

Corporate Medical Policy

Venous and Arterial Thrombosis Risk Testing AHS – M2041

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Description of Procedure or Service

Definitions

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).

Related Policies

Cardiovascular Disease Risk Assessment AHS –G2050

Genetic Testing for Lipoprotein A Variant(s) as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment AHS- M2082

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for venous and arterial thrombosis risk testing when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore, member benefit language should be reviewed before applying the terms of this medical policy.

When Venous and Arterial Thrombosis Risk Testing is covered

1. Genetic testing for Factor V Leiden mutation and Prothrombin gene G20210A mutation is considered medically necessary in patients without recurrent VTE risk factors (for example, surgery, prolonged immobilization, collagen vascular disease, malignancy, certain hematologic disorders) in any of the following situations:
 - a. Age <50, any venous thrombosis
 - b. Venous thrombosis in unusual sites (such as hepatic, mesenteric, and cerebral veins)
 - c. Recurrent venous thrombosis
 - d. Venous thrombosis and a strong family history of thrombotic disease

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- e. Venous thrombosis in pregnant women or in women taking oral contraceptives
 - f. First- and second-degree relatives of individuals with venous thrombosis under age 50
 - g. Myocardial infarction in female smokers under age 50
 - h. Before administration of oral contraceptives, targeted testing of women with a personal or family history of venous thrombosis
2. Reimbursement for testing for protein C deficiency, protein S deficiency and antithrombin III deficiency is allowed in patients without recurrent VTE risk factors (for example, surgery, prolonged immobilization, collagen vascular disease, malignancy, certain hematologic disorders) in any of the following situations. Testing should be performed at least six weeks after acute thrombotic event and while the patient is not taking anticoagulants
- a. Age <50, any venous thrombosis
 - b. Venous thrombosis in unusual sites (such as hepatic, mesenteric, and cerebral veins)
 - c. Recurrent venous thrombosis
 - d. Venous thrombosis and a strong family history of thrombotic disease
 - e. Venous thrombosis in pregnant women or in women taking oral contraceptives
 - f. Relatives of individuals with venous thrombosis under age 50
 - g. Myocardial infarction in female smokers under age 50
 - h. Before administration of oral contraceptives, targeted testing of women with a personal or family history of venous thrombosis
 - i. Individuals with warfarin induced skin necrosis
 - j. Infants who develop Neonatal Purpura Fulminans

When Venous and Arterial Thrombosis Risk Testing is not covered

1. Reimbursement is not allowed for MTHFR genetic testing for hypercoagulable evaluation or for “at risk” family members.
2. Genetic Testing for inherited thrombophilia is considered not medically necessary for the following situations:
 - a. Evaluation of recurrent fetal loss, placental abruption, preeclampsia, or fetal growth restriction
 - b. Evaluation of arterial thrombosis not attributable to paradoxical emboli
 - c. Routine screening in the general population
 - d. Routine screening of asymptomatic women considering oral contraceptive use or hormone replacement therapy
 - e. Routine screening of asymptomatic pregnant women
 - f. Prenatal or preimplantation testing
 - g. Routine newborn screening
3. Testing for other factors, including the factor V HR2 variant, or prothrombin G1199A variant, or factor VII R353Q variant, or factor 13B V34L variant or PAI-1, as well as multi-gene panel testing is considered not medically necessary.
4. Venous thrombosis risk testing as part of a pre-transplant evaluation test is considered not medically necessary.
5. Genetic testing for Factor V Leiden mutation and Prothrombin gene G20210A mutation to determine arterial thrombosis risk is considered not medically necessary.

Policy Guidelines

Background

A thrombus is “an aggregate of coagulated blood within the vascular system or heart which contains platelet, fibrin, leukocytes, and red blood cells in varying amounts” (Herrmann, 2018). This aggregate of blood can be problematic as it can 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, 2018). 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 (Kearon, 2018; Thompson, 2018). DVT of the lower extremities may cause symptoms, such as swelling or edema in the lower extremities, pain, and warmth in the affected area (Kearon, 2018). 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, 2018). 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, 2018). Approximately 50–60% of the variance in VTE incidence are attributed to genetic effects (Crous-Bou, Harrington, & Kabrhel, 2016).

FVL mutations cause coagulation factor V to be unresponsive to activated protein C. 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, 2018a). Protein C may also be genetically deficient, but this mutation is only seen in 2–5% of individuals with a VTE (Kearon, 2018). Protein S, a cofactor for the activated protein C control mechanism, and deficiencies in this protein may also confer additional risk for VTE (Bauer, 2017).

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% (Bauer, 2018c). 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% (Bauer, 2018b).

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, 2018). 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).

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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, Bucciarelli, Passamonti, & Martinelli, 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).

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 are 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. Also, 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).

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Murphy and Sabath (2019) have compared the accuracy and reliability of two tests: a genotypic assay which identifies FVL mutations, and a phenotypic activated protein C 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.

Applicable Federal Regulations

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). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

American College of Medical Genetics and Genomics (ACMG) (ACMG, 2018)

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

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

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

Testing may be considered in following circumstances:

- Females under the age of 50 who smoke tobacco and have a history of acute myocardial infarction
- Siblings of individuals known to be homozygous for factor V Leiden or factor II c.*97G>A, because they have a 1 in 4 chance of being a homozygote
- Asymptomatic pregnant female or female contemplating pregnancy, with a first-degree relative with unprovoked VTE or VTE provoked by pregnancy or contraceptive use

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- 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.98G>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.98G>A status may alter pregnancy related thrombophilia (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, Curry, & Toriello, 2013)

American Society of Hematology (ASH) (Lim et al., 2018)

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 ($\leq 5\%$), 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 ($\leq 5\%$).”
- “*Suggests* using a strategy starting with D-dimer for excluding PE in a population with intermediate prevalence/PTP ($\sim 20\%$), 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 ($\sim 20\%$).”
- “*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 ($\geq 50\%$).”
- “*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 ($\leq 10\%$), 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 ($\leq 10\%$).”
- “*Recommends against* using a positive D-dimer alone to diagnose DVT in a population with intermediate prevalence/PTP ($\sim 25\%$).”
- “*Recommends against* using a positive D-dimer alone to diagnose DVT in a population with high prevalence/PTP ($\geq 50\%$).”
- “*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%).”

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- “*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).”

Society for Vascular Medicine (SVM) (SVM)

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

The American College of Obstetricians and Gynecologists (ACOG) (ACOG, 2013)

The 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 does not recommend “testing for inherited thrombophilias in women who have experienced recurrent fetal loss or placental abruption ... because it is unclear if anticoagulation reduces recurrence.” Additionally, ACOG does not support testing for inherited thrombophilia in women with a history of preeclampsia or fetal growth restriction.

ACOG recommends that screening for inherited thrombophilias should include testing for “factor V Leiden mutation; prothrombin G20210A mutation; and antithrombin, protein C, and protein S deficiencies.” Also, it is recommended that testing be performed “(after 6 weeks) from the thrombotic event and while the patient is not pregnant and not taking anticoagulation or hormonal therapy.”

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) (EGAPP, 2011)

“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 (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. 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).”

American Society of Hematology (ASH) (ASH, 2013; Lim et al., 2018)

The 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).

The Anticoagulation Forum (Stevens et al., 2016)

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

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- ” 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) (Barnes, 2017)

Recent 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.

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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 (Barnes, 2017).”

American Society for Clinical Pathology (ASCP) (ASCP, 2017)

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 (ASCP, 2017).”

European Society of Cardiology (ESC) (Konstantinides et al., 2019)

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).”

Scottish Intercollegiate Guidelines Network (SIGN) (SIGN, 2014)

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

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Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81240, 81241, 81291, 81400, 81479, 85300, 85301, 85302, 85303, 85305, 85306, 85307

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For policy titled: Venous Thrombosis Risk Testing AHS – M2041

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Specialty Matched Consultant Advisory Panel review 10/2020

Medical Director review 10/2020

Policy Implementation/Update Information

For policy titled: Venous Thrombosis Risk Testing AHS – M2041

- 1/1/2019 New policy developed. BCBSNC will provide coverage for venous thrombosis risk testing when it is determined to be medically necessary because the criteria and guidelines have been met. Medical Director review 1/1/2019. (jd)
- 5/14/19 Reviewed by Avalon 1st Quarter 2019 CAB. Minor revision to Description section and “Related Policies” section added. When Not Covered section reformatted, no change to policy intent. Policy guidelines and references updated. Medical Director review 5/2019. (jd)
- 10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (gm)
- 3/31/20 Specialty Matched Consultant Advisory Panel review 3/2020. Medical Director review 3/2020. (jd)

For policy titled: “Venous and Arterial Thrombosis Risk Testing AHS – M2041

- 5/12/20 Title changed from Venous Thrombosis Risk Testing to Venous and Arterial Thrombosis Risk Testing. Under When Not Covered section, changed items #2 and #3 from “investigational” to “not medically necessary; added items #4 and #5. Policy guidelines and references updated. Medical Director review 4/2020. (jd)
- 11/10/20 Specialty Matched Consultant Advisory Panel review 10/2020. Medical Director review 10/2020. (jd)

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