Testing for Factor V Leiden and Prothrombin (20210G->A)
Recommendation from the EGAPP Working Group

Background: Venous thromboembolism (VTE) is a common source of morbidity and mortality in the United States. Individuals who have experienced one episode of unprovoked VTE are at increased risk for suffering a recurrent thrombotic event. There are many risk factors for unprovoked VTE including some genetic factors. The two most common genetic risk factors are Factor V Leiden (FVL) and the 20210G->A mutation in the prothrombin gene (PTM) (mutation frequencies given below). Carrying a single FVL mutation increases the risk for unprovoked VTE by 4-7 fold over the annual background risk, while carrying two FVL mutations results in a 9-80 fold increase. PTM mutations (1 or 2) result in a modest 2-4 increased risk. Individuals with the combination of one FVL and one PTM mutation have an estimated 20 fold increased risk.

Clinical question: “Does FVL mutation testing, alone or in combination with PT[M] mutation testing, lead to improved clinical outcomes (e.g., avoidance of recurrent VTE) in adults with a personal history of VTE or to improved outcomes (e.g., avoidance of an initial VTE) in adult family members of mutation positive individuals? Are the testing results useful in medical, personal, or public health decision-making?”

Population under consideration: These recommendations apply to adults with a history of Idiopathic (unprovoked) VTE and their asymptomatic adult family members. The recommendations do not extend to individuals with other known risk factors for thrombosis, such as contraceptive use.

Recommendations: 1
Adequate evidence to recommend against routine testing for FVL and/or PTM in the following circumstances:

1. Adults with idiopathic 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.

Rationale:
- In patients with a VTE, presence of a FVL and/or PTM mutation does not alter treatment
- In relatives of a patient with VTE and a FVL mutation:
  - Identification of a single FVL mutation in the relative is estimated to result in 35 unprovoked VTE per 10,000 annually (compared to background of 10 VTE per 10,000). Anticoagulant treatment would be estimated to lead to 100 hemorrhagic events per 10,000, a risk 3 times higher than developing a VTE—an unfavorable benefit/risk ratio.
  - Anticoagulant treatment in a relative with 2 FVL mutations could lead to a favorable benefit/risk ratio (estimated 180 unprovoked VTE per 10,000 compared with 100 per
There are no published data on this approach in asymptomatic patients.

- In relatives of a patient with VTE and a PTM mutation data are not available to address the benefits and risks of anticoagulation in asymptomatic patients, but given that the risk of unprovoked VTE is lower, the benefit/risk ratio is expected to be less favorable than for FVL.
- Cost-effectiveness modeling studies in this area require updating with current VTE risk estimates but are suggestive that routine FVL/PTM testing is not cost-effective.

**Recommendation from other groups:**
American College of Chest Physicians: “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.”

**Estimated mutation frequency:**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Non-Hispanic White</th>
<th>Hispanic White</th>
<th>African-American</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVL one copy</td>
<td>5.10%</td>
<td>2.00%</td>
<td>1.20%</td>
</tr>
<tr>
<td>FVL two copies</td>
<td>65/10^5</td>
<td>10/10^5</td>
<td>4/10^5</td>
</tr>
<tr>
<td>PTM one copy</td>
<td>2.20%</td>
<td>2.20%</td>
<td>0.60%</td>
</tr>
<tr>
<td>PTM two copies</td>
<td>12/10^5</td>
<td>12/10^5</td>
<td>&lt;1/10^5</td>
</tr>
</tbody>
</table>

It is estimated that 22 per 10^5 individuals will carry one copy each of FVL/PTM

**References/Resources**