Factor II/Prothrombin 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.

<table>
<thead>
<tr>
<th>Procedure addressed by this guideline</th>
<th>Procedure code</th>
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</thead>
<tbody>
<tr>
<td>F2 Targeted Mutation Analysis</td>
<td>81240</td>
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</tbody>
</table>

What is prothrombin thrombophilia

Definition

Prothrombin thrombophilia is a genetic disorder that increases one’s risk for developing abnormal blood clots (venous thromboembolism or VTE).¹

- Prothrombin thrombophilia is caused by a genetic change, or mutation, in the F2 gene called G20210A (20210G>A or c.*97G>A).¹⁻³
  - The F2 gene produces a protein that helps to initiate the formation of blood clots.¹
  - The prothrombin mutation is a gain of function mutation that shifts the F2 gene into overdrive, increasing one’s risk of VTE.¹
  - The prothrombin mutation is one of several mutations linked to an increase risk for blood clotting.²⁻³
- The formation of abnormal blood clots can lead to conditions like deep vein thrombosis (DVT) and pulmonary embolism.¹⁻²
- There has been conflicting evidence about the association of inherited thrombophilias and other pregnancy complications, such as severe preeclampsia, intrauterine growth restriction, and placental abruption.⁴⁻⁵
- About 1-3% of the European population have at least one prothrombin mutation.¹⁻²⁻⁴
  - Inheriting one prothrombin mutation (heterozygous) increases one’s risk for developing VTE approximately 2-fold to 4-fold compared to non-carriers.¹⁻⁶
  - First-degree relatives of an individual who is heterozygous for the G20210A mutation are at 50% risk of carrying the same mutation.⁷
Inheriting two prothrombin mutations (homozygous) is rare. The prevalence among the general population is 0.001-0.012% and 0.2-4% among individuals with VTE. The annual risk of VTE in homozygous is not clear but has been reported to be approximately 1.1%/year.\(^8\)

Inheriting a prothrombin mutation with other genetic risk factors such as Factor V Leiden also significantly increases the risk for developing VTE.\(^1,8\)

- Definitive diagnosis of prothrombin thrombophilia relies on both clinical and genetic testing.\(^2,3\)

### Test information

- Factor II/prothrombin analysis looks for the G20210A mutation, and determines how many copies of that mutation are present.\(^2,3\) Understanding the number of prothrombin mutations in a suspected case is essential for proper diagnosis, management, and screening. The detection rate for prothrombin mutation analysis is virtually 100%.\(^2,5\)

- Individuals with the prothrombin mutation often have mildly elevated prothrombin levels. These levels can be measured directly in suspected cases of prothrombin thrombophilia.\(^2\) However, levels vary among individuals and even overlap significantly with the normal range.\(^2\) Prothrombin levels are therefore not reliable for the diagnosis of prothrombin thrombophilia, and mutation analysis remains the best choice for definitive diagnosis.\(^2\)

### Guidelines and evidence

- Thrombophilia in pregnancy guidelines from the American College of Obstetricians and Gynecologists (ACOG 2018) state:\(^4\)
  
  - “Screening for inherited thrombophilias is useful only when results will affect management decisions, and it is not useful in situations in which treatment is indicated for other risk factors."

  - Targeted assessment for inherited thrombophilia may also be considered in the following clinical scenarios: A personal history of VTE, with or without a recurrent risk factor, and no prior thrombophilia testing and a first-degree relative (e.g., parent or sibling) with a history of high-risk inherited thrombophilia. In this setting, targeted testing for the known thrombophilia can be considered if testing will influence management.

  - “Among women with personal histories of VTE, recommended screening tests for inherited thrombophilias should include factor V Leiden mutation; prothrombin G20210A mutation; and antithrombin, protein S, and protein C deficiencies.”
“Screening for inherited thrombophilias is not recommended for women with a history of fetal loss or adverse pregnancy outcomes including abruption, preeclampsia, or fetal growth restriction because there is insufficient clinical evidence that antepartum prophylaxis with unfractionated heparin or low-molecular-eight heparin prevents recurrence in these patients.”

Consensus guidelines from the College of American Pathologists (CAP, 2002) related to diagnostic issues in thrombophilia have been issued. These guidelines were obtained by evaluating the literature since 1996 and were accepted if 70% consensus were reached. The guidelines are summarized below:

- Prothrombin G20210A testing should be performed in the following individuals:
  - A first VTE before age 50 years
  - A first unprovoked VTE at any age
  - A history of recurrent VTE
  - Venous thrombosis at unusual sites such as the cerebral, mesenteric, portal, or hepatic veins
  - VTE during pregnancy or the puerperium
  - VTE associated with the use of oral contraceptives or hormone replacement therapy (HRT)
  - A first VTE at any age in an individual with a first-degree family member with a VTE before age 50 years
  - Women with unexplained fetal loss after the first trimester

- Prothrombin G20210A testing may be considered in the following individuals/circumstances, but is more controversial:
  - Selected women with unexplained early-onset severe preeclampsia, placental abruption, or significant intrauterine growth retardation
  - A first VTE related to tamoxifen or other selective estrogen receptor modulators (SERM)
  - Female smokers under age 50 years with a myocardial infarction
  - Individuals older than age 50 years with a first provoked VTE in the absence of malignancy or an intravascular device
  - Asymptomatic adult family members of people with one or two known prothrombin G20210A alleles, especially those with a strong family history of VTE at a young age
  - Asymptomatic female family members of people with known prothrombin thrombophilia who are pregnant or considering oral contraception or pregnancy

- Prothrombin G20210A testing is not recommended for the following:
- General population screening
- Routine initial testing during pregnancy
- Routine initial testing prior to the use of oral contraceptives, HRT, or SERMs
- Prenatal or newborn testing
- Routine testing in asymptomatic children
- Routine initial testing in adults with arterial thrombosis

- A consensus statement from the American College of Medical Genetics (ACMG, 2001) on factor V Leiden mutation analysis also provided guidance about prothrombin testing. These older guidelines generally agree with the CAP guidelines of 2002.\(^5\)

- A technical standard published by ACMG in 2018 states the following:\(^8\)
  - "Testing for factor V Leiden and factor II c*97G>A is recommended in the following circumstances:
    - A first unprovoked VTE, especially <50 years old
    - VTE at unusual sites (such as hepatic portal, mesenteric, and cerebral veins)
    - Recurrent VTE
    - Personal history of VTE with (a) two or more family members with a history of VTE or (b) one first-degree relative with VTE at a young age
    - Patients with low activated protein C (APC) resistance activity"

An Agency for Health Care Research and Quality supported systematic review (AHRQ, 2009) found that, while mutation analysis is effective at identifying prothrombin mutations, “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.”\(^9\)

- Evaluation of Genomic Applications in Practice and Prevention Working Group (EGAPP, 2011) found sufficient evidence to recommend against Prothrombin mutation analysis in the following scenarios:\(^6\)
  
  a) Adult with idiopathic VTE,
  
b) Asymptomatic adult family members of patient with VTE and a Prothrombin gene mutation for the purpose of considering primary prophylactic anticoagulation.

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 II mutation, AND

Individual has at least one of the following clinical or family history factors suggesting a higher likelihood of having inherited thrombophilia:
• Provoked venous thromboembolism (VTE) at a young age (<50 years), or
• History of recurrent VTE, or
• VTE in an unusual site, such as those involving the hepatic, portal, mesenteric, or cerebral veins, or
• VTE associated with pregnancy or oral contraceptive use, or
• VTE associated with hormone replacement therapy, selective estrogen receptor modulators (SERMs), or tamoxifen, or
• Personal and close family history of VTE, or
• Unprovoked VTE at any age, or
• Family history of venous thrombosis at a young age (<50 years), or
• Women experiencing recurrent pregnancy loss (2 or more failed clinical pregnancies), or
• Women with a history of other unexplained poor pregnancy outcomes, including severe preeclampsia, placental abruption, fetal growth retardation, and stillbirth, or
• Family history of prothrombin gene mutation, particularly when results may impact oral contraceptive use or pregnancy management, or
• Myocardial infarction before age 50 in a female who smokes, AND

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

References


