



# 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 ..... 12/15/2010**  
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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 ©2010 CIGNA

## Coverage Policy

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

- diagnostic testing in ANY of the following situations:
  - 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
  - myocardial infarction in female smokers under age 50
  - recurrent pregnancy loss (i.e., two or more consecutive pregnancy losses)
- predictive testing in asymptomatic first-degree\* relatives of individuals with proven symptomatic thrombophilia

\*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) mutation (i.e., Arg506Gln) is the most common heritable prothrombotic risk factor in the United States (Agency for Healthcare Research and Quality [AHRQ], 2009). The mutation is a change in the gene coding for the factor V protein; which results in the elimination of one of three activated protein C (APC) cleavage sites in factor V. As a result, factor V is inactivated to a lesser extent and persists longer in the circulation, leading to more thrombin generation (AHRQ, 2009). This leads to an increased tendency to form abnormal clots in the blood vessels. The Leiden mutation accounts for 90% to 95% of APC resistance. The clinical expression of the FVL mutation is variable, however. Many individuals with the FVL allele never develop thrombosis (GeneReviews, 2010).

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 (i.e., 2-10- fold risk) (AHRQ, 2009; Deitcher, 2009; American College of Medical Genetics [ACMG], 2006). This risk is further increased in combination with pregnancy (9-fold), oral contraceptive use (36-fold), hormone replacement therapy (13- to 16-fold), and is a risk factor for myocardial infarction in young women who smoke (i.e., >30-fold risk) (Deitcher, 2009). Individuals homozygous for the FVL mutation have an 18-80 times greater risk of venous thromboembolism (VTE) (GeneReviews, 2010; Deitcher, 2009).

VTE is a common, complex disease with variable severity, age of onset and interaction with genetic and environmental factors. The exposure of mutation carriers to environmental risk factors compounds the possibility of VTE. Predisposing factors include: travel, older age, central venous catheter use, pregnancy, organ transplantation, injury, and surgery. These predisposing factors are associated with the first thrombotic episode in at least 50% of individuals with a factor V Leiden allele (GeneReviews, 2010). Additional VTE risk factors for women include the use of oral contraceptives, hormone replacement therapy (HRT), and selective estrogen receptor modulators (SERM) (GeneReviews, 2010; Heit, 2000).

The FVL gene polymorphism is the most common inherited genetic disorder among pregnant women with a history of VTE, occurring in approximately 44% of cases (Laubach, 2008). It has been associated with risk of first trimester miscarriage, poor pregnancy outcomes and other possible serious maternal complications. A progressive decrease in activated protein C during pregnancy compounds the prothrombotic effect of the FVL mutation. Women with FVL mutation can develop placental thrombosis and, in turn, complications associated with placental hypoxia such as preeclampsia and hemolysis, elevated liver enzymes and low platelets (HELLP), placental abruption, intrauterine growth restriction, stillbirth, and possibly first trimester miscarriage.

Decisions on testing and prophylactic treatment for thrombophilic disorders should be based on a risk/benefit assessment. To ensure proper risk stratification and therapeutic management, testing may be recommended in women who present with either a family or personal history of VTE, or with recurrent pregnancy loss (Laubach, 2008; Grody, 2006; Rai, 2002; Bloomenthal, 2002; Cleary-Goldman, 2003; Glueck, 2007). 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 (GeneReviews, 2010).

### **Genetic Testing for Factor V Leiden (FVL)**

The diagnosis of factor V Leiden (FVL) thrombophilia is made either using a coagulation screening test or by deoxyribonucleic acid (DNA) analysis of the F5 gene, which encodes the factor V protein (GeneReviews, 2010). Genetic tests for FVL have a 98-100% analytical validity and accurately predict the presence of the FVL gene mutation (Agency for Healthcare Research and Quality [AHRQ], 2009). The conventional "gold standard" method for FVL detection is the sequencing of the specific genetic region of the gene of interest. Because of the complexity and high costs associated with sequencing, a number of other reference methods are used (AHRQ, 2009). 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. 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). While technically possible, prenatal testing does not seem relevant for this complex disorder, in which the genetic change is common in the general population and is predisposing to, but not predictive of, thrombosis (GeneReviews, 2010).

### **Clinical Utility of Genetic Testing for FVL**

A number of professional societies/organizations endorse genetic testing to determine the presence of the FVL mutation as an option to inform treatment. Testing for the mutation allows for prophylactic and/or ongoing clinical management including thromboprophylaxis and/or modification of risk factors, if appropriate. Potential consequences of identifying a thrombophilic defect in a patient with venous thromboembolism (VTE) include prolonging the anticoagulant therapy beyond three-six months, or prescribing a more aggressive thromboprophylaxis in at-risk situations such as surgery, pregnancy or prolonged immobility (Roldan, 2009). Genetic testing for the FVL mutation is considered appropriate for selected individuals.

**Federal Drug Administration (FDA):** The FDA has given 510K approval to several DNA-based laboratory tests designed to test for FVL including the INFINITI System Assay (AutoGenomics, Inc., 2007, Carlsbad, CA) and the LightCycler (PCR) Instrument Version 1.2 (Roche Applied Sciences, 2003, Indianapolis, IN).

### **Literature Review**

Rodgers et al. (2010) reported results of a meta-analysis and systematic review of prospective cohort studies to estimate the association of maternal FVL or prothrombin gene mutation (PGM) carrier status and placenta mediated pregnancy complications. The findings demonstrated that FVL is likely weakly associated with pregnancy loss and that neither FVL nor PGM are associated with pre-eclampsia or birth of a small for gestational age (SGA) infant. The authors note further research is required to determine if FVL or PGM are associated with placental abruption and whether PGM is associated with important increases in pregnancy loss. The study demonstrated that the odds of pregnancy loss in women with FVL appears to be 52% higher as compared with women without FVL; however, the absolute event rate for pregnancy loss is low in women with FVL compared with those with the FVL mutation (4.2% versus 3.2%, respectively).

On behalf of the AHRQ, Segal et al. (2009) published an evidence report/technology assessment that reviewed evidence from 124 studies to determine whether FVL testing alone, or in combination with prothrombin G20210A leads to improved clinical outcomes in adults with a personal history of venous thromboembolism (VTE), or in adult family members of mutation-positive individuals. The authors reported that there was no direct evidence in the studies that addressed this primary objective. The AHRQ noted the assays used in the studies reviewed have high analytical validity. Heterozygosity and homozygosity for FVL in probands are predictive of recurrent VTE (odds ratio [OR] =1.56, and 2.65, respectively). Heterozygosity for FVL predicts VTE in family members (OR=3.5) as does homozygosity for FVL (OR=18). There was high-grade evidence that anti-coagulation reduces recurrent events in probands with FVL or prothrombin G20210A; there was low-grade evidence that the relative reduction with treatment is comparable to that seen in individuals without mutations. There was moderate evidence to support the conclusion that neither harms nor benefits of testing have been demonstrated conclusively. A single study supported the hypothesis that clinicians might change management based on test results. Decision-analysis models suggest that testing may be cost-effective in select individuals.

Biron-Andreani et al. (2009) reported results of a systematic review and a meta-analysis of the literature to estimate precisely the association of the FVL mutation with the risk of first, or recurrent, pregnancy-related venous thromboembolism. The risk of late fetal loss was higher in women who were homozygous compared with those who were non-carriers (13.7% versus 1.4%, respectively, odds ratio 11.41). It was similar in women

who were heterozygous and in non-carriers (3.1% versus 1.4%,  $p=0.68$ ). The percentage of women with early fetal loss was similar in the three groups ( $p=0.81$ ). The live-birth rate was 80%, 84%, and 85%, respectively, for women who were homozygous, heterozygous, and non-carriers ( $p=0.88$ ).

Marchiori et al. (2007) conducted a systematic review of prospective studies to assess the risk of recurrent venous thromboembolism (VTE) associated with heterozygous carriage of factor V Leiden (FVL) and prothrombin G20210A (PTM) mutations. The studies included a total of 3203 patients, 557 of whom were heterozygous carriers of FVL. 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. 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) performed a systematic review and meta-analysis (i.e., Thrombosis: Risk and Economic Assessment of Thrombophilia Screening [TREATS]) to establish the risk of clinical complication associated with thrombophilia in women who used oral estrogen therapy, women who were pregnant, and individuals who had undergone major orthopedic surgery. The study also measured the relative cost-effectiveness in universal and selective, history-based screening for thrombophilia. Eighty-one studies were included in the review. The authors reported the highest risk of VTE in individuals who used oral contraception and hormone replacement therapy was in women with FVL (odds ratio [OR] 15.62 and 13.16 respectively). The meta-analysis also suggested that during pregnancy, women with FVL were at a significantly higher risk to develop VTE and 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. They 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."

Gonzalez-Porrás et al. (2006) studied the impact of the prothrombin G20210A and FVL mutations 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. 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 FVL in arterial thrombosis. Four hundred sixty-eight consecutive patients with an acute ischemic stroke or transient ischemic attack before age 60 were included in the study. The authors reported the risk of stroke increased 8.8 fold in women who had FVL and smoked. This study suggests that there may be a significant increase in the risk of ischemic cerebrovascular events in this cohort of women.

Kim et al. (2003) conducted a meta-analysis of published case-control and cohort studies to determine the influence of FVL, 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 FVL and arterial ischemic events. The overall odds ratio (OR) was 1.21. Specifically, the relationships with myocardial infarction, ischemic stroke, and peripheral vascular disease were 1.10, 1.27, and 0.91, respectively. The studies demonstrated that individuals <50 years with the FVL mutation were at a greater risk for arterial ischemic events compared with older individuals with the FVL mutation. The authors also found that of the studies that reported male and female patients, arterial ischemic events occurred more frequently in women with FVL 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**

**American College of Chest Physicians (ACCP):** The 7<sup>th</sup> 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 Leiden (FVL). 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. Due to the increased risk, antithrombotic therapy should be considered in these patients (Bates, 2004).

**American College of Medical Genetics (ACMG):** On behalf of the ACMG, Grody et al. (2006) recommended 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:

- venous thrombosis, age over 50, except when active malignancy is present
- relatives of individuals known to have FVL. Knowledge that they have FVL 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)

**American College of Obstetricians and Gynecologists (ACOG):** Clinical Management Guidelines regarding inherited thrombophilias in pregnancy (2010) note based on limited or inconsistent scientific evidence inherited thrombophilia testing in women who have experienced recurrent fetal loss or placental abruption is not recommended because it is unclear whether anticoagulation reduces recurrence. The Guidelines also noted that there is insufficient evidence to recommend screening or treatment for thrombophilias in women with previous intrauterine growth restriction or preeclampsia.

Recommendations based primarily on consensus and expert opinion note screening for inherited thrombophilias should include FVL mutation; prothrombin G20210A mutation; and antithrombin, protein C, and protein S deficiencies. Additionally all patients with inherited thrombophilias should undergo individualized risk assessment, which may modify management decisions.

**American Heart Association (AHA):** The AHA (2003) published a statement supporting the ACMG guidelines. "Patients who develop a deep vein thrombus (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 FVL, 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 FVL and other causes of hereditary thrombophilia."

**Pregnancy and Thrombosis Working Group:** A consensus report and recommendation for prevention and treatment of VTE and adverse pregnancy outcome (Duhl, et al., 2007) was published in 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—some studies show a positive relationship, and other studies show no relationship. According to the group, most of the research did demonstrate that factor V Leiden (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.

**European Genetics Foundation, the Cardiovascular Disease Educational and Research Trust, the Mediterranean League on Thromboembolism, and the International Union of Angiology:** Nicolaidis 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 FVL 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 FVL 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

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

**Royal College of Obstetricians and Gynaecologists (RCOG):** The RCOG (2004) notes that thrombophilia screening, including FVL if activated protein C (APC) resistance is abnormal, should be considered in patients with personal or family (first- or second-degree family member) history of venous thrombus embolism who are taking or considering taking hormone replacement therapy. Universal screening is not recommended.

### Summary

Factor V Leiden (FVL) is the most common inherited cause of thrombophilia in the U.S. 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 mutation may assist in the prevention and proper treatment of VTE. Based on evidence in the published, peer-reviewed scientific literature, and the consensus guidelines/statements of professional specialty organizations, testing for FVL may be appropriate for selected individuals.

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## Coding/Billing Information

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

**Covered when medically necessary:**

<b>CPT®*</b> <b>Codes</b>	<b>Description</b>
83890	Molecular diagnostics; molecular isolation or extraction, each nucleic acid type (ie, DNA or RNA)
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie, DNA or RNA)
83892	Molecular diagnostics; enzymatic digestion, each enzyme treatment
83894	Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide), each nucleic acid preparation
83896	Molecular diagnostics; nucleic acid probe, each
83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
83903	Molecular diagnostics; mutation scanning, by physical properties (eg, single strand conformational polymorphisms [SSCP], heteroduplex, denaturing gradient gel electrophoresis [DGGE], RNA'ase A), single segment, each
83904	Molecular diagnostics; mutation identification by sequencing, single segment, each segment
83908	Molecular diagnostics; amplification, signal, each nucleic acid sequence
83912	Molecular diagnostics; interpretation and report

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

<b>ICD-9-CM</b> <b>Diagnosis</b> <b>Codes</b>	<b>Description</b>
410.00-410.92	Acute myocardial infarction
444.0-444.9	Arterial embolism and thrombosis
452	Portal vein thrombosis
453.0-453.9	Other venous embolism and thrombosis
557.0	Acute vascular insufficiency of intestine
634.00-634.92	Spontaneous abortion
646.30	Habitual aborter, unspecified as to episode of care or not applicable
646.33	Habitual aborter, antepartum condition or complication
671.50-671.54	Other phlebitis and thrombosis in pregnancy and the puerperium
V12.51	Personal history of venous thrombosis and embolism

**Experimental/Investigational/Unproven:**

<b>ICD-9-CM</b> <b>Diagnosis</b> <b>Codes</b>	<b>Description</b>
V78.8	Special screening for other disorders of blood and blood-forming organs
V78.9	Special screening for unspecified disorder of blood and blood-forming organs
V82.71	Screening for genetic disease carrier status
V82.79	Other genetic screening
	All other codes

\*Current Procedural Terminology (CPT®) ©2010 American Medical Association: Chicago, IL.

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## Policy History

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

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