiencies of protein S, C, or antithrombin, they do not require lifelong anticoagulation.
9. Currently available thrombophilia tests are insufficient to identify inherited risks of VTE. Therefore, a negative test should not be interpreted as a patient being free of thrombophilia.
10. Testing for the antiphospholipid antibody syndrome may be useful in patients with unprovoked VTE if there is clinical equipoise about extended anticoagulation courses. It can also be useful to determine warfarin versus direct oral anticoagulant therapy" (G. D. Barnes, 2017; Connors, 2017).

American Society for Clinical Pathology

ASCP has published guidelines with Choosing Wisely which state: "Do not test for Protein C, Protein S, or Antithrombin (ATIII) levels during an active clotting event to diagnose a hereditary deficiency

because these tests are not analytically accurate during an active clotting event. . . These assays may be useful to test for an acquired deficiency (i.e., disseminated intravascular coagulation) in consumptive coagulopathies. These tests are not analytically accurate during an active clotting event. Moreover, they are not clinically actionable at the time of an acute clot, because the same therapeutic intervention (anticoagulation) is performed regardless of the results. Deferral to the outpatient/non-acute setting allows for the testing to be done at a time when the results would change patient management, i.e., ceasing or continuing anticoagulation. Because anticoagulation may also impact the determination of results (e.g., Protein C and Protein S decrease on warfarin, while ATIII is actually elevated), testing while on anticoagulants may also yield misleading results and should be avoided" (ASCP, 2017).

In 2019, an additional guideline was put forth by the ASCP on Choosing Wisely: "Do not perform a hypercoagulable workup in patients taking direct factor Xa or direct thrombin inhibitors." The guideline explained that the use of certain direct oral anticoagulants may render the results of such workups uninterpretable and inaccurate (ASCP, 2019).

European Society of Cardiology

The ESC has published guidelines for the diagnosis and management of acute PE. These guidelines state:

- "D-dimer measurement and clinical prediction rules should be considered to rule out PE during pregnancy or the post-partum period
- Plasma D-dimer measurement, preferably using a highly sensitive assay, is recommended in outpatients/emergency department patients with low or intermediate clinical probability, or those that are PE-unlikely, to reduce the need for unnecessary imaging and irradiation
- A D-dimer test, using an age-adjusted cut-off or adapted to clinical probability, should be considered as an alternative to the fixed cut-off level
- D-dimer measurement is not recommended in patients with high clinical probability, as a normal result does not safely exclude PE, even when using a highly sensitive assay
- Assessment of the RV [right ventricle] by imaging methods or laboratory biomarkers should be considered, even in the presence of a low PESI [Pulmonary Embolism Severity Index] or a negative sPESI [simplified Pulmonary Embolism Severity Index]" (Konstantinides et al., 2019).

In 2021, the ESC Working Group released guidelines on diagnosis and management of acute deep vein thrombosis. These guidelines suggest that "ELISA D-dimer or highly sensitive immunoturbidimetric tests should be measured in 'unlikely' clinical probability patients to exclude DVT diagnosis" (Mazzolai et al., 2022).

Scottish Intercollegiate Guidelines Network

Regarding laboratory tests in the assessment of thrombosis risk, SIGN has stated that "Routine laboratory screening for heritable thrombophilias is not recommended" (SIGN, 2014).

American Society for Clinical Laboratory Science (ASCLS)

In 2021, ASCLS published guidelines on Choosing Wisely to suggest against ordering a homocysteine assay as part of the thrombophilia work up. “An elevated homocysteine level is not a clotting disorder and should not be included in thrombophilia testing panels” (ASCLS, 2021).

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

II. Applicable Codes

Code	Description	Comment
85300	Clotting inhibitors or anticoagulants; antithrombin III, activity	
85301	Clotting inhibitors or anticoagulants; antithrombin III, antigen assay	
85302	Clotting inhibitors or anticoagulants; protein C, antigen	
85303	Clotting inhibitors or anticoagulants; protein C, activity	
85305	Clotting inhibitors or anticoagulants; protein S, total	
85306	Clotting inhibitors or anticoagulants; protein S, free	
85307	Activated Protein C (APC) resistance assay	

III. Definitions

Term	Meaning

IV. Related Policies

Policy Number	Policy Description
N/A	N/A

Procedure codes appearing in Reimbursement Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

V. Reference Materials

ACOG. (2013). ACOG Practice Bulletin No. 138: Inherited thrombophilias in pregnancy. *Obstet Gynecol*, *122*(3), 706-717. https://doi.org/10.1097/01.AOG.0000433981.36184.4e
ACOG. (2018). ACOG Practice Bulletin No. 197 Summary: Inherited Thrombophilias in Pregnancy. *Obstet Gynecol*, *132*(1), 249-251. https://doi.org/10.1097/aog.0000000000002705
Algahtani, F. H., & Stuckey, R. (2019). High factor VIII levels and arterial thrombosis: illustrative case and literature review. *Ther Adv Hematol*, *10*, 2040620719886685. https://doi.org/10.1177/2040620719886685
ASCLS. (2021). American Society for Clinical Laboratory Science. https://www.choosingwisely.org/clinician-lists/ascls7-do-not-order-a-homocysteine-assay-as-part-of-the-thrombophilia-work-up/
ASCP. (2017). *American Society for Clinical Pathology*. http://www.choosingwisely.org/clinician-lists/ascp-testing-for-protein-c-protein-s-or-antithrombin-during-active-clotting-event/
ASCP. (2019). *American Society of Clinical Pathology*. American Society of Clinical Pathology. https://www.choosingwisely.org/clinician-lists/ascp-hypercoagulable-workup/
ASH. (2013). *ASH - Testing for thromboembolism | Choosing Wisely* http://www.choosingwisely.org/clinician-lists/american-society-hematology-testing-for-thrombophilia-in-adults/
Bank, I., Libourel, E. J., Middeldorp, S., Hamulyak, K., van Pampus, E. C., Koopman, M. M., Prins, M. H., van der Meer, J., & Buller, H. R. (2005). Elevated levels of FVIII:C within families are associated with an increased risk for venous and arterial thrombosis. *J Thromb Haemost*, *3*(1), 79-84. https://doi.org/10.1111/j.1538-7836.2004.01033.x

Barnes, G. (2017, 06/05/2017). *Thrombophilia Testing for Provoked VTE*. American College of Cardiology. Retrieved 02/13/2019 from https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2017/06/05/12/46/thrombophilia-testing-in-provoked-venous-thromboembolism

Barnes, G. D. (2017). *Thrombophilia Testing and Venous Thrombosis*. American College of Cardiology. https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2017/10/20/11/18/thrombophilia-testing-and-venous-thrombosis

Bartholomew, J. R. (2017). Update on the management of venous thromboembolism. *Cleve Clin J Med*, *84*(12 Suppl 3), 39-46. https://doi.org/10.3949/ccjm.84.s3.04

Bashford, M. T., Hickey, S. E., Curry, C. J., Toriello, H. V., American College of Medical, G., Genomics Professional, P., & Guidelines, C. (2020). Addendum: ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing. *Genetics in Medicine*, *22*(12), 2125-2125. https://doi.org/10.1038/s41436-020-0843-0

Bauer, K. (2021a, 11/16/2021). *Protein C deficiency*. https://www.uptodate.com/contents/protein-c-deficiency

Bauer, K. (2021b, 11/16/2021). *Protein S deficiency*. https://www.uptodate.com/contents/protein-s-deficiency

Bauer, K. (2021c, 12/20/2021). *Prothrombin G20210A mutation*. https://www.uptodate.com/contents/prothrombin-g20210a-mutation

Bauer, K. (2022, 10/25/2022). *Clinical presentation and diagnosis of the nonpregnant adult with suspected deep vein thrombosis of the lower extremity*. https://www.uptodate.com/contents/clinical-presentation-and-diagnosis-of-the-nonpregnant-adult-with-suspected-deep-vein-thrombosis-of-the-lower-extremity

Bauer, K. (2023, 01/04/2023). *Factor V Leiden and activated protein C resistance*. https://www.uptodate.com/contents/factor-v-leiden-and-activated-protein-c-resistance

Bauer, K., & Lip, G. (2022a, 10/25/2022). *Evaluating adult patients with established venous thromboembolism for acquired and inherited risk factors*. https://www.uptodate.com/contents/evaluating-adult-patients-with-established-venous-thromboembolism-for-acquired-and-inherited-risk-factors

Bauer, K., & Lip, G. (2022b, 10/25/2022). *Overview of the causes of venous thrombosis*. https://www.uptodate.com/contents/overview-of-the-causes-of-venous-thrombosis

Bauer, K. A. (2021, 10/28/2021). *Lab Interpretation: Positive factor V Leiden or abnormal activated protein C resistance in adults*. https://www.uptodate.com/contents/positive-factor-v-leiden-or-abnormal-activated-protein-c-resistance-in-adults

Byrnes, J. R., & Wolberg, A. S. (2017). Red blood cells in thrombosis. *Blood*, *130*(16), 1795-1799. https://doi.org/10.1182/blood-2017-03-745349

Carroll, B. J., & Piazza, G. (2018). Hypercoagulable states in arterial and venous thrombosis: When, how, and who to test? *Vasc Med*, *23*(4), 388-399. https://doi.org/10.1177/1358863x18755927

Chiasakul, T., De Jesus, E., Tong, J., Chen, Y., Crowther, M., Garcia, D., Chai-Adisaksopha, C., Messe, S. R., & Cuker, A. (2019). Inherited Thrombophilia and the Risk of Arterial Ischemic Stroke: A Systematic Review and Meta-Analysis. *J Am Heart Assoc*, *8*(19), e012877. https://doi.org/10.1161/jaha.119.012877

Connors, J. M. (2017). Thrombophilia Testing and Venous Thrombosis. In *N Engl J Med* (Vol. 377, pp. 2298). https://doi.org/10.1056/NEJMc1713797

Crous-Bou, M., Harrington, L. B., & Kabrhel, C. (2016). Environmental and genetic risk factors associated with venous thromboembolism. *Semin Thromb Hemost*, *42*(8), 808-820. https://doi.org/10.1055/s-0036-1592333

Curtis, C., Mineyko, A., Massicotte, P., Leaker, M., Jiang, X. Y., Floer, A., & Kirton, A. (2017). Thrombophilia risk is not increased in children after perinatal stroke. *Blood*, *129*(20), 2793-2800. https://doi.org/10.1182/blood-2016-11-750893

EGAPP. (2011). 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*, *13*(1), 67-76. https://doi.org/10.1097/GIM.0b013e3181fbe46f

Ferriero, D. M., , Fullerton, H. J., , Bernard, T. J., Billinghurst, L., , Daniels, S. R., , DeBaun, M. R., , deVeber, G., , Ichord, R. N., , Jordan, L. C., , Massicotte, P., , . . . Nursing, A. H. A. S. C. a. C. o. C. a. S. (2019). Management of Stroke in Neonates and Children: A Scientific Statement From the American Heart Association/American Stroke Association. *Stroke*, *50*(3). https://doi.org/ http://dx.doi.org/10.1161/str.0000000000000183

Gupta, A., Sarode, R., & Nagalla, S. (2017). Thrombophilia Testing in Provoked Venous Thromboembolism: A Teachable Moment. *JAMA Internal Medicine*, *177*(8), 1195-1196. https://doi.org/10.1001/jamainternmed.2017.1815

Herrmann, J. (2018). *Clinical Cardio-Oncology*. Elsevier. https://doi.org/https://doi.org/10.1016/C2015-0-01414-9

Hickey, S. E., Curry, C. J., & Toriello, H. V. (2013). ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing. *Genet Med*, *15*(2), 153-156. https://doi.org/10.1038/gim.2012.165

Kleindorfer, D. O., Towfighi, A., Chaturvedi, S., Cockroft, K. M., Gutierrez, J., Lombardi-Hill, D., Kamel, H., Kernan, W. N., Kittner, S. J., Leira, E. C., Lennon, O., Meschia, J. F., Nguyen, T. N., Pollak, P. M., Santangeli, P., Sharrief, A. Z., Smith, S. C., Jr., Turan, T. N., & Williams, L. S. (2021).

2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. *Stroke*, *52*(7), e364-e467. https://doi.org/10.1161/str.0000000000000375

Konstantinides, S. V., Meyer, G., Becattini, C., Bueno, H., Geersing, G. J., Harjola, V. P., Huisman, M. V., Humbert, M., Jennings, C. S., Jimenez, D., Kucher, N., Lang, I. M., Lankeit, M., Lorusso, R., Mazzolai, L., Meneveau, N., Ainle, F. N., Prandoni, P., Pruszczyk, P., . . . Zamorano, J. L. (2019). 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Respir J*, *54*(3). https://doi.org/10.1183/13993003.01647-2019

Kujovich, J. L. (2011). Factor V Leiden thrombophilia. *Genet Med*, *13*(1), 1-16. https://doi.org/10.1097/GIM.0b013e3181faa0f2

Kujovich, J. L. (2018). Factor V Leiden Thrombophilia. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. H. Bean, K. Stephens, & A. Amemiya (Eds.), *GeneReviews((R))*. University of Washington, Seattle. https://www.ncbi.nlm.nih.gov/books/NBK1368/

Lee, E. J., Dykas, D. J., Leavitt, A. D., Camire, R. M., Ebberink, E., García de Frutos, P., Gnanasambandan, K., Gu, S. X., Huntington, J. A., Lentz, S. R., Mertens, K., Parish, C. R., Rezaie, A. R., Sayeski, P. P., Cromwell, C., Bar, N., Halene, S., Neparidze, N., Parker, T. L., . . . Lee, A. I. (2017). Whole-exome sequencing in evaluation of patients with venous thromboembolism. *Blood Adv*, *1*(16), 1224-1237. https://doi.org/10.1182/bloodadvances.2017005249

Lehman, L. L., Beaute, J., Kapur, K., Danehy, A. R., Bernson-Leung, M. E., Malkin, H., Rivkin, M. J., & Trenor, C. C. (2017). Workup for Perinatal Stroke Does Not Predict Recurrence. *Stroke*, *48*(8), 2078-2083. https://doi.org/10.1161/STROKEAHA.117.017356

Lim, W., Le Gal, G., Bates, S. M., Righini, M., Haramati, L. B., Lang, E., Kline, J. A., Chasteen, S., Snyder, M., Patel, P., Bhatt, M., Patel, P., Braun, C., Begum, H., Wiercioch, W., Schünemann, H. J., & Mustafa, R. A. (2018). American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. *Blood Adv*, *2*(22), 3226. https://doi.org/10.1182/bloodadvances.2018024828

Linkins, L. A., & Takach Lapner, S. (2017). Review of D-dimer testing: Good, Bad, and Ugly. *Int J Lab Hematol*, *39 Suppl 1*, 98-103. https://doi.org/10.1111/ijlh.12665

Mazzolai, L., Ageno, W., Alatri, A., Bauersachs, R., Becattini, C., Brodmann, M., Emmerich, J., Konstantinides, S., Meyer, G., Middeldorp, S., Monreal, M., Righini, M., & Aboyans, V. (2022). Second consensus document on diagnosis and management of acute deep vein thrombosis: updated document elaborated by the ESC Working Group on aorta and peripheral vascular diseases and the ESC Working Group on pulmonary circulation and right ventricular function. *European Journal of Preventive Cardiology*. https://doi.org/10.1093/eurjpc/zwab088

Murphy, C. H., & Sabath, D. E. (2019). Comparison of Phenotypic Activated Protein C Resistance Testing With a Genetic Assay for Factor V Leiden. *Am J Clin Pathol*, *151*(3), 302-305. https://doi.org/10.1093/ajcp/aqy142

NATF. (2019). *Genetic Risk Factors for Blood Clots and the Role of Genetic Testing*. https://natfonline.org/2019/01/genetic-risk-factors-blood-clots-role-genetic-testing/

Onda, S., Furukawa, K., Haruki, K., Hamura, R., Shirai, Y., Yasuda, J., Shiozaki, H., Gocho, T., Shiba, H., & Ikegami, T. (2021). d-dimer-based screening for early diagnosis of venous thromboembolism after hepatectomy. *Langenbeck's Archives of Surgery*, *406*(3), 883-892. https://doi.org/10.1007/s00423-020-02058-9

Ordieres-Ortega, L., Demelo-Rodríguez, P., Galeano-Valle, F., Kremers, B. M. M., ten Cate-Hoek, A. J., & ten Cate, H. (2020). Predictive value of D-dimer testing for the diagnosis of venous thrombosis in unusual locations: A systematic review. *Thrombosis Research*, *189*, 5-12. https://doi.org/https://doi.org/10.1016/j.thromres.2020.02.009

Ortel, T. L., Neumann, I., Ageno, W., Beyth, R., Clark, N. P., Cuker, A., Hutten, B. A., Jaff, M. R., Manja, V., Schulman, S., Thurston, C., Vedantham, S., Verhamme, P., Witt, D. M., D. Florez, I., Izcovich, A., Nieuwlaat, R., Ross, S., J. Schünemann, H., . . . Zhang, Y. (2020). American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*, *4*(19), 4693-4738. https://doi.org/10.1182/bloodadvances.2020001830

Previtali, E., Bucciarelli, P., Passamonti, S. M., & Martinelli, I. (2011). Risk factors for venous and arterial thrombosis. *Blood Transfus*, *9*(2), 120-138. https://doi.org/10.2450/2010.0066-10

Raffini, L., Mahoney, D. H., & Armsby, C. (2022). Thrombophilia testing in children and adolescents. *UpToDate*. https://www.uptodate.com/contents/thrombophilia-testing-in-children-and-adolescents?topicRef=1354&source=see_link#H1628041305

Segal, J. B., Brotman, D. J., Emadi, A., Necochea, A. J., Samal, L., Wilson, L. M., Crim, M. T., & Bass, E. B. (2009). Outcomes of genetic testing in adults with a history of venous thromboembolism. *Evid Rep Technol Assess (Full Rep)*(180), 1-162. https://pubmed.ncbi.nlm.nih.gov/20629476/

SIGN. (2014). *Prevention and management of venous thromboembolism* https://www.sign.ac.uk/media/1060/sign122.pdf

Stevens, S. M., Woller, S. C., Bauer, K. A., Kasthuri, R., Cushman, M., Streiff, M., Lim, W., & Douketis, J. D. (2016). Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. *J Thromb Thrombolysis*, *41*, 154-164. https://doi.org/10.1007/s11239-015-1316-1

SVM. (2013, 02/21/2013). *Don't do work up for clotting disorder (order hypercoagulable testing) for patients who develop first episode of deep vein thrombosis (DVT) in the setting of a known cause.*

ABIM. http://www.choosingwisely.org/clinician-lists/society-vascular-medicine-clotting-disorder-workup-after-first-episode-of-deep-vein-thrombosis/
Thompson, B. T., Kabrhel, Christopher. (2022, 02/18/2022). *Overview of acute pulmonary embolism in adults*. https://www.uptodate.com/contents/overview-of-acute-pulmonary-embolism-in-adults
Zhang, S., Taylor, A. K., Huang, X., Luo, B., Spector, E. B., Fang, P., & Richards, C. S. (2018). 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*, *20*(12), 1489-1498. https://doi.org/10.1038/s41436-018-0322-z

VI. Revision History

Revision Date	Summary of Changes
03/01/2023	Literature review necessitated the following changes in coverage criteria: Removed coverage criteria pertaining to genetic testing (CC1, 3, 4, 7, 8, 9, 11). Due to the integration between plasma testing and genetic testing, scientific information and guidelines pertaining to genetic testing remain within this policy and a new Note 2 has been added to convey that plasma testing should be done in conjunction with genetic testing, even if the policy no longer addresses the genetic risk factor testing. New Note 2: “Note 2: In addition to plasma testing (protein C deficiency, protein S deficiency, antithrombin III deficiency), risk factor testing for individuals suspected of having a hereditary and/or acquired thrombophilia should include genetic testing for Factor V Leiden and Prothrombin gene G20210A mutations.” Protein C and protein S deficiency (**but NOT antithrombin III deficiency**) are specific to warfarin-induced skin necrosis and in infants who develop neonatal purpura fulminans. Thus, risk factors that qualify for all 3 (protein C, protein S, and antithrombin III deficiency) are found in CC1. Addition of new CC2: “2) For individuals with warfarin-induced skin necrosis or for infants who develop neonatal purpura fulminans, plasma testing for protein C deficiency and protein S deficiency (see Note 1) MEETS COVERAGE CRITERIA.” New CC6: “6) For all situations, activated protein C (aPC) resistance assay DOES NOT MEET COVERAGE CRITERIA.” See PRISM portal and redlined Avalon Base Policy for clarity and consistency edits. Removed CPT codes 81240, 81241, 81291, 81400, 81479, 0278U

healthfirst
Health Insurance for New Yorkers

Disclaimer

Healthfirst's claim edits follow national industry standards aligned with CMS standards that include, but are not limited to, the National Correct Coding Initiative (NCCI), the National and Local Coverage Determination (NCD/LCD) policies, appropriate modifier usage, global surgery and multiple procedure reduction rules, medically unlikely edits, duplicates, etc. In addition, Healthfirst's coding edits incorporate industry-accepted AMA and CMS CPT, HCPCS and ICD-10 coding principles, National Uniform Billing Editor's revenue coding guidelines, CPT Assistant guidelines, New York State-specific coding, billing, and payment policies, as well as national physician specialty academy guidelines (coding and clinical). Failure to follow proper coding, billing, and/or reimbursement policy guidelines could result in the denial and/or recoupment of the claim payment.

This policy is intended to serve as a resource for providers to use in understanding reimbursement guidelines for professional and institutional claims. This information is accurate and current as of the date of publication. It provides information from industry sources about proper coding practice. However, this document does not represent or guarantee that Healthfirst will cover and/or pay for services outlined. Reimbursement decisions are based on the terms of the applicable evidence of coverage, state and federal requirements or mandates, and the provider's participation agreement. This includes the determination of any amounts that Healthfirst or the member owes the provider.