


MEDICAL POLICY	Genetic Testing: Inherited Thrombophilias (All Lines of Business except Medicare)
Effective Date: 5/1/2022	Medical Policy Number: 266
 5/1/2022	Medical Policy Committee Approved Date: 11/17; 4/18; 12/18; 12/19; 3/2020; 05/2021; 09/2021; 4/2022
Medical Officer	Date

See Policy CPT CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:

All lines of business except Medicare

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

POLICY CRITERIA

Factor V Leiden (FVL) Thrombophilia (F5 Gene) and Prothrombin G20210A Thrombophilia (F2 Gene)

- I. Genetic testing for factor V Leiden (G1691A) or prothrombin (G20210A) variants may be considered **medically necessary and covered** when an individual meets **any** of the following criteria (A. - C.):
 - A. Pregnant individual who is not taking anticoagulation therapy **and** meets any **one** of the following criteria (1.-3.):
 - 1. A personal history of unprovoked (unknown cause) venous thromboembolism (VTE); **or**
 - 2. First-degree blood relative (i.e., parent, full-sibling, child) with antithrombin deficiency,

MEDICAL POLICY

**Genetic Testing: Inherited
Thrombophilias
(All Lines of Business except
Medicare)**

- double heterozygosity or homozygosity for FVL or prothrombin G20210A; **or**
3. First-degree blood relative (i.e., parent, full-sibling, child) with venous thromboembolism (VTE) before age 50 years; **or**
- B. Non-pregnant individual under the age of 50 years presenting with an unprovoked VTE. An unprovoked VTE is a VTE in the absence of strong risk factors (e.g., major trauma, major surgery, immobility, or major illness).
 - C. Non-pregnant individual of any age with one of the following (1. – 3.):
 1. Currently presenting with a VTE (second event) **and** also has a personal history of a prior VTE (first event – treated or untreated); **or**
 2. Currently presenting with a VTE (first event) **and** also has a first-degree blood relative (i.e., parent, full-sibling, child) with a history of recurrent VTE (two or more VTE); **or**
 3. Personal history of two or more VTEs.
- II. Genetic testing for factor V Leiden (G1691A) or prothrombin (G20210A) variants is considered **not medically necessary and not covered** for individuals in the following populations:
- A. Asymptomatic, non-pregnant, adult with or without a family history of VTE or high-risk thrombophilia.
 - B. General population screening.
 - C. Testing in an asymptomatic newborn or child.
 - D. Active malignancy.
 - E. Heparin-induced thrombocytopenia with thrombosis.
 - F. Inflammatory bowel disease.
 - G. Retinal vein thrombosis including that in the setting of preeclampsia.
 - H. Testing due to adverse pregnancy outcomes including but not limited to recurrent fetal loss, placental abruption, fetal growth restriction, or preeclampsia.
- III. Genetic testing for factor V Leiden (G1691A) or prothrombin (G20210A) variants is considered **investigational and not covered** for any other scenario not listed in criterion I or II, including but not limited to the following:
- A. When testing for other genetic variants in the genes encoding factor V and prothrombin (e.g., the HR2 allele).
 - B. Preimplantation genetic testing.
 - C. Prenatal testing or routine testing during pregnancy.

Other Genes

- IV. Genetic testing of all other genes to diagnose inherited thrombophilia, including but not limited to variants in the *MTHFR* gene, is considered **investigational and is not covered**. This includes but is not limited the following panels:

MEDICAL POLICY	Genetic Testing: Inherited Thrombophilias (All Lines of Business except Medicare)
-----------------------	--

A. Versiti™ Thrombosis Panel (Versiti™ Diagnostic Laboratories)

Link to [Policy Summary](#)

CPT CODES

All Lines of Business Except Medicare	
Prior Authorization Required	
81240	F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
81241	F5 (coagulation factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant
81400	Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis) – when used for [N48K variant F2 (coagulation factor 2) (eg, hereditary hypercoagulability), 1199G>A variant F5 (coagulation factor V) (eg, hereditary hypercoagulability)]
Not Covered	
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
0278U	Hematology (genetic thrombosis), genomic sequence analysis of 12 genes, blood, buccal swab, or amniotic fluid

DESCRIPTION

Inherited Thrombophilias

Inherited thrombophilias are a group of conditions that predispose an individual to thrombosis (clot formation). Approximately, 30% to 50% of patients with a venous thromboembolism (VTE) are identified as having an inherited thrombophilia. Factor V Leiden (FVL) is the most common inherited thrombophilia. The majority of the remaining cases are caused by the prothrombin gene variant G20210A, deficiencies in protein S, protein C, and antithrombin.

FVL thrombophilia is characterized by a poor anticoagulant response to activated protein C (APC). As such, an APC resistance assay has a sensitivity and specificity for FVL approaching 100%. Despite the high sensitivity and specificity of the APC assay for the FVL variant, genetic testing is recommended in individuals with an abnormal APC test result in order to distinguish patients with one copy of the FVL variant (called a heterozygote) from those with two copies of the FVL variant (called a homozygote). The clinical expression of the condition and the risk of VTE is dependent on the number copies of the FVL variant a patient carries. It has been reported that the risk for VTE in adults is increased three- to eightfold in FVL heterozygotes and nine to 80-fold in homozygotes.¹ Risks for patients heterozygous for

MEDICAL POLICY	Genetic Testing: Inherited Thrombophilias (All Lines of Business except Medicare)
-----------------------	--

FVL and for the prothrombin G20210A variants fall somewhere in between FVL homozygotes and heterozygotes.

Interestingly, because of the increased incidence of a second thrombophilic defect among symptomatic individuals with inherited thrombophilia, evaluation of patients should include genetic testing for both the FVL and prothrombin G20210A variants in addition to an APC assay.²

Venous Thromboembolism (VTE)

VTE is a common complex (multifactorial) disease in which genetic risk factors and environmental factors play a role. To add to the complexity, the causal genetic factors are not completely penetrant, since not all mutation carriers develop VTE during life, and have variable expressivity of severity and age of onset of the disease.

The influence of genetics is supported by the fact that family history of VTE has been consistently reported to be a risk factor for VTE independent of the presence of known thrombophilic genetic abnormalities. Moreover, the carriers of FVL with a family history of VTE have been reported to be more prone to VTE than those without a family history.³

In addition to genetic risk factors, there are a number of acquired risk factors such as advanced age, cancer, immobility, and recent trauma, surgery, and hospitalization. Important gender risk factors for VTE are pregnancy and hormone treatment. Compared to age-matched non-pregnant women, the risk of VTE is increased 5 to 10 times during the antepartum period and 15 to 35 times after delivery; current oral contraceptive use or hormonal replacement therapy are associated with a 2 to 6 times increased risk of VTE.

Testing Strategy

With the few exceptions listed in criteria and summarized in the clinical practice guidelines recommended below, most patients who present with VTE do not benefit from testing for hypercoagulable disorders.⁴ This is suggested because clinical management would not be altered based on the results of knowing whether or not an inheritable defect exists in most patients with an initial episode of VTE. The identification of an inheritable defect has also not been shown to reduce mortality or VTE recurrence.

Factor V Leiden

Factor V Leiden (FVL) thrombophilia is the most common inherited thrombophilia. FVL refers to a specific variant (c.1691G>A; p.Arg506Gln) in the *F5* gene, which encodes the factor V protein. In Caucasian populations, approximately 5% of individuals carry the FVL variant. However, the frequency of the FVL variant is much lower in other ethnicities.

Factor V is a coagulation factor that promotes clotting by converting prothrombin to thrombin, a protein necessary for the formation of fibrin (the primary component of blood clots). After clot formation, factor

MEDICAL POLICY	Genetic Testing: Inherited Thrombophilias (All Lines of Business except Medicare)
-----------------------	--

V is inactivated by a complex of two proteins: protein C and its co-factor protein S. In patients with FVL-related thrombophilia, there is a resistance to activated protein C (APC), which leads to a hypercoagulable state and an increased risk for VTE. In addition to the number of copies of the FVL variants a patient carries, VTE risk may be increased in patients with additional precipitating factors, such as pregnancy or the use of oral contraceptives or hormone replacement therapy.

Since FVL is common, individuals may be heterozygous for the FVL variant, homozygous for the FVL variant, or carry FVL in combination with other common thrombophilia-associated variants (such as the prothrombin variant c.20210G>A). Individuals that carry one copy of the FVL variant and one copy of the prothrombin c.20210G>A variant are called double heterozygotes. In these individuals, the risk for VTE may be higher and the onset may be earlier, when compared with FVL heterozygotes. However, it is important to note that the penetrance of FVL is incomplete and many individuals who carry FVL may never develop a VTE, even in the presence of additional precipitating factors.

Prothrombin G20210A Variant

The variant G20210A (c.*96G>A) in the prothrombin gene has been shown to result in elevated plasma prothrombin levels. The prevalence of prothrombin G20210A is approximately 2% in healthy individuals and 7% in individuals affected with VTE.

A key part of the clotting mechanism is the activation of prothrombin to thrombin, which is required for the conversion of soluble fibrinogen to insoluble fibrin. The causal relationship for prothrombin G20210A is likely due to elevated plasma prothrombin levels that may influence risk of thrombosis through two pathways: (a) excessive fibrin formation; or (b) down-regulation of fibrinolysis.

Methylenetetrahydrofolate reductase (MTHFR) Gene

The homozygous variant C677T (c.677C>T) in the MTHFR gene, which is present in approximately 14% of the general population, is suspected of playing a role in familial thrombosis through elevated homocysteine levels, a metabolite derived from the amino acid methionine. However, causality for MTHFR C677T in thrombotic events is controversial and the mechanism is unclear.

Prophylactic Anticoagulation Treatment

Per GeneReviews assessment of genetic testing and treatment of inherited thrombophilias:^{1,2}

“Prevention of Primary Manifestations

In the absence of a history of thrombosis, long-term anticoagulation is not routinely recommended for asymptomatic individuals who are heterozygous for the factor V Leiden allele or the prothrombin 20210G>A because the 1%-3%/year risk for major bleeding from warfarin is greater than the estimated less than 1%/year risk for thrombosis.”

MEDICAL POLICY	Genetic Testing: Inherited Thrombophilias (All Lines of Business except Medicare)
-----------------------	--

GeneReviews indicate that a short course of prophylactic anticoagulation may be considered in asymptomatic individuals in high-risk clinical settings, “such as surgery, pregnancy, or prolonged immobilization, although currently no evidence confirms the benefit of primary prophylaxis for all asymptomatic carriers.”

GeneReviews give the following recommendations regarding anticoagulation therapy in pregnant individuals:

“No consensus exists on the optimal management of factor V Leiden or prothrombin-related thrombophilia during pregnancy; guidelines are similar to those for individuals who are not pregnant. Until more specific guidelines are defined by prospective trials, decisions about anticoagulation should be individualized based on the thrombophilic defects, coexisting risk factors, and personal and family history of thrombosis.

Prophylactic anticoagulation during pregnancy is not routinely recommended in asymptomatic heterozygous women with no history of thrombosis. These women should be warned about potential thrombotic complications, counseled about the risks and benefits of anticoagulation during pregnancy, and offered a four- to six-week course of anticoagulation after delivery, as the greatest thrombotic risk is in the initial postpartum period.

[Prophylactic anticoagulation during pregnancy] is recommended for women with a factor V Leiden allele and a history of unprovoked VTE. Unfractionated or low molecular-weight heparin should be given during pregnancy, followed by a four- to six-week course of anticoagulation post-partum.”

REVIEW OF EVIDENCE

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the clinical utility of genetic testing for inherited thrombophilias. Below is a summary of the available evidence identified through March of 2022. The clinical utility of testing for genetic variants is addressed for distinct patient populations, including non-pregnant individuals with and without a personal history of VTE, and pregnant women, and other indications including thromboses in unusual locations.

Non-pregnant Individuals with or without a Personal History of VTE

In 2003, Baglin et al. published the results of a prospective cohort study designed to assess the incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors, including the presence of the FVL or prothrombin gene mutations.⁵ In total, the study followed 570 unselected patients who had had a first episode of objectively proven VTE, 85% of which were tested for heritable thrombophilic defects. Sixteen percent of patients with initial VTE were positive for FVL, and 4% positive for the prothrombin mutation. Over two years of follow-up, 63 patients (11%) had a recurrent VTE. The authors reported that, after two years of follow-up, patients with unprovoked VTE who were heterozygous for factor V Leiden or the prothrombin gene mutation had a low risk of recurrence, which

MEDICAL POLICY	Genetic Testing: Inherited Thrombophilias (All Lines of Business except Medicare)
-----------------------	--

did not differ significantly from the risk among patients without inherited thrombophilia (hazard ratio, 1.34; 95% confidence interval [CI], 0.73 to 2.46; $p = 0.35$). The authors concluded that testing for heritable thrombophilia did not predict recurrence in unselected patients after their first episode of VTE. However, clinical risk factors associated with the first episode of VTE did predict risk of recurrence.

In 2005, Christiansen et al. published the results of a prospective study designed to estimate the recurrence rate of thrombotic events in patients after a first thrombotic event, including 474 patients that followed up for mean of 7.3 years.⁶ During follow-up, 90 patients had a recurrent thrombotic event. The authors reported that the risk of recurrence was low for patients with inherited thrombophilia as compared with those who did not have inherited thrombophilia, with an adjusted hazard ratio of 0.7 (95% CI, 0.3 to 2.0) for patients with the prothrombin gene mutation and 1.3 (95% CI, 0.8 to 2.1) for those with FVL. The authors concluded that inherited thrombophilias did not play an important role in the risk of a recurrent thrombotic event and that testing for defects did not play a role in prophylactic strategies.

In 2007, Coppens et al. published the results of a retrospective study of clinical practices in the Netherlands that investigated, in part, the management decisions made on the basis of results yielded by testing for inherited thrombophilias.⁷ Two thousand consecutive patients were identified in whom tests for APC resistance, FVL, prothrombin 20210A mutation, antithrombin, protein C or protein S activity were ordered between November 2003 and March 2004, and questionnaires were sent to the ordering physicians within six months of the test. Results from 1134 returned questionnaires were analyzed. Based on the results of the test, 10% of patients had an altered the duration of anticoagulant treatment, and 12% of the patients had intensified prophylaxis in high-risk episodes. However, testing for thrombophilia yielded no specific clinical management for 77% of patients. The authors concluded that “even when thrombophilia tests do change patient management, it is debatable whether or not these decisions are rational. Ideally, diagnostic and management strategies should be tested in randomized controlled trials in order to ascertain their validity.”

In 2008, Coppens et al. published the results of a case-control study designed to investigate whether testing for inherited thrombophilia reduces the risk of recurrent VTE through management alterations such as prolonged use of anticoagulants, avoidance of or intensified prophylaxis in high risk situations.⁸ Cases included 197 patients from the MEGA study who had had a recurrent event during follow-up, compared to 324 age- and sex- matched controls who did not have a recurrence during follow-up. Thrombophilia tests were performed in 35% of cases and in 30% of controls. The authors reported an OR for recurrence was 1.2 (95% CI: 0.9 –1.8) for tested versus non-tested patients, indicating that testing does not reduce the risk of recurrent VTE in patients who have experienced a first episode.

In 2009, Hindorff et al. published the results of a survey that assessed motivating factors for physician ordering of FVL genetic tests, surveying 112 primary care physicians with prior FVL test use.⁹ Generally, physicians reported similar motivating factors for ordering FVL, which were consistent with existing practice guidelines. In addition, more than half of the physicians indicated that they use results in clinical practice, with 83-92% reporting that they use results to counsel patients on risk of recurrence, 75-85%

MEDICAL POLICY	Genetic Testing: Inherited Thrombophilias (All Lines of Business except Medicare)
-----------------------	--

reporting that they use results to make treatment changes, and 67% reporting that they make clinical decisions about venous thrombosis prevention based on test results.

In 2014, Grandone et al. published results from a cohort study designed to determine the role of thrombophilia screening in 157 unselected infertile women that underwent assisted reproductive technologies.¹⁰ All women had at least one cycle before the thrombophilia test and one cycle after the test. Overall, 15 (9.6%) women carried thrombophilia. Live births and the likelihood of delivering a live-born child were not associated with the presence of thrombophilia. Authors concluded that thrombophilia screening before assisted reproductive technologies was not useful in discriminating women with a worse pregnancy prognosis.

In 2016, Kudo et al. published the results of a retrospective study that assessed the clinical utility of thrombophilia testing for VTE patients in public hospitals in Australia, including data from 152 patients.¹¹ Overall, 74 patients (49%) were tested with thrombophilia screen with 27 patients returning positive results (37%). Heterozygous factor V Leiden and heterozygous prothrombin variants were the most common results, with ten patients testing positive for FVL and five patients with the prothrombin variant. Only 1.2% of patients had documented changes to the duration of anticoagulation due to positive test results. The authors concluded that thrombophilia testing did not significantly influence decision-making.

Individuals at High Risk of VTE due to Hormone Use

In 2006, Wu et al. reported the findings of a systematic review of screening for thrombophilia in women in high-risk situations (the Thrombosis: Risk and Economic Assessment of Thrombophilia Screening [TREATS] study).¹² In the analysis of complications in women using oral estrogen preparations, nine studies were included. The reviewers reported that the highest risk of VTE in oral contraceptive users was observed in women with FVL (OR: 15.62; 95% CI: 8.66 - 28.15). For hormone replacement therapy, a significant association was found in women with FVL (OR: 13.16; 95% CI: 4.28 - 40.47). However, the reviewers stated that, "in view of the prevalence of thrombophilia and the low prevalence of VTE in non-users of combined oral contraceptives, the absolute risk remains low." Neither prothrombin G20210A mutation nor any variant in the *MTHFR* gene were found to be associated with the use of oral contraceptives or with hormone replacement therapy.

Individuals at High Risk of VTE due to Surgery

In the 2006 Wu TREATS systematic review described above, the analysis of complications in women patients undergoing major orthopedic surgery included eight studies.¹² Significant associations were found between FVL and postoperative VTE following elective hip or knee replacement surgery (OR: 1.86; 95% CI: 1.27 - 2.74). Prothrombin G20210A was significantly associated with postoperative pulmonary embolism (OR: 9.14; 05% CI: 2.27 - 36.89). The reviewers stated that these associations were observed in patients who were given preoperative thromboprophylaxis and are, therefore, of limited clinical significance. *MTHFR* variants were not found to be associated with increased risk of postoperative VTE.

MEDICAL POLICY	Genetic Testing: Inherited Thrombophilias (All Lines of Business except Medicare)
-----------------------	--

Other Indications

No studies were identified that reported on the clinical utility of genetic testing for inherited thrombophilias for other patient populations; including: individuals with venous thrombosis in unusual sites (e.g., cerebral, portal, hepatic, mesenteric) and individuals under 50 years of age with family history or other risk factors. Although studies have found associations between the presence of FVL and/or the prothrombin G20210A variants and vein thrombosis at unusual sites, such as portal, hepatic and cerebral veins; these studies did not report if the presence of the a genetic variant impacted medical management, or if altered therapeutic management led to improved health outcomes such as prevention of recurrence.

Pregnant Women and Risk of VTE

In 2006, Robertson et al. published the results of a systematic review of nine studies that assessed the risk of VTE in pregnant women with inherited thrombophilias without a family history of VTE.¹³ Both the FVL and the prothrombin G20210A mutation, but not the thermolabile methylene tetrahydrofolate reductase variant (MTHFR C677T), were associated with a statistically significant increase in the risk of pregnancy-related VTE. The highest risks were associated with homozygosity for FVL (OR: 34.4; 95% CI: 9.9-120.1) or the prothrombin G20210A variant (OR: 26.4; 95% CI: 1.2-559.3). Heterozygosity for FVL (OR: 8.3; 95% CI: 5.4-12.7) and prothrombin G20210A (OR: 6.8; 95% CI: 2.5-18.8) were associated with lower, but still significant risks.

Also in 2006, one group published two meta-analyses that used slightly different study inclusion criteria to determine the estimate of association of the FVL mutation with pregnancy related VTE.¹⁴ The risk estimate of VTE obtained from meta-analysis of case-control studies was significantly high (OR: 8.6; 95% CI: 4.8-12.6). However, the analysis that included only cohort studies showed a lower pooled OR of 4.5 (95% CI: 1.8-10.9).

In the 2006 Wu TREATS systematic review described above, the analysis of the effectiveness of prophylactic treatments in preventing VTE and adverse pregnancy outcomes in women with thrombophilia during pregnancy included 72 studies.¹² The reviewers reported that, based on the meta-analysis, the highest risk in pregnancy was found for VTE and FVL, with homozygous FVL carriers being 34 times more likely to develop VTE in pregnancy than non-carriers. Significant risks for individual thrombophilic defects were also established for early pregnancy loss with prothrombin G20210A (OR: 2.49; 95% CI 1.24 - 5.00); recurrent pregnancy loss with FVL (OR:1.91; 95% CI 1.01 - 3.61) and prothrombin G20210A (OR: 2.70; 95% CI 1.37 - 5.35); late pregnancy loss with FVL (OR: 2.06; 95% CI 1.10 - 3.86); preeclampsia with MTHFR variants (OR: 1.32; 95% CI: 1.05 - 1.66); placental abruption with prothrombin G20210A (OR: 7.71; 95% CI: 3.01 - 19.76); and intrauterine growth restriction with prothrombin G20210A (OR: 2.91; 95% CI: 1.13 - 7.54) and with homozygous FVL (OR: 15.20; 95% CI: 1.32 to 174.96).

MEDICAL POLICY	Genetic Testing: Inherited Thrombophilias (All Lines of Business except Medicare)
-----------------------	--

Adverse Pregnancy Outcomes

In 2005, Dizon-Townson et al. published the results of a Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) study that estimated the frequency of pregnancy-related thromboembolic events among carriers of the factor V Leiden (FVL) mutation without a personal history of thromboembolism, and evaluated the impact of maternal and fetal FVL mutation status on the risk of adverse outcomes.¹⁵ This study was a multicenter, prospective, observational cohort of unselected singleton gestations that were genotyped for the FVL variant. In total, 134 FVL mutation carriers were identified among 4,885 pregnant women (2.7%), with both FVL mutation status and pregnancy outcomes available. The authors reported that no thromboembolic events occurred among the FVL mutation carriers, but three pulmonary emboli and one deep venous thrombosis occurred (0.08%, 95% confidence interval 0.02-0.21) in FVL mutation non-carriers. In the nested carrier-control analysis (n = 339), no differences in adverse pregnancy outcomes were observed between FVL mutation carriers and controls. Maternal FVL mutation-positive status was not associated with increased pregnancy loss, preeclampsia, placental abruption, or small for gestational age births. The authors concluded that among women with no history of thromboembolism, maternal heterozygous carriage of the FVL mutation is associated with a low risk of venous thromboembolism in pregnancy. According to the study, neither universal screening for the FVL mutation, nor treatment of low-risk carriers during pregnancy was indicated.

In 2010, Silver et al. published the results of a study that evaluated whether maternal carriage of the prothrombin gene G20210A mutation was associated with pregnancy loss, preeclampsia, placental abruption, or small for gestational age (SGA) neonates.¹⁶ This was a secondary analysis of the Eunice Kennedy Shriver NICHD factor V Leiden study described above.¹⁵ A total of 4,167 first-trimester samples tested for the prothrombin G20210A mutation. Overall, 157 (3.8%) women had the prothrombin gene mutation (156 heterozygous and one homozygous). In a multivariable analysis controlling for several confounders, the carriers of the prothrombin G20210A mutation had similar rates of pregnancy loss, preeclampsia, SGA neonates, and abruption compared with non-carriers. The investigators concluded that there was no association between the prothrombin G20210A mutation and pregnancy loss, preeclampsia, abruption, or SGA neonates and that screening women without a history of thrombosis or adverse pregnancy outcomes for this mutation.

In 2012, Bradley et al. published a systematic review that evaluated if testing reproductive age women with recurrent pregnancy loss for factor V Leiden and prothrombin c.20210G>A variants resulted in improved pregnancy outcomes, reporting test performance, effect sizes, and treatment effectiveness.¹⁷ Sixty case-control and 16 cohort studies were used for the analyses. For Factor V Leiden testing the sensitivity and specificity were 98.8% and 99.3% respectively; and for prothrombin testing, 98.3% and 99.6%, respectively. The reviewers stated that there was a significant degree of heterogeneity among the included studies. No studies were identified that directly addressed the balance of benefits and harms related to factor V Leiden/prothrombin testing and whether interventions improved the likelihood of a successful pregnancy in women with RPL who carry one or two factor V Leiden/prothrombin variants. The reviewers stated that RCTs have generally been underpowered for women with factor V Leiden/prothrombin-related recurrent pregnancy loss, and, therefore, the

MEDICAL POLICY	Genetic Testing: Inherited Thrombophilias (All Lines of Business except Medicare)
-----------------------	--

evidence was inadequate to determine if anticoagulant treatments are effective in this population. Given the lack of benefit, and the potential harms, the reviewers concluded that factor V Leiden/prothrombin testing and treatment in women with RPL is likely to be associated with a net harm.

In 2012, Tormene et al. published the results from a large cohort study that evaluated whether the administration of low-molecular-weight heparin (LMWH) during pregnancy was effective in preventing obstetric complications and pregnancy-related venous thromboembolism (VTE), including 416 women with confirmed FVL or prothrombin G20210A mutations.¹⁸ The authors reported that LMWH therapy was associated with a decreased risk of miscarriage in carriers of FVL and/or prothrombin variants (OR, 0.52; 95% CI, 0.29-0.94) and a decrease of VTE (OR, 0.05; 95% CI, 0.01-0.21). However, LMWH therapy had no effect on the risk of pregnancy complications such as preeclampsia, placental abruption, and small for gestational age newborn in carriers of FVL and/or prothrombin. Unfortunately, the results were not stratified by genotype and the patient population was heterogeneous in that it included women recruited variety of reasons for performing thrombophilia testing.

Later studies continue to replicate the above findings in similar cohort studies of pregnant women with a history of recurrent miscarriage.¹⁹

Other Genes and Other Genetic Variants

Other genes have been investigated to aid in the diagnosis of inherited thrombophilia. This includes but is not limited to *MTHFR*. According to Hayes, the evidence regarding associations between risk of venous thrombosis and *MTHFR* variants is conflicting.²⁰ Hayes noted several large meta-analyses reporting statistically significant increased risk of venous thrombosis for specific *MTHFR* variants that were present in some geographic cohorts, though not others.

CLINICAL PRACTICE GUIDELINES

American College of Obstetricians and Gynecologists (ACOG)

In 2018, ACOG replaced Practice Bulletin #138 on inherited thrombophilias in pregnancy with #197 by the same title.²¹ The bulletin stresses that screening for inherited thrombophilias is useful only when results will affect management decisions, and not useful in situations in which treatment is indicated for other risk factors. With respect to *MTHFR*, specifically:

“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.”

MEDICAL POLICY	Genetic Testing: Inherited Thrombophilias (All Lines of Business except Medicare)
-----------------------	--

American College of Medical Genetics (ACMG)

In 2013, ACMG published an evidence-based Practice Guideline stating that *MTHFR* polymorphism testing had minimal clinical utility and recommended the following:²²

- “MTHFR polymorphism genotyping should not be ordered as part of the clinical evaluation for thrombophilia or recurrent pregnancy loss
- MTHFR polymorphism genotyping should not be ordered for at-risk family members”

The guidelines noted that in individuals who have a known thrombophilia (Factor V Leiden or prothrombin) the majority of studies indicate that MTHFR genotype status does not alter their thrombotic risk to a clinically significant degree. In addition, studies evaluating the role of *MTHFR* polymorphisms and pregnancy loss have only found modest associations between *MTHFR* variants and pregnancy loss or other adverse pregnancy outcomes, such as pre-eclampsia.

American College of Chest Physicians (ACCP)

In 2012, the ACCP published recommendations addressing VTE, thrombophilia, antithrombotic therapy, and pregnancy, as a part of their “Antithrombotic Therapy and Prevention of Thrombosis” evidence-based clinical practice guidelines.²³ The guidelines included two recommendations that identified pregnant women at increased risk of VTE based on the presence of either the FVL or the prothrombin 20210A mutations, but not mutations in the *MTHFR* gene. Both of the recommendations were weak recommendations, based on moderate quality evidence. The ACCP guidelines recommended the following:

- “For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and have a positive family history for VTE, we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or vitamin K antagonists targeted at INR 2.0 to 3.0 rather than no prophylaxis (Grade 2B).
- For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and who do not have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or vitamin K antagonists targeted at INR 2.0 to 3.0 rather than routine care (Grade 2B).”

The ACCP did not have any other recommendations regarding antithrombotic therapy that were based on genetic risk factors. This includes the “Antithrombotic Therapy for VTE Disease” section of the 2012 “Antithrombotic Therapy and Prevention of Thrombosis” guidelines.²⁴ The panel stated that inherited thrombophilia was not considered to be a primary factor for estimating risk of recurrence and that the presence of these additional factors did not strongly or consistently predict risk of recurrence enough to influence recommendations on duration of therapy.

MEDICAL POLICY	Genetic Testing: Inherited Thrombophilias (All Lines of Business except Medicare)
-----------------------	--

More recently, the updated 2021 CHEST Guideline and Expert Panel Report “Antithrombotic Therapy for VTE Disease” did not address testing for inherited thrombophilias in their recommendations.²⁵

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group is an initiative launched and funded by the Centers for Disease Control and Prevention (CDC) which provides systematic evidence-based recommendations for genetic testing.²⁷ In 2011, EGAPP published recommendations that addressed genetic testing for FVL and prothrombin, which included the following recommendations on the clinical utility of genetic testing of these variants for idiopathic VTE:

- “(R)ecommend against routine testing for FVL and/or prothrombin 20210G/A (PT) in the following circumstances (based on moderate evidence):
 - 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.
 - Asymptomatic adult family members of patients with VTE and an FVL or prothrombin G20210A variant (PT) mutation, for the purpose of considering primary prophylactic anticoagulation. Potential benefits are unlikely to exceed potential harms.”

The EGAPP working group also noted that, “the evidence was insufficient to determine whether FVL/PT testing might have clinical utility for identifying FVL homozygosity among asymptomatic family members of adults with idiopathic VTE.”

POLICY SUMMARY

Testing for Factor V Leiden (FVL) Thrombophilia (F5 Gene) and Prothrombin G20210A Thrombophilia (F2 Gene)

There is limited research showing that genetic testing for specific variants of Factor V Leiden (FVL) and prothrombin may help diagnose an inherited thrombophilia. This doesn’t mean that it will not improve overall health outcomes, more studies are needed to know for sure. Despite the need for more research, clinical practice guidelines recommend genetic testing for Factor V Leiden (FVL) and prothrombin for specific patient populations, such as in pregnant individuals with certain risk factors and high-risk patients who present have a history of a venous thromboembolism. Therefore, genetic testing of Factor V Leiden (FVL) and prothrombin may be considered medically necessary and covered when policy criteria are met.

Despite a lack of research, clinical practice guidelines recommend against testing certain populations for specific variants of Factor V Leiden (FVL) and prothrombin in certain clinical settings, including asymptomatic, non-pregnant, adult with or without a family history of VTE or high-risk thrombophilia; general population screening; testing in an asymptomatic newborn or child; active malignancy; heparin-

MEDICAL POLICY	Genetic Testing: Inherited Thrombophilias (All Lines of Business except Medicare)
-----------------------	--

induced thrombocytopenia with thrombosis; inflammatory bowel disease; retinal vein thrombosis including that in the setting of preeclampsia; and testing due to adverse pregnancy outcomes including but not limited to recurrent fetal loss, placental abruption, fetal growth restriction, or preeclampsia. Therefore, FVL and prothrombin testing for these populations is considered not medically necessary and not covered.

There is not enough research to know if Factor V Leiden (FVL) and prothrombin (PT) gene variant testing improves overall health outcomes for those who are not specifically recommended for testing or those specifically recommended to avoid testing according to clinical practice guidelines. Therefore, genetic testing for FVL and PT variants is considered investigational and not covered when policy criteria are not met.

Other Genetic Testing for Inherited Thrombophilia

There may be research that suggests other types of genetic testing, such as testing for the *MTHFR* gene for inherited thrombophilias improves health outcomes. However, there is also research that shows that testing for gene variants other than those specified above for *F2* and *F5* does not improve overall health outcomes. More research is needed to know for sure. Clinical practice guidelines based on research do not recommend testing for *MTHFR* other genes besides what is outlined above. Therefore, genetic testing of all other genes to diagnose or screen for inherited thrombophilia is considered investigational and is not covered.

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously

MEDICAL POLICY	Genetic Testing: Inherited Thrombophilias (All Lines of Business except Medicare)
-----------------------	--

considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

MEDICAL POLICY CROSS REFERENCES

- Genetic Studies and Counseling
- Genetic Testing: Inherited Thrombophilias (Medicare only)
- Genetic Testing: Reproductive Planning and Prenatal Testing (All Lines of Business Except Medicare)
- Genetic Testing: Reproductive Planning and Prenatal Testing (Medicare Only)

REFERENCES

1. GeneReviews. Factor V Leiden Thrombophilia. May 14, 1999; Last Update: January 4, 2018. <https://www.ncbi.nlm.nih.gov/books/NBK1368/>. Accessed 3/23/2022.
2. GeneReviews. Prothrombin-Related Thrombophilia. July 25, 2006; Last Update: Last Update: February 4, 2021. <https://www.ncbi.nlm.nih.gov/books/NBK1148/>. Accessed 3/23/2022.
3. Simone B, De Stefano V, Leoncini E, et al. Risk of venous thromboembolism associated with single and combined effects of Factor V Leiden, Prothrombin 20210A and Methylenetetrahydrofolate reductase C677T: a meta-analysis involving over 11,000 cases and 21,000 controls. *European journal of epidemiology*. 2013;28(8):621-647.
4. UpToDate. Evaluating adult patients with established venous thromboembolism for acquired and inherited risk factors. Literature review current through: Feb 2022. This topic last updated, Dec 2, 2021. <https://www.uptodate.com/contents/evaluating-adult-patients-with-established-venous-thromboembolism-for-acquired-and-inherited-risk-factors>. Accessed 3/23/2022.
5. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. *Lancet (London, England)*. 2003;362(9383):523-526.
6. Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR. Thrombophilia, clinical factors, and recurrent venous thrombotic events. *JAMA*. 2005;293(19):2352-2361. <https://www.ncbi.nlm.nih.gov/pubmed/15900005>
7. Coppens M, van Mourik JA, Eckmann CM, Buller HR, Middeldorp S. Current practise of testing for inherited thrombophilia. *Journal of thrombosis and haemostasis : JTH*. 2007;5(9):1979-1981.
8. Coppens M, Reijnders JH, Middeldorp S, Doggen CJ, Rosendaal FR. Testing for inherited thrombophilia does not reduce the recurrence of venous thrombosis. *Journal of thrombosis and haemostasis : JTH*. 2008;6(9):1474-1477.
9. Hindorff LA, Burke W, Laberge AM, et al. Motivating factors for physician ordering of factor V Leiden genetic tests. *Archives of internal medicine*. 2009;169(1):68-74.
10. Grandone E, Villani M, Tiscia GL, et al. Clinical Pregnancies and Live Births in women approaching ART: a follow-up analysis of 157 women after thrombophilia screening. *Thrombosis research*. 2014;133(2):168-172.
11. Kudo M, Lee HL, Yang IA, Masel PJ. Utility of thrombophilia testing in patients with venous thrombo-embolism. *Journal of thoracic disease*. 2016;8(12):3697-3703.

MEDICAL POLICY**Genetic Testing: Inherited
Thrombophilias
(All Lines of Business except
Medicare)**

12. Wu O, Robertson L, Twaddle S, et al. Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. *Health technology assessment (Winchester, England)*. 2006;10(11):1-110.
13. Robertson L, Wu O, Langhorne P, et al. Thrombophilia in pregnancy: a systematic review. *British journal of haematology*. 2006;132(2):171-196.
14. Biron-Andreani C, Schved JF, Daures JP. Factor V Leiden mutation and pregnancy-related venous thromboembolism: what is the exact risk? Results from a meta-analysis. *Thrombosis and haemostasis*. 2006;96(1):14-18.
15. Dizon-Townson D, Miller C, Sibai B, et al. The relationship of the factor V Leiden mutation and pregnancy outcomes for mother and fetus. *Obstetrics and gynecology*. 2005;106(3):517-524.
16. Silver RM, Zhao Y, Spong CY, et al. Prothrombin gene G20210A mutation and obstetric complications. *Obstetrics and gynecology*. 2010;115(1):14-20.
17. Bradley LA, Palomaki GE, Bienstock J, Varga E, Scott JA. Can Factor V Leiden and prothrombin G20210A testing in women with recurrent pregnancy loss result in improved pregnancy outcomes?: Results from a targeted evidence-based review. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2012;14(1):39-50.
18. Tormene D, Grandone E, De Stefano V, et al. Obstetric complications and pregnancy-related venous thromboembolism: the effect of low-molecular-weight heparin on their prevention in carriers of factor V Leiden or prothrombin G20210A mutation. *Thrombosis and haemostasis*. 2012;107(3):477-484.
19. Levkova M, Hachmeriyani M, Stoyanova M, Miteva V, Angelova L. Comparison between thrombophilic gene polymorphisms among high risk patients. *Rom J Intern Med*. 2020;58(1):20-26. <https://www.ncbi.nlm.nih.gov/pubmed/31469659>
20. Hayes. GTE Clinical Utility Report. MTHFR Genetic Testing In Common Clinical Conditions. Aug 17, 2017. Annual Review: May 23, 2021. <https://evidence.hayesinc.com/report/gti.mthfrdeficiency4179>. Accessed 3/23/2022.
21. ACOG Practice Bulletin No. 197: Inherited Thrombophilias in Pregnancy. *Obstetrics and gynecology*. 2018;132(1):e18-e34. <https://www.ncbi.nlm.nih.gov/pubmed/29939939>
22. Hickey SE, Curry CJ, Toriello HV. ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2013;15(2):153-156. <https://www.ncbi.nlm.nih.gov/pubmed/23288205>
23. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e691S-e736S.
24. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e419S-e496S.
25. Stevens SM, Woller SC, Baumann Kreuziger L, et al. Executive Summary: Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. *Chest*. 2021;160(6):2247-2259. <https://doi.org/10.1016/j.chest.2021.07.056>

MEDICAL POLICY	Genetic Testing: Inherited Thrombophilias (All Lines of Business except Medicare)
-----------------------	--

26. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest*. 2016;149(2):315-352.

27. 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. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2011;13(1):67-76.