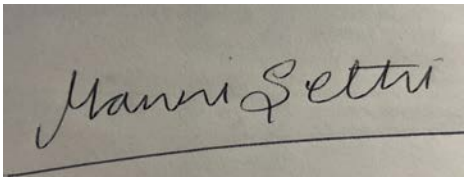
Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: AmeriHealth Caritas Pennsylvania Community HealthChoices	**Submission Date**: 10/27/2023
Policy Number: ccp.1176	**Effective Date:** 1/2016 **Revision Date:** October 1, 2023
Policy Name: Genetic testing for G1691A polymorphism factor V Leiden	
Type of Submission – Check all that apply: **New Policy** **x Revised Policy*** **Annual Review – No Revisions** **Statewide PDL**	
***All revisions to the policy must be highlighted using track changes throughout the document.** **Please provide any clarifying information for the policy below:** See tracked changes below.	
Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Genetic testing for G1691A polymorphism factor V Leiden

Clinical Policy ID: CCP.1176

Recent review date: 10/2023

Next review date: 2/2025

Policy contains: Factor V Leiden; genetic G1691A testing; inherited thrombophilia; venous thromboembolism.

AmeriHealth Caritas Pennsylvania Community HealthChoices has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania Community HealthChoices when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania Community HealthChoices will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are not guarantees of payment.

Coverage policy

Genetic testing for factor V Leiden thrombophilia is clinically proven and, therefore, may be medically necessary for members who meet all of the following criteria:

- Results of genetic testing will directly impact and change clinical management of the member.
- Technical and clinical performance of the genetic test is supported by published peer-reviewed medical literature.
- Second-generation activated protein C resistance test results are positive, excluding members who present on (Kadauke, 2014; Shaheen, 2012):
    - Lupus anticoagulants.
    - Direct thrombin inhibitor therapy.
    - Factor Xa inhibitor therapy.
- Any of the following clinical indications (Zhang, 2018):
    - Asymptomatic member who is pregnant or contemplating pregnancy, is not on anticoagulation therapy, and has a first-degree blood family member (i.e., parent, full-sibling, or child) with an unprovoked venous thromboembolism or a venous thromboembolism provoked by pregnancy or contraceptive use.
    - Asymptomatic member who is pregnant or contemplating pregnancy or estrogen use and has a first-degree blood relative (i.e., parent, full-sibling, or child) with a history of venous thromboembolism and is a known carrier for factor V Leiden.

- Asymptomatic member who is pregnant or contemplating pregnancy with a personal history of non-estrogen-related venous thromboembolism or venous thromboembolism provoked by a minor risk factor, if knowledge of the factor V Leiden status may alter pregnancy-related thromboprophylaxis.
- First venous thromboembolism and either:
  - A first-degree blood family member (i.e., parent, full-sibling, or child) with a history of venous thromboembolism at a young age (e.g., before age 50 years).
  - Two or more family members with a history of venous thromboembolism.
- Venous thromboembolism in unusual sites (such as hepatic, mesenteric, and cerebral veins).
- History of recurrent venous thromboembolism.

Limitations

All other uses of genetic testing for factor V Leiden thrombophilia are not medically necessary, including, but not limited to (Zhang, 2018):

- Random general population screening.
- Routine testing of members with a personal or family history of arterial thrombotic disorders.
- Routine prenatal testing.
- Routine newborn screening.
- Routine screening prior to oral contraception use or hormone replacement therapy.
- Asymptomatic minors as venous thromboembolism rarely occurs before young adulthood even in the homozygous state.
- Women with a history of fetal loss or adverse pregnancy outcomes, including abruption, preeclampsia, or fetal growth restriction, in the absence of a history of venous thromboembolism (American College of Obstetricians and Gynecologists, 2018).
- Screening for hidden malignancy in the presence of an unprovoked venous thromboembolism.

In members diagnosed with cancer, testing for factor V Leiden and other genetic mutations should be determined on a case-by-case basis as part of an overall thromboembolic risk assessment (National Comprehensive Cancer Network, 2023).

In general, genetic testing for a particular disorder is limited to once per lifetime.

Alternative covered services

Routine laboratory tests for coagulopathy may be ordered by a family practice or primary physician.

Background

The protein product — coagulation factor V — of the factor V gene G1691A plays a critical role in the formation of blood clots (Genetics Home Reference, 2010). To counter the effects of factor V, a molecule called activated protein C inactivates factor V to prevent blood clots from growing too large. A specific mutation in the factor V gene (called factor V Leiden) causes factor V to inactivate more slowly than normal. As a result, the clotting process continues longer than usual, increasing the chance of developing abnormal blood clots.

Factor V Leiden is the most common inherited form of prothrombotic allele, affecting 1% to 5% of the world's population (Au, 2023). Factor V zygosity is one of many variables involved in thrombophilic disorders and impacts the likelihood of idiopathic venous thromboembolism. The initial risk of thrombosis and risk of recurrence of thrombosis are higher in individuals with homozygous factor V Leiden than their heterozygous counterparts. Individuals with factor V Leiden often have additional risk factors that contribute to the development of venous clots, such as older age, surgery, oral contraceptive use, hormonal replacement therapy, pregnancy, and

malignancy. The risk of an unprovoked venous thromboembolism is increased further with a positive family history of venous thromboembolism, and even more so when the family member had the thrombotic event before age 50 or with multiple affected family members (Shaheen, 2012).

The factor V Leiden mutation is found in 90% to 95% of all people with activated protein C resistance (Zhang, 2018). Screening for factor V may identify individuals at high risk for future thromboembolism and thus aid in selection of at-risk individuals for prophylactic anticoagulant therapy. The laboratory diagnosis is made using an activated protein C resistance screening test or deoxyribonucleic acid analysis of the factor V gene (Genetics Home Reference, 2010). The most cost-effective approach is to test first for activated protein C resistance and confirm positive results with molecular testing; if a direct genetic test is used initially, activated protein C resistance testing is unnecessary (Shaheen, 2012).

Findings

For cancer screenings, there is limited evidence that identification of cancer occurs earlier and the cancer is less advanced when venous thromboembolism screening is employed (Robertson, 2015). The authors evaluated the effectiveness of testing for undiagnosed cancer in patients with a first episode of unprovoked venous thromboembolism to reduce cancer- and venous thromboembolism-related morbidity and mortality, though the pertinent studies did not indicate factor V zygosity. The results were imprecise at best and could not be consistently aligned with either harm or benefit from the practice. The authors noted that further good-quality large-scale randomized controlled trials are required before firm conclusions can be made in this regard.

In 2017, a systematic review (Bradley, 2012) estimated test performance, effect sizes, and treatment effectiveness in women with recurrent pregnancy loss who were offered factor V and/or F2 testing to identify candidates for anticoagulation. Analytic sensitivity and specificity for factor V and F2 testing were high. The results suggested that carriers of factor V were more likely to experience pregnancy loss than non-carriers (odds ratios = 1.93 and 2.03, respectively). The authors concluded that anticoagulation treatments were ineffective (except in antiphospholipid antibody syndrome); moreover, they were associated with significant treatment-related harms.

The Canadian Health Technology Expert Review Panel (2015) developed evidence-based guidance on the optimal use of genetic testing for G1691A polymorphism in patients with unprovoked venous thromboembolism. They identified an association between factor V mutations and first unprovoked venous thromboembolism but no association between the presence of these mutations and increased risk of venous thromboembolism recurrence. They identified no evidence that this information resulted in either changes in the clinical management or improved health outcomes. Testing for factor V mutations is associated with additional costs for testing and frequent requests for consultation with a specialist, as well as costs associated with extended anticoagulation therapy for patients who test positive. In the absence of evidence that testing is clinically effective, the costs of routine testing are not justified. They recommended not routinely testing for factor V Leiden and prothrombin mutations in patients with a first unprovoked venous thromboembolism.

In 2018, we added one systematic review (Alhazzani, 2018), an update of a previously included Cochrane review (Robertson, 2017 update of 2015), and three guidelines (American College of Medical Genetics, 2001; American College of Obstetricians and Gynecologists, 2018; National Comprehensive Cancer Network, 2018). Alhazzani and colleagues (2018) suggest an association between factor V gene polymorphism and risk of ischemic stroke in cases with onset at young age (≤ 40 years). However, included studies were underpowered and often recruited patients who were suspected of having a prothrombotic genetic predisposition. A previous meta-analysis found that when limited to studies that recruited patients from consecutive hospitalizations or neurology referrals, the association between factor V gene polymorphism and risk of ischemic stroke was no longer significant

(Hamedani, 2013). The new results by Alhazzani (2018) fail to clarify this uncertainty and do not support routine screening for factor V Leiden in patients with first-ever ischemic stroke.

Long-standing guidance from American College of Medical Genetics and Genomics (2001) presents recommendations for types of and indications for factor V Leiden testing. The American College of Obstetricians and Gynecologists (2018) recommends screening for inherited thrombophilias, including factor V Leiden mutation, in pregnant women or women planning pregnancy with a history of venous thromboembolism, but not for pregnant women with a history of fetal loss or adverse pregnancy outcomes. The guidance recommends thromboprophylaxis based on the patient's zygosity, history of venous thromboembolism, anticoagulation therapy status, and first-degree relative history of venous thromboembolism.

Factor V Leiden is associated with an increased incidence of cancer-associated venous thromboembolism. The National Comprehensive Cancer Network (2018) recommends testing for factor V Leiden and other genetic mutations on a case-by-case basis as part of an overall thromboembolic risk assessment. These recommendations support a change in the medical necessity for factor V Leiden testing. The policy ID was changed from CP# 05.01.03 to CCP.1176.

In 2019, we added a systematic review and meta-analysis (Cavalcante, 2019) that found no association between recurrent miscarriage and inherited thrombophilias in women with polycystic ovarian syndrome using coagulation biomarkers for this condition (for factor V Leiden, odds ratio = 0.74; 95% confidence interval 0.38 to 1.45; P = .38; five studies). We updated the National Comprehensive Cancer Network (2019) guideline on cancer-associated venous thromboembolic disease with no changes made to their recommendations for factor V testing.

We replaced the 2001 American College of Medical Genetics and Genomics technical standard on venous thromboembolism laboratory testing with an updated version (Zhang, 2018), resulting in the following changes to our policy that direct factor V testing toward members who would most benefit from the genetic information:

- We redefined the family history criteria to the indication for members with a first venous thromboembolism.
- We clarified family history criteria for indications relating to asymptomatic pregnant women and women contemplating pregnancy or estrogen use.
- We added two indications to the limitations section for which the evidence does not support medical necessity.

In 2020, we updated the policy references with no changes to the policy.

In 2021, we updated the National Comprehensive Cancer Network (2021; update of 2019) guideline on cancer-associated venous thromboembolic disease, with no changes to testing recommendations. One systematic review and meta-analysis (Romiti, 2020) of 95 studies found no clear correlation between presence of retinal vascular occlusion and prevalence of acquired and inherited thrombophilias, including factor V Leiden. These findings do not support routine thrombophilia screening in individuals with retinal vascular occlusion. No policy changes are warranted.

In 2022, we updated the National Comprehensive Cancer Network (2022, update of 2021) guideline on cancer-associated venous thromboembolic disease, with no changes to testing recommendations. We also added several systematic reviews, including

- One study (n = 1,115) which found 9.2% of women with recurrent miscarriage had thrombophilia (over half being factor V Leiden), similar to the general population, leading authors to recommend against screening women with recurrent miscarriage (Shehata, 2022).

- Another review of 24 studies (n = 13,571) of patients with venous thromboembolism showed 21% had heterozygous factor V Leiden, and the risk ratio was 1.46; authors conclude factor V Leiden plays only a marginal role in assessing risk for recurrent venous thromboembolism (Eppenberger, 2022).

No policy changes are warranted.

In 2023, we updated the National Comprehensive Cancer Network reference (2023, update of 2022). We added meta-analyses:

- Of 42 studies of adults 18 to 65, Factor V Leiden increased the risk of ischemic stroke by 75% (Tsalta-Mladenov, 2023).
- Of four studies (n = 792) persons with Factor V Leiden, that showed risk of venous thromboembolism was most common in those with blood type AB, more than double that in types B and O (Bawazir, 2022).

No policy changes are warranted.

References

On July 17, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “thrombophilia/diagnosis” (MeSH), “thrombophilia/genetics” (MeSH), “Leiden,” and “factor V.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

7/2015: initial review date and clinical policy effective date: 1/2016

8/2017: Policy references updated.

9/2018: Policy references updated. Coverage and policy ID changed.

9/2019: Policy references updated. Coverage modified.

10/2020: Policy references updated.

10/2021: Policy references updated.

10/2022: Policy references updated.

10/2023: Policy references updated.