Medicare Local Coverage Determination Policy

# JM Palmetto - MolDX: Genetic Testing for Hypercoagulability / Thrombophilia (Factor V Leiden, Factor II Prothrombin, and MTHFR)

CPT: 81240 (Factor II Prothrombin), 81241 (Factor V Leiden), 81291 (MTHFR)

## CMS Policy for Alabama, Georgia, North Carolina, South Carolina, Tennessee, Virginia, and West Virginia

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**Coverage Indications, Limitations, and/or Medical Necessity**

**Indications and Limitations**

This is a non-coverage policy for genetic testing for thrombophilia testing for the Factor V Leiden (FVL) variant in the F5 gene, the G20210G>A (G20210A) variant in the F2 gene, and the MTHFR gene which encodes the 5,10-methylenetetrahydrofolate reductase enzyme. Genetic testing for these genes for all risk factors, signs, symptoms, diseases, or conditions, including cardiovascular risk assessment, are non-covered except for pregnant patients.

Testing for FVL and F2 G20210A mutations is indicated for pregnant patients who have a history of personal VTE associated with a non-recurrent (transient) risk factor who are not otherwise receiving anticoagulant prophylaxis. The results of genetic testing can inform risk stratification for venous thromboembolism (VTE) recurrence and subsequent need for antenatal prophylaxis. However, Medicare will not add coverage of thrombophilia testing for pregnant women because they likely represent a very small group of potential Medicare (disabled) patients. Claims submitted on this limited Medicare population will deny per the policy, but should be appealed for coverage with submission of medical records supporting the necessity for testing, and specify how testing changed anticoagulant prophylaxis management for the patient.

**Background**

Thrombophilia (or hypercoagulability) is the propensity to develop thrombosis due to either an acquired or inherited defect in the coagulation system. The major clinical manifestation of thrombophilia is VTE. Acquired thrombophilia risk factors include but are not limited to advancing age (> 50), trauma, malignancy, chemotherapy, major surgery, immobilization, pregnancy, estrogen, inflammation, antiphospholipid antibody syndrome, myeloproliferative disorders, heparin-induced thrombocytopenia, liver disease, nephrotic syndrome, and prolonged air travel. Inherited thrombophilia risk factors include deficiencies in antithrombin, Protein C, Protein S, mutations in FVL and F2, and dysfibrinogenemias. Mixed or unknown risk factors include hyperhomocysteinemia, elevated levels of Factor VIII, acquired Protein C resistance in the absence of Factor V Leiden, and elevated levels of Factors IX and XI.

Testing for thrombophilia may consist of functional testing, antigenic testing, and genetic testing. Functional testing for thrombophilia may include tests such as

- Anti-phospholipid antibody (lupus anticoagulant);
- Protein C;
- Protein S;
- Activated Protein C resistance (a surrogate for Factor V Leiden mutation);
- Factor VIII
- Fibrinogen
- C-reactive protein
- Homocysteine levels

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Antigenic testing may be performed to identify specific glycoprotein antibodies associated with abnormal functional anti-phospholipid antibody studies, or to subtype deficiencies detected by decreased Protein S, Protein C and Antithrombin functional activity. VTE is characteristically seen in deficiencies in Protein C, Protein S and antithrombin, as well as with FVL and F2 mutations. This is unlike the combination of arterial and venous thrombosis associated with hyperhomocysteinemia and lupus anticoagulant.

**Genetic Testing for Thrombophilia**

Genetic testing is available for a number of types of inherited thrombophilia, including mutations in the FVL, F2 and MTHFR genes. However, the clinical utility of testing is uncertain. The clinical utility of genetic testing depends on the ability of testing results to change management that results in improved clinical outcomes. The clinical utility of genetic testing for thrombophilia is based on the overall risk of thromboembolism and the risk/benefit ratio of treatment, primarily with anticoagulants.

During the previous 5 years, a number of guidelines and/or position statements on testing for thrombophilia have been published. In 2011, The Evaluation of Genomic Applications in Practice and Prevention Working Groups (EGAPP) addressed genetic testing for FVL and F2 mutations. The expert consensus recommended:

- There is no evidence that knowledge of FVL/F2 mutation status in patients with VTE affects anticoagulation treatment to avoid recurrence;
- There is convincing evidence that anticoagulation beyond three months reduces recurrence of VTE, regardless of mutation status;
- There is no evidence that knowledge of FVL/F2 mutation status among symptomatic family members of patients with VTE leads to anticoagulation aimed at avoiding initial episodes of VTE (See note).

**Note:** The Medicare benefit applies only to individuals with signs and symptoms of disease. There is no Medicare benefit for assessment of thrombosis risk in asymptomatic patients (aka screening for inherited thrombophilia) or in asymptomatic individuals whose relatives have documented inherited thrombophilia.

In 2008, the American College of Chest Physician's (ACCP) published guidelines for the treatment of thromboembolic disease stated the following concerning genetic testing for thrombophilia:

- The presence of hereditary thrombophilia has not been used as a major factor to guide duration of anticoagulation for VTE in these guidelines because evidence from prospective studies suggests that these factors are not major determinates of the risk of recurrence.

In the 2012 ACCP Clinical Practice Guidelines, Guyatt et al (2012) and Bates et al (2012) make the following recommendations for treatment and management of VTE:

- In persons with asymptomatic thrombophilia (ie, without a previous history of VTE), we recommend against the long - term daily use of mechanical or pharmacologic thromboprophylaxis to prevent VTE;
- 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 low- molecular-weight heparin (LMWH) and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or vitamin K antagonists (VKAs) targeted at INR 2.0 to 3.0 rather than no prophylaxis;

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- For all pregnant women with prior VTE, we suggest postpartum prophylaxis for 6 weeks with prophylacticor intermediate-dose LMWH or VKAs targeted at INR 2.0 to 3.0 rather than no prophylaxis;
- For pregnant women at low risk of recurrent VTE (single episode of VTE associated with a transient risk factor not related to pregnancy or use of estrogen), we suggest clinical vigilance antepartum rather than antepartum prophylaxis;
- For pregnant women at moderate to high risk of recurrent VTE (single unprovoked VTE, pregnancy- or estrogen-related VTE, or multiple prior unprovoked VTE not receiving long-term anticoagulation), we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH rather than clinical vigilance or routine care.

In the 2013 American Congress of Obstetricians and Gynecologists (ACOG) clinical management guidelines for inherited thrombophilia in pregnancy, ACOG experts note that the following guidelines are based on limited or inconsistent scientific evidence:

- "Screening for thrombophilia is controversial. It is useful only when results will affect management decisions, and it is not useful in situations where treatment is indicated for other risk factors.
- Screening may be considered in the following clinical settings:
  - A personal history of VTE that was associated with a non-recurrent risk factor (eg, fractures, surgery, and prolonged immobilizations).
  - A first-degree relative (eg, parent or sibling) with a history of high-risk thrombophilia." (See note below)

ACOG also stated that testing for inherited thrombophilia in women who have experienced recurrent fetal loss or placental abruption is not recommended because it is unclear if anticoagulation therapy reduces recurrence. They indicate that there is insufficient clinical evidence that antepartum prophylaxis with unfractionated heparin or low molecular weight heparin (LMWH) prevents recurrence in these patients, and note insufficient evidence to either screen for or treat women with inherited thrombophilia including complications such as fetal growth restriction or preeclampsia.

On behalf of the American College of Medical Genetics (ACMG) (reaffirmed in 2006), Grody, et al (2001) recommended testing for FVL for the following indications:

- Age under 50, any venous thrombosis;
- Venous thrombosis in unusual sites (such as hepatic, mesenteric, and cerebral veins;
- Recurrent venous thrombosis;
- Venous thrombosis and a strong family history of thrombotic disease;
- Venous thrombosis in pregnant women or women taking oral contraceptives;
- Relatives of individuals with venous thrombosis under age 50;
- Myocardial infarction in female smokers under age 50.

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ACMG suggested that FVL testing may also be considered in the following situations:

- Venous thrombosis, age over 50, except when active malignancy is present;
- Relatives of individuals known to have FVL. Knowledge that they have the FVL mutation may influence management of pregnancy and may be a factor in decision-making regarding oral contraceptive use;
- Women with recurrent pregnancy loss or unexplained severe preeclampsia, placental abruption, intrauterine fetal growth retardation, or stillbirth. Knowledge of FVL carrier status may influence management of future pregnancies.

FVL testing is not recommended for the following:

- A general population screen;
- A routine initial test during pregnancy or prior to the use of oral contraceptives, hormone replacement therapy (HRT) or selective estrogen receptor modulators (SERMs);
- A prenatal or newborn test, or as a routine test in asymptomatic children;
- A routine initial test in individuals with arterial thrombosis (testing may be considered, however, in selected young individuals [under age 50] with unexplained arterial thrombosis in the absence of other risk factors for atherosclerotic vascular disease).

In 2013, (ACMG) published a practice guideline on the lack of evidence for MTHFR polymorphism testing. Among a number of recommendations, ACMG experts concluded:

- 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.

**Non-coverage Summary**

Genetic testing for inherited thrombophilias is controversial. While the association between FVL and F2 mutations and increased risk for VTE is apparent, the actual impact of this increased risk on clinical management is less certain. Older professional society guidelines recommend genetic testing for thrombophilia for a wide range of indications, while more recent consensus statements and recommendations suggest much more limited clinical utility of testing.

The population for which genetic testing results have direct implications for treatment is pregnant women with a previous history of VTE associated with a transient risk factor (e.g., surgery, trauma). These women would typically not be treated with antepartum anticoagulant prophylaxis unless they were found to have a genotype associated with a high risk of VTE recurrence (FVL homozygosity, F2 G20210A homozygosity, or compound heterozygosity for FVL and F2 G20210A). Genetic testing for these patients is indicated.

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There may also be benefit to screening pregnant women with a family history of known thrombophilia, as those women found to have a high risk genotype would be offered antenatal prophylactic anticoagulant therapy even in the absence of a personal history of VTE. However, the Medicare benefit applies only to patients with signs and symptoms of disease and does not include screening in asymptomatic patients.

Finally, despite many earlier publications suggesting a link between MTHFR polymorphisms and a risk for a wide spectrum of obstetric and cardiovascular complications, it is now accepted that MTHFR genotype alone is not associated with VTE. There is no clinical indication for MTHFR genotyping in any population.

There is insufficient evidence in the published peer-reviewed scientific literature to support coverage for genetic testing for inherited thrombophilias outside the pregnant women as described above. Genetic testing for FVL and F2 G20210A is considered investigational for all other indications. However, Medicare may consider coverage for FVL and/or F2 genetic testing in unusual circumstances where testing will change clinical management of the patient. Denied claims can be appealed with supporting evidence of specific medical necessity. Only providers with evidence of formal training with board eligibility or certification in hematology/oncology, hematopathology or coagulation disorders at an accredited program satisfy reasonable and necessary criteria for these tests. There is broad consensus in the medical literature that MTHFR genotyping has no clinical utility in any clinical scenario. This testing is considered investigational and is NOT a Medicare benefit..

**Documentation Requirements**

The patient's medical record must contain documentation that fully supports the medical necessity for services included within this LCD. (See “Coverage Indications, Limitations, and/or Medical Necessity") This documentation includes, but is not limited to, relevant medical history, physical examination, and results of pertinent diagnostic tests or procedures.

Documentation supporting the medical necessity should be legible, maintained in the patient's medical record, and must be made available to the J11 MAC upon request.

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There is a frequency associated with this test. Please refer to the Limitations or Utilization Guidelines section on previous page(s).

The ICD10 codes listed below are the top diagnosis codes currently utilized by ordering physicians for the limited coverage test highlighted above that are also listed as medically supportive under Medicare's limited coverage policy. **If you are ordering this test for diagnostic reasons that are not covered under Medicare policy, an Advance Beneficiary Notice form is required.**

| Code | Description |
|---|---|
| N/A | N/A |

Visit **QuestDiagnostics.com/MLCP** to view current limited coverage tests, reference guides, and policy information.

*To view the complete policy and the full list of medically supportive codes, please refer to the CMS website reference* www.cms.gov ▶

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**Disclaimer:**
This diagnosis code reference guide is provided as an aid to physicians and office staff in determining when an ABN (Advance Beneficiary Notice) is necessary. Diagnosis codes must be applicable to the patient's symptoms or conditions and must be consistent with documentation in the patient's medical record. Quest Diagnostics does not recommend any diagnosis codes and will only submit diagnosis information provided to us by the ordering physician or his/her designated staff. The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed.