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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<tbody>
<tr>
<td>F2 Targeted Mutation Analysis</td>
<td>81240</td>
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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.¹⁻³
  - The F2 gene produces a protein that helps to initiate the formation of blood clots.¹
  - The prothrombin mutation 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
- Prothrombin thrombophilia is also linked to an increased risk of miscarriage or other pregnancy complications like preeclampsia, slow fetal growth, and placental abruption.¹⁻²
- About 2% of Caucasians have at least one prothrombin mutation.¹⁻²
  - Inheriting one prothrombin mutation increases one’s risk for developing VTE threefold.¹
  - Inheriting two prothrombin mutations increases one’s risk twentyfold.¹
Inheriting a prothrombin mutation with other genetic risk factors such as Factor V Leiden also significantly increases the risk for developing VTE.  

Definitive diagnosis of prothrombin thrombophilia relies on both clinical and genetic testing.

Test information

Factor II mutation analysis looks for the G20210A mutation, and determines how many copies of that mutation are present. 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%.

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

Guidelines and evidence

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 2002.4

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.” 5

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
Testing is indicated in individuals who meet ANY of the following criteria:3,6-9

• Provoked venous thromboembolism (VTE) at a young age (<50 years); or
• Recurrent VTE; or
• Unusual VTE 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
pregnancies10); 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, particularly in female smokers

References
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3. McGlennen RC, Key NS. Clinical and Laboratory Management of the Prothrombin


