Factor V Leiden Testing for Thrombophilia

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

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<th>Procedure addressed by this guideline</th>
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What is Factor V Leiden thrombophilia

Definition

About 1 in 1000 people in the U.S. experiences a first venous thromboembolism (VTE) each year, and about one-third of symptomatic patients will develop pulmonary embolism (PE). VTE is a multifactorial condition, usually arising from a combination of genetic, acquired and circumstantial events and risk factors.

- A variant in the factor V gene (F5), called factor V Leiden (FVL), is the most common genetic risk factor for thrombophilia (hypercoagulability) among Caucasians.
  - F5 plays a critical role in forming blood clots.
  - A molecule called activated protein C (APC) keeps the size of clots in check by turning off F5 when clots have formed completely.
  - The FVL variant prevents APC from inactivating F5, increasing the chance of developing abnormal blood clots.
  - The FVL variant is one of several changes in the F5 gene that are reportedly linked to an increase risk of blood clotting.

- The risk for FVL-related thrombosis depends on whether one or two FVL variants are present and additional risk factors, such as prothrombin gene variants.
  - A single FVL variant increases the risk for initial VTE up to 3-8 fold. Two FVL variants increases the risk more dramatically at 18-80 fold. While the risk of subsequent VTE is significantly increased in anyone with a history of VTE, the risk for recurrent VTE attributable to a FVL variant after a first event is much more modest with a pooled odds ratio of 1.56 for single variant and 2.65 for two variants.
The increased risk for pregnancy-related VTE is estimated at 8 fold with a single FVL variant and 20-40 fold with two variants.\textsuperscript{3}

The risk for oral contraceptive-related VTE is estimated at 16 fold with a single FVL variant and over 100 fold with two variants.\textsuperscript{3}

FVL mutations have also appeared to have a small but significant association with some poor pregnancy outcomes in retrospective studies. However, more recent prospective data does not support an increased incidence of pregnancy loss among those with an FVL variant.\textsuperscript{5} There has been conflicting evidence about the association of these variants with other pregnancy complications, such as severe preeclampsia, intrauterine growth restriction, and placental abruption.\textsuperscript{3,5}

Inheriting an FVL variant with other genetic risk factors also significantly increases the risk for developing VTE. For example, inheriting both a single FVL variant and a single prothrombin variant appears to increase the risk for VTE 20 fold.\textsuperscript{3}

- The frequency of FVL varies by ethnicity with about 5\% of Caucasians, 2\% of Hispanics, and 1\% of African Americans in the US having one FVL variant.\textsuperscript{4} About 1 in 1500 Caucasian people have two variants.\textsuperscript{4}

### Test information

- Factor V Leiden genotyping looks specifically for the Leiden variant (1691G>A; R506Q) in the F5 gene. The detection rate for genotyping is virtually 100\%.\textsuperscript{3} Genotyping can determine how many Leiden variants a person has and therefore can provide information about relative risk of clotting. Understanding the number of Leiden variants in a suspected case is essential for proper diagnosis and management.

- In addition to factor V Leiden genotyping, the modified APC resistance assay is available to detect factor V Leiden thrombophilia. This assay makes use of the fact that the Leiden variant creates a protein that resists inactivation by activated protein C (APC). The APC resistance assay is effective, but does not determine how many copies of the Leiden variant are present. Therefore, if positive, factor V Leiden genotyping is recommended to confirm the findings and quantify the number of variants present.\textsuperscript{3}

- Proposed uses for a positive test result include:
  - Treatment decisions for preventing recurrent VTE in an affected person
  - Primary prevention of VTE in at-risk relatives
  - Decisions about use of oral contraceptives, hormone replacement therapy, or other estrogen-containing therapies
Management decisions for preventing VTE or other possibly associated complications in pregnancy

Guidelines and evidence

- Early consensus statements from the American College of Medical Genetics (ACMG, 2001)\(^6\) and the College of American Pathologists (CAP, 2002)\(^7\) recommended factor V Leiden (FVL) variant testing in the populations most likely to have a mutation. These included:
  - VTE at a young age (<50 years)
  - Recurrent VTE
  - Unusual VTE site, such as those involving the hepatic, portal, mesenteric, or cerebral veins
  - VTE associated with pregnancy or oral contraceptive use
  - VTE associated with hormone replacement therapy, selective estrogen receptor modulators (SERMs), or tamoxifen
  - Personal and close family history of VTE
  - Unprovoked VTE at any age
  - Family history of VTE at a young age (<50 years)

- An Agency for Health Care Research and Quality (AHRQ, 2009) supported systematic review found that, while variant analysis is effective at identifying FVL variants, “the incremental value of testing individuals with VTE for these mutations is uncertain. The literature does not conclusively show that testing individuals with VTE or their family members for FVL or prothrombin G20210A confers other harms or benefits. If testing is done in conjunction with education, it may increase knowledge about risk factors for VTE.” \(^8\)

- The Evaluation of Genomic Applications in Practice and Prevention (EGAPP, 2011), an initiative of the CDC Office of Public Health Genomics, evaluated the clinical utility evidence for two limited scenarios:
  a) anticoagulation duration to prevent recurrence in people with idiopathic VTE and
  b) primary VTE prevention in their at-risk relatives. They specifically exclude individuals with other risk factors for VTE, such as estrogen-containing therapy use. EGAPP makes the following recommendations:\(^4\)
    - [EGAPP] found adequate evidence to recommend against routine testing for Factor V Leiden (FVL) and/or prothrombin 20210G>A (PT) in the following circumstances: (1) 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.
(2) Asymptomatic adult family members of patients with VTE and an FVL or PT mutation, for the purpose of considering primary prophylactic anticoagulation. Potential benefits are unlikely to exceed potential harms.

- Because anticoagulation is associated with significant risks and these mutations are associated with relatively low absolute VTE risk, the potential harms of overtreatment in these scenarios appears to outweigh the benefits of testing. However, test results may be used for other treatment decisions, such as anticoagulation in high-risk situations (e.g., surgery, pregnancy, long-distance travel), avoidance of estrogen-containing therapies, or the use of low-risk preventive measures (e.g., compression hose, activity counseling, smoking cessation). The authors noted that the evidence was insufficient to determine if testing might have utility in some situations, such as for influencing patient behavior or identifying those with homozygous mutations or combined thrombophilias. Therefore, these findings have limited application to the broader decision about who should be tested.

- Several other organizations have issued guidelines that help inform a decision about clinical utility by defining the change, or lack of change, in management of patients with known FVL thrombophilia in specific clinical circumstances.

  - VTE management:
    - The American College of Chest Physicians (ACCP, 2008) recommends the same management for unprovoked VTE or VTE associated with a transient (reversible) risk factor (such as estrogen-containing therapies) irrespective of FVL results.⁹
    - These guidelines add “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 determinants of the risk of recurrence.” ⁹
    - Also note that the above referenced EGAPP (2011) study specifically addresses this test use and finds “There is no evidence that knowledge of FVL/PT mutation status in patients with VTE affects anticoagulation treatment to avoid recurrence.” “There is convincing evidence that anticoagulation beyond 3 months reduces recurrence of VTE, regardless of mutation status.” ⁴
  
  - Pregnancy management:
    - The American College of Chest Physicians (ACCP, 2008) recommends the same management for VTE in a current pregnancy or for those with a prior VTE history during or outside of pregnancy irrespective of FVL results. However, if a higher risk thrombophilia is present, such as two Leiden variants or a combination of a Leiden and prothrombin variant, ACCP recommends some form of treatment and not simply surveillance.¹⁰
Thrombophilia in pregnancy guidelines from the American College of Obstetricians and Gynecologists (ACOG, 2013) state:

- Testing is controversial and is “is useful only when results will affect management decisions, and is not useful in situations where treatment is indicated for other risk factors.” However, they add that screening “may be considered” for those with “A personal history of venous thromboembolism that was associated with a non-recurrent risk factor (e.g. fractures, surgery, and prolonged immobilization). The recurrence risk among untreated pregnant women with such a history and a thrombophilia was 16% (odds ratio, 6.5; 95% confidence interval, 0.8–56.3).”

- They add “Testing for inherited thrombophilias in women who have experienced recurrent fetal loss or placental abruption is not recommended because it is unclear if anticoagulation therapy reduces recurrence. Although there may be an association in these cases, there is insufficient clinical evidence that antepartum prophylaxis with unfractionated heparin or low molecular weight heparin (LMWH) prevents recurrence in these patients”

-o Estrogen-containing therapy decisions:

- American College of Obstetricians and Gynecologists (ACOG, 2006) contraceptive use guidelines state “Combination contraceptives are not recommended for women with a documented history of unexplained venous thromboembolism or venous thromboembolism associated with pregnancy or exogenous estrogen use, unless they are taking anticoagulants.” Therefore, estrogen-containing drugs are contraindicated based on a history of VTE alone irrespective of FVL results.

- American Association of Clinical Endocrinologists (AACE, 2011) menopause guidelines says only the following about menopausal hormone therapy (MHT): “Estrogen therapy has been associated with an increased risk of venous thromboembolic disease within 1 to 2 years after initiation of therapy. The increased relative risk (RR) is high, but the increased absolute risk is quite small…The incidence was greater with increasing age, obesity, and factor V Leiden mutations (45 [EL 1; RCT]). Women with a history of venous thromboembolic disease should be carefully advised about this risk when MHT is being considered.”

-o Family history of a Leiden variant:

- The above referenced EGAPP (2011) statement specifically addresses this test use for VTE prophylaxis and found “There is no evidence that knowledge of FVL/PT mutation status among asymptomatic family members of patients with VTE leads to anticoagulation aimed at avoiding initial episodes of VTE.”
American College of Obstetricians and Gynecologists (ACOG, 2010) states that testing is controversial and should only be done when the results will change management. However, they add that screening “may be considered” for those with “A first-degree relative (eg, parent or sibling) with a history of high-risk thrombophilia.”

Generally, estrogen-containing drugs must be approached with caution in anyone with a significant family history of VTE or known FVL and/or PT mutations, but no US evidence-based guidelines were identified that addressed testing in this scenario. Guidelines from the British Society for Haematology (BSH, 2010) most directly address FVL and PT testing in at-risk relatives for the purposes of deciding about estrogen-containing therapies. They recommend considering “alternative contraceptive or transdermal HRT [hormone replacement therapy]” when a first-degree relative: “has not been tested or is negative… Testing for heritable thrombophilia will provide an uncertain estimate of risk and is not recommended (1C).” or “has been tested and the result is positive… Offer alternative contraception, counsel that negative result would not exclude increased risk. However, testing may assist in counseling of selected women particularly if a high risk thrombophilia has been identified in the symptomatic relative (C).”

The evidence supporting an association between FVL variants and thrombosis is adequate (clinical validity). However, there are no clinical situations in which FVL testing is either mandatory or specifically recommended in guidelines due to generally insufficient clinical utility data. Factor V Leiden genotyping may have some utility in limited circumstances where there is a recognized increased risk to have at least one mutation based on established risk factors, where the results will be used to direct management beyond the current VTE, and particularly when individuals are found to have a combination of more than one factor V Leiden mutation or additional genetic thrombophilias (despite the absence of reliable indicators). If testing is performed, there should be a specific plan for how the results will impact management.

Criteria

Introduction

Requests for Factor V Leiden are reviewed using these criteria.

- Genetic Counseling
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- Previous Genetic Testing:
No previous genetic testing for Factor V Leiden mutation, AND

- Individual has at least one of the following risk factors suggesting a higher likelihood of having one or more factor V Leiden variants:
  - Unprovoked/idiopathic venous thromboembolism at any age, or
  - History of recurrent venous thromboembolism, or
  - Venous thrombosis at an unusual site (e.g., cerebral, mesenteric, hepatic, and portal veins), or
  - Venous thromboembolism during pregnancy or the puerperium, or
  - Venous thromboembolism associated with the use of estrogen-containing therapies (e.g., oral contraceptives or hormone replacement therapy), or
  - A personal history of any venous thromboembolism combined with a first-degree family member with venous thromboembolism before the age of 50 years, AND

- Test results will be used for guiding management decisions beyond simply therapy of a current first venous thrombosis event or related future prophylaxis decisions, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

The following factor V Leiden genotyping test applications are specifically considered investigational and/or experimental:

- Testing without clear evidence of an increased likelihood of having at least one factor V Leiden variant. This includes but is not limited to:
  - Testing performed as part of expanded cardiovascular disease screening
  - Testing based on the presence of conditions with unclear evidence including stroke, myocardial infarction, pregnancy loss, and pregnancy complications

**Benefit exclusion**

**Exclusions and other considerations**

Testing unaffected individuals (e.g. carrier testing, predictive testing, presymptomatic testing, etc) is a BCBSAZ benefit exclusion and, therefore, not eligible for reimbursement.

**References**


12. Goodman NF, Cobin RH, Ginzburg SB, Katz IA, Woode DE; American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of