



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject Genetic Testing for Factor V Leiden Thrombophilia**

**Effective Date ..... 12/15/2008**  
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**Coverage Policy Number .....0255**

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## Hyperlink to Related Coverage Policies

Genetic Counseling  
 Genetic Testing of Heritable Disorders  
 Recurrent Pregnancy Loss: Diagnosis and Treatment

### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2008 CIGNA

## Coverage Policy

**CIGNA covers genetic testing for factor V Leiden thrombophilia as medically necessary when ANY of the following criteria are met:**

- age ≤ 50, any history of unexplained venous thrombosis
- age ≤ 50 with unexplained arterial thrombosis in the absence of other risk factors for atherosclerotic vascular disease
- venous thrombosis in unusual sites (such as portal 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
- asymptomatic first-degree\* relatives of individuals with proven symptomatic thrombophilia
- myocardial infarction in female smokers under age 50
- recurrent pregnancy loss (i.e., two or more consecutive pregnancy losses)

\*A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children.

**All individuals undergoing genetic testing for any reason should have both pre- and post-test genetic counseling with a physician or a licensed or certified genetic counselor.**

**CIGNA does not cover genetic testing for factor V Leiden thrombophilia for the following indications, because they are considered not medically necessary (this list may not be all-inclusive):**

- as a general population screen
  - as a routine screening test during pregnancy or prior to the use of oral contraceptives, hormone replacement therapy (HRT), or selective estrogen receptor modulators (SERMs)
  - as a prenatal or newborn test, or as a routine test in asymptomatic children
  - as a routine initial test in individuals with arterial thrombosis
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## **General Background**

Factor V Leiden (FVL) is the most common inherited cause of thrombophilia. FVL thrombophilia is a mutation of the factor V gene which causes greater resistance to activated protein C (APC), resulting in increased thrombin generation and a hypercoagulable state. The FVL mutation is found in 5.27% of Caucasian Americans and progressively less in other racial groups. The frequency of heterozygotes is approximately 5–7% and of homozygotes approximately 0.02% (Spector, 2005).

FVL is characterized by an increased risk for venous thrombosis but can also be associated with pregnancy complications and recurrent pregnancy loss, as well as myocardial infarction in young female smokers. FVL is inherited in an autosomal dominant manner in heterozygotes and in an autosomal recessive manner in homozygotes (Spector, 2005). Both heterozygotes and homozygotes are at increased risk of occurrence or recurrence of venous thrombosis. Individuals who are heterozygous for the FVL mutation have a slightly increased risk of venous thrombosis (3–7 times); homozygous individuals have a much greater thrombotic risk (80 times). The absolute incidence of venous thrombosis in patients with the FVL mutation ranges from 0.19% per year to 0.45% per year, compared to 0.10% per year in individuals without the mutation (Kujovich, 2007). Asymptomatic first degree relatives of individuals with proven symptomatic thrombophilia have an absolute incidence of thrombosis of 1.7%/year and a fourfold greater relative risk of thrombosis (Kujovich, 2007; Nicolaides, 2005).

FVL is present in heterozygous form in approximately 12–20% of venous thromboembolism (VTE) patients (Press, et al., 2002). VTE is a common, complex disease with variable expressivity as well as genetic and environmental interactions. Its severity and age of onset may vary. Not all mutation carriers develop VTE. The exposure of mutation carriers to clinical (environmental) risk factors also compounds the possibility of VTE. Independent risk factors for VTE include older age, confinement to a hospital or nursing home, recent surgery that required anesthesia, trauma sufficient to necessitate hospitalization, malignant neoplasm (with or without chemotherapy), neurological disease along with chronic extremity paresis, superficial vein thrombosis, and prior central venous catheter or transvenous pacemaker insertion. Additional VTE risk factors for women include the use of oral contraceptives, hormone replacement therapy (HRT), and selective estrogen receptor modulators (SERM) (Heit, 2000).

Although it is unclear whether factor V Leiden causes risk of first trimester miscarriage, poor pregnancy outcomes and other possible serious maternal complications have been associated with the FVL mutation. Several authors recommend testing in women with recurrent pregnancy loss (Grody, et al., 2006; Rai, et al., 2002; Bloomenthal, et al., 2002; Cleary-Goldman, et al., 2003; Glueck, et al., 2007). The recommendations by the Royal College of Obstetricians and Gynaecologists (RCOG) (2003) state, “In the absence of randomized trials, the poor pregnancy outcome associated with factor V Leiden mutation, coupled with the maternal risks during pregnancy, may justify routine screening for factor V Leiden and offering thromboprophylaxis for those with the mutation and evidence of placental thrombosis.”

A consensus report and recommendation for prevention and treatment of venous thromboembolism and adverse pregnancy outcome (Duhl, et al., 2007) was published in November 2007 by the Pregnancy and Thrombosis Working Group. The authors acknowledged that no clear conclusions can be drawn from the studies they reviewed regarding an association between inherited thrombophilias and adverse pregnancy outcomes. According to the group, most of the research did demonstrate that FVL is not typically associated with pregnancy loss prior to 10 weeks’ gestation and that more evidence exists suggesting that a loss after 10 weeks’ gestation may be associated with these disorders.

## Testing Recommendations for FVL

The American College of Medical Genetics (ACMG) (Grody, 2006), recommends testing 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

Testing may also be considered in the following situations (Grody, 2006):

- venous thrombosis, age over 50, except when active malignancy is present
- relatives of individuals known to have factor V Leiden. Knowledge that they have factor V Leiden 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 factor V Leiden carrier status may influence management of future pregnancies.

FVL testing is not recommended for the following (Grody, 2006):

- a general population screen
- a routine initial test during pregnancy or prior to the use of oral contraceptives, HRT or SERM
- 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)

## Testing Strategy

When appropriate clinical care requires testing for FVL, either direct deoxyribonucleic acid (DNA)-based genotyping or an FVL-specific functional assay is recommended. Individuals who test positive by a functional assay should then be further studied with the DNA test for confirmation and to distinguish heterozygotes from homozygotes and those on heparin therapy, or with known lupus anticoagulant should proceed directly to molecular genetic testing if the modified functional assay is not used (Kujovich, 2007). The DNA method is recommended for testing relatives of individuals known to have FVL thrombophilia (ACMG, 2006).

## Literature Review

Marchiori et al. (2007) conducted a systematic review of prospective studies to assess the risk of recurrent VTE associated with heterozygous carriage of FVL and prothrombin G20210A (PTM) mutations. Eleven studies were included in the review, ten (seven prospective cohort studies and three randomized trials) of which examined the risk of recurrent VTE in heterozygous carriers of FVL. The studies included a total of 3203 patients, 557 of whom were heterozygous carriers of FVL. The duration of follow-up was 0.75 to 8.3 years. Recurrent thromboembolism occurred in 114 of the 557 heterozygous FVL carriers (20.5%) and in 382 of the 2646 non-carriers (14.4%). This data suggests that heterozygous carriers of the FVL mutation may have an increased risk of recurrent VTE when compared to non-carriers.

Wu et al. (2006) in the Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study performed a systematic review and meta-analysis to establish the risk of clinical complication associated with thrombophilia in women who used oral estrogen therapy, women who were pregnant and patients who had undergone major orthopedic surgery. They also measured the relative cost-effectiveness in universal and selective, history-based screening for thrombophilia. Eighty-one studies were included in the review, nine for oral estrogen, 72 for pregnancy and eight for orthopedic surgery. The authors reported the highest risk of VTE in oral contraception and hormone replacement therapy was in women with FVL (odds ratio (OR) 15.62 and 13.16 respectively). The meta-analysis suggested that during pregnancy, women with FVL were at a significantly higher risk to develop VTE and also to experience recurrent pregnancy loss (OR 2.06) or late pregnancy loss

(2.06). The OR for the association between FVL and postoperative VTE following hip or knee replacement surgery was 1.86. The authors found that regardless of patient group, selective screening based on the personal or family history of VTE was more cost-effective than universal screening in all four screening scenarios. The authors concluded, "Universal thrombophilia screening in women prior to prescribing oral estrogen preparations, in women during pregnancy and in patients undergoing major orthopedic surgery is not supported by the evidence. The findings from this study show that selective screening based on prior VTE history is more cost-effective than universal screening." The authors also recommended that large prospective studies be conducted to refine the risks and establish the association of thrombophilias and venous thromboembolism among hormone users and in patients undergoing orthopedic surgery.

Gonzalez-Porrás et al. (2006) studied the impact of the prothrombin G20210A mutation and the factor V Leiden mutation on recurrent deep vein thrombosis (DVT). The study prospectively monitored 259 patients after the first episode of DVT. The heterozygote FVL mutation was present in 29 patients (16%), heterozygote G20210A mutation in 21 patients (12%), and five patients had a double defect involving FVL and G20210A. Recurrent venous thrombosis developed in five of the 29 patients with FVL mutation, three of the 21 patients with G20210A mutation, and three of the five patients with the double defect. The authors concluded that the risk of recurrent venous thrombosis in patients who were heterozygous for FVL or G20210A alone was similar to patients who had neither mutation, but the risk was high in patients carrying the double defect.

Lalouschek et al. (2005) reported on the role of factor V Leiden in arterial thrombosis. In total, 468 consecutive patients with an acute ischemic stroke or transient ischemic attack (TIA) before age 60 were included in the study. In men, 4% of the patients and 7% of the controls had FVL. In women, 10% of the patients and 6% of the controls were FVL carriers. The authors reported the risk of stroke increased 8.8 fold in women who had FVL and smoked. This study suggested that there may be a significant increase in the risk of ischemic cerebrovascular events in women up to 60 years of age who smoked and had the FVL mutation.

Nicolaides et al. (2005), in the International Consensus Statement for Thrombophilia and Thromboembolism, provided guidelines for investigation and management of patients with thrombophilia with or without venous thromboembolism (VTE). According to the authors, heterozygote factor V Leiden is found in 0–15% of the normal population, 20% of patients with venous thrombosis and in 40% of families with thrombophilia, whereas the homozygote factor V Leiden mutation is found in only 0.02% of the normal population, but the relative risk is high. The authors researched the etiology, testing, diagnosis, risk factors, prevention and management of thrombophilia. Based on this research, the authors concluded that screening for thrombophilia should occur in:

- all patients with a first episode of spontaneous VTE
- patients with VTE under the age of 50, even with a transient predisposing factor
- patients with VTE whose only risk factor is oral contraceptive therapy or pregnancy. However, screening with other than the molecular tests should be performed at least two weeks after delivery or hormone therapy cessation.
- patients with recurrent VTE, irrespective of the presence of risk factors
- patients with recurrent superficial thrombophlebitis without cancer in the absence of varicose veins
- patients with VTE at unusual sites such as cerebral venous sinus, mesenteric or hepatic veins, and retinal vein occlusion under the age of 50
- patients with warfarin-induced skin necrosis and neonates with purpura fulminans not related to sepsis
- asymptomatic first-degree relatives of individuals with proven symptomatic thrombophilia. The authors felt this was particularly important for females in the child-bearing years.
- two consecutive or three nonconsecutive abortions at any gestational age, or one fetal death after week 20
- severe preeclampsia
- children with VTE

Kim et al. (2003) conducted a meta-analysis of published case-control and cohort studies to determine the influence of factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase C677T (MTHFR C677T) mutations on the arterial circulatory system. A total of 56 studies (54,547 patients) were reviewed. Thirty-three studies, including 25,053 patients, involved the association of factor V Leiden and arterial ischemic events. The overall OR was 1.21. Specifically, the relationships with myocardial infarction (MI), ischemic stroke, and peripheral vascular disease (PVD) were 1.10, 1.27, and 0.91, respectively. According to

the authors, the studies demonstrated that patients under 50 years of age were at a greater risk for arterial ischemic events than older patients with the factor V Leiden mutation. The authors found that of the studies that reported male and female patients, arterial ischemic events occurred more frequently in women with factor V Leiden mutations. The authors concluded that the association between these specific inherited mutations and acute arterial thrombosis is modest and, therefore, routine screening is not warranted. They suggested testing for these mutations should be restricted to “patients less than 55 years of age, particularly in the absence of traditional atherosclerosis risk factors, women receiving oral contraceptives or hormone replacement therapy, patients with early saphenous vein graft occlusion or when paradoxical embolism is strongly suspected.”

### Professional Societies/Organizations

The American Heart Association (2003) published a statement supporting the ACMG guidelines. “Patients who develop a DVT or pulmonary embolism (PE) and are from a family with a confirmed factor V Leiden diagnosis should be tested. Likewise, even if there is no family history of factor V Leiden, anyone who has had a DVT or PE that is unexplained, recurrent, occurred at a young age (under 50), occurred during pregnancy, was associated with hormone use, or developed in an unusual site (such as the veins of the brain or abdomen) may benefit from testing for factor V Leiden and other causes of hereditary thrombophilia.”

The 7th American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy Evidence Based Guidelines states the results of the evidence for maternal thrombophilia and pregnancy complications are inconsistent. The guidelines referenced a recent meta-analysis which indicated there was an association between fetal loss and factor V. Their recommendations for women with recurrent spontaneous abortion, second trimester miscarriage, or a history of intrauterine fetal death are that patients should be screened for underlying congenital thrombophilias (Bates, 2004).

The National Society of Genetic Counselors for Recurrent Miscarriage (Laurino, et al., 2005) reported that the evidence supports testing for FVL.

### Summary

Factor V Leiden (FVL) is the most common inherited cause of thrombophilia. Although there are no clinical features specific for FVL, it is suspected in individuals with a history of venous thromboembolism (VTE) or pulmonary embolism and in families with a high incidence of VTE. Diagnosis of the FVL mutations may assist in the prevention and proper treatment of VTE.

Based on evidence in the published, peer-reviewed scientific literature, and the position of professional specialty organizations, testing for FVL may be appropriate for unexplained recurrent pregnancy loss.

## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary:**

CPT®*	Description
	Multiple/varied

HCPCS Codes	Description
S3843	DNA analysis of the F5 gene for susceptibility to Factor V Leiden thrombophilia

ICD-9-CM Diagnosis Codes	Description
	Multiple/varied

\*Current Procedural Terminology (CPT®) © 2007 American Medical Association: Chicago, IL.

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## Policy History

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<b><u>Pre-Merger Organizations</u></b>	<b><u>Last Review Date</u></b>	<b><u>Policy Number</u></b>	<b><u>Title</u></b>
CIGNA HealthCare	12/15/2007	0255	Genetic Testing for Factor V Leiden Thrombophilia

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.