

If a conflict arises between a Clinical Payment and Coding Policy ("CPCP") and any plan document under which a member is entitled to Covered Services, the plan document will govern. If a conflict arises between a CPCP and any provider contract pursuant to which a provider participates in and/or provides Covered Services to eligible member(s) and/or plans, the provider contract will govern. "Plan documents" include, but are not limited to, Certificates of Health Care Benefits, benefit booklets, Summary Plan Descriptions, and other coverage documents. BCBSOK may use reasonable discretion interpreting and applying this policy to services being delivered in a particular case. BCBSOK has full and final discretionary authority for their interpretation and application to the extent provided under any applicable plan documents.

Providers are responsible for submission of accurate documentation of services performed. Providers are expected to submit claims for services rendered using valid code combinations from Health Insurance Portability and Accountability Act ("HIPAA") approved code sets. Claims should be coded appropriately according to industry standard coding guidelines including, but not limited to: Uniform Billing ("UB") Editor, American Medical Association ("AMA"), Current Procedural Terminology ("CPT®"), CPT® Assistant, Healthcare Common Procedure Coding System ("HCPCS"), ICD-10 CM and PCS, National Drug Codes ("NDC"), Diagnosis Related Group ("DRG") guidelines, Centers for Medicare and Medicaid Services ("CMS") National Correct Coding Initiative ("NCCI") Policy Manual, CCI table edits and other CMS guidelines.

Claims are subject to the code edit protocols for services/procedures billed. Claim submissions are subject to claim review including but not limited to, any terms of benefit coverage, provider contract language, medical policies, clinical payment and coding policies as well as coding software logic. Upon request, the provider is urged to submit any additional documentation.

Venous and Arterial Thrombosis Risk Testing

Policy Number: CPCPLAB058

Version 1.0

Approval Date: April 12, 2023

Plan Effective Date: November 1, 2023

Description

BCBSOK has implemented certain lab management reimbursement criteria. Not all requirements apply to each product. Providers are urged to review Plan documents for eligible coverage for services rendered.

Reimbursement Information:

- 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 **Notes 1 and 2**) may be reimbursable in any of the following situations.
 - a. For individuals less than 50 year 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 s
- e. For first-and second-degree relatives (See **Note 2**) of individuals who have 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
- i. For individuals with warfarin-induced skin necrosis
- j. For infants who develop Neonatal Purpura Fulminans
- 2. Venous thrombosis risk testing for superficial venous thrombosis (including superficial thrombophlebitis and varicosities) **is not reimbursable**.
- 3. For all situations, all activated protein C (aPC) resistance assay is not reimbursable.
- 4. Deep venous thrombosis (DVT) risk testing as part of a pre-transplant evaluation test **is not reimbursable**.

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.

Procedure Codes

The following is not an all-encompassing code list. The inclusion of a code does not guarantee it is a covered service or eligible for reimbursement.

Codes
85300, 85301, 85302, 85303, 85305, 85306, 85307

References:

ACOG. (2013). ACOG Practice Bulletin No. 138: Inherited thrombophilias in pregnancy. *Obstet Gynecol*, *122*(3), 706-717. <u>https://doi.org/10.1097/01.AOG.0000433981.36184.4e</u>

ACOG. (2018). ACOG Practice Bulletin No. 197 Summary: Inherited Thrombophilias in Pregnancy. *Obstet Gynecol*, *132*(1), 249-251. <u>https://doi.org/10.1097/aog.00000000002705</u>

Algahtani, F. H., & Stuckey, R. (2019). High factor VIII levels and arterial thrombosis: illustrative case and literature review. *Ther Adv Hematol*, *10*, 2040620719886685. <u>https://doi.org/10.1177/2040620719886685</u>

ASCLS. (2021). American Society for Clinical Laboratory Science. <u>https://www.choosingwisely.org/clinician-lists/ascls7-do-not-order-a-homocysteine-assay-as-part-of-the-thrombophilia-work-up/</u>

ASCP. (2017). American Society for Clinical Pathology. <u>http://www.choosingwisely.org/clinician-lists/ascp-testing-for-protein-c-protein-s-or-antithrombin-during-active-clotting-event/</u>

ASCP. (2019). *American Society of Clinical Pathology*. American Society of Clinical Pathology. <u>https://www.choosingwisely.org/clinician-lists/ascp-hypercoagulable-workup/</u>

ASH. (2013). ASH - Testing for thromboembolism | Choosing Wisely http://www.choosingwisely.org/clinician-lists/american-society-hematology-testing-forthrombophilia-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. <u>https://doi.org/10.1111/j.1538-7836.2004.01033.x</u>

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

Barnes, G. D. (2017). *Thrombophilia Testing and Venous Thrombosis*. American College of Cardiology. <u>https://www.acc.org/latest-in-cardiology/ten-points-to-</u>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. <u>https://doi.org/10.3949/ccjm.84.s3.04</u>

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. <u>https://doi.org/10.1038/s41436-020-0843-0</u>

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

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-nonpregnantadult-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*. <u>https://www.uptodate.com/contents/overview-of-the-causes-of-venous-thrombosis</u>

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

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). <u>https://doi.org/10.1056/NEJMc1713797</u>

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. <u>https://doi.org/10.1055/s-0036-1592333</u>

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. <u>https://doi.org/10.1182/blood-2016-11-750893</u>

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). <u>https://doi.org/http://dx.doi.org/10.1161/str.00000000000183</u>

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

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. <u>https://doi.org/10.1038/gim.2012.165</u>

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. <u>https://doi.org/10.1161/str.00000000000375</u>

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 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. <u>https://doi.org/10.1097/GIM.0b013e3181faa0f2</u>

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. <u>https://www.ncbi.nlm.nih.gov/books/NBK1368/</u>

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. <u>https://doi.org/10.1182/bloodadvances.2017005249</u>

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. <u>https://doi.org/10.1161/STROKEAHA.117.017356</u>

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. <u>https://doi.org/10.1182/bloodadvances.2018024828</u>

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. <u>https://doi.org/10.1111/ijlh.12665</u>

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*. <u>https://doi.org/10.1093/eurjpc/zwab088</u>

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. <u>https://doi.org/10.1093/ajcp/aqy142</u>

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. <u>https://doi.org/10.2450/2010.0066-10</u>

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

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* <u>https://www.sign.ac.uk/media/1060/sign122.pdf</u>

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. <u>https://doi.org/10.1007/s11239-015-1316-1</u>

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. <u>http://www.choosingwisely.org/clinician-lists/society-vascular-medicine-clotting-disorder-workup-after-first-episode-of-deep-vein-thrombosis/</u>

Thompson, B. T., Kabrhel, Christopher. (2022, 02/18/2022). *Overview of acute pulmonary embolism in adults*. <u>https://www.uptodate.com/contents/overview-of-acute-pulmonary-embolism-in-adults</u>

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. <u>https://doi.org/10.1038/s41436-018-0322-z</u>

Policy Update History:

11/1/2022	New policy
8/15/2023	Document updated with literature review. Reimbursement information revised for clarity. Added: For all situations, all activated protein C (aPC) resistance assay is not reimbursable. References revised; some added, others removed.