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Guidance on the Use of Factor V Leiden  
and Prothrombin Mutation Testing in  
Patients With a First Unprovoked  
Thromboembolic Episode

*Supporting Informed Decisions*

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This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the “source documentation”) available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation.

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# 1 GUIDANCE

Venous thromboembolism (VTE) is a condition that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT refers to the formation of a blood clot in a deep vein, typically in the leg. These clots can dislodge and travel to the lung, resulting in PE. The annual incidence of VTE is between one and two events per 1,000 in the general population.<sup>1,2</sup> VTE is a significant cause of morbidity and mortality.<sup>1,2</sup> Treatment for VTE usually consists of parenteral anticoagulation followed by long-term oral anticoagulation therapy to prevent recurrence.<sup>3</sup>

Thrombophilias are a group of disorders that disturb the balance of the coagulation cascade, leading to an increased risk of VTE.<sup>4</sup> Thrombophilias can be inherited, acquired, or due to a combination of inherited and acquired factors. Inherited thrombophilias are due to mutations in the genes that encode coagulation proteins, the most common being factor V Leiden (FVL) and prothrombin gene (PG) mutations.<sup>5-7</sup> Commercial tests are available to detect mutations in these genes with high accuracy.<sup>8</sup> While the use of these tests in clinical practice varies across Canada, they are often ordered as a panel with other tests<sup>9</sup> after a first VTE when other provoking factors, such as trauma, surgery, or malignancy, are absent. In some cases, the duration of anticoagulation therapy may be increased in patients with positive test results. Positive test results may also lead to testing of family members. Negative test results for FVL and PG only exclude these specific mutations, not the clinical condition of thrombophilia.

Despite the high prevalence of testing for FVL and PG mutations in patients with a first unprovoked VTE, the clinical utility of testing in this population remains uncertain. To assist decision-makers considering implementation or reassessment of testing practices for FVL or PG mutations in patients with unprovoked VTE, CADTH conducted a systematic review<sup>10</sup> of the clinical evidence and performed a health economic analysis comparing testing with no testing. Based on these assessments and clinical expertise, CADTH's Health Technology Expert Review Panel (HTERP) developed the following recommendation:

**HTERP recommends that patients with a first unprovoked VTE should not routinely be tested for factor V Leiden and prothrombin mutations.**

## **Rationale:**

- While an association was identified between FVL and PG mutations and first unprovoked VTE, the evidence showed that the presence of these mutations did not increase the risk of VTE recurrence.
- No evidence was identified to guide changes in the clinical management of patients with a first unprovoked VTE on the basis of results from FVL and PG mutation testing, and there was no evidence of improved health outcomes resulting from testing.
- Testing for FVL and PG mutations is associated with additional costs because of the cost of the tests and frequent requests for consultation with a specialist, as well as costs associated with extended anticoagulation therapy for patients who test positive. In the absence of evidence that testing is clinically effective, the costs of routine testing are not justified.

### Implementation Considerations:

- The recommendation is presented with the caveat that there is currently a paucity of evidence regarding the clinical outcomes associated with FVL and PG mutation testing. More research is required in this area.
- This recommendation applies only to patients with an unprovoked first VTE. HTERP acknowledged that there are other patient groups and clinical scenarios that may benefit from testing for FVL and PG mutations; hence, these tests should remain available to clinicians who treat thromboembolic disorders.
- HTERP considered that the clinical utility of a negative test is unclear, as FVL and PG mutations are only two of many possible inherited thrombophilias. A negative test for these mutations may therefore provide false reassurance to patients and clinicians.
- If FVL or PG mutation tests are performed and mutation(s) are identified, testing of family members without a history of VTE is unlikely to provide benefit. The risk of symptomatic disease among these individuals who test positive is very low, and the risk-benefit profile of prophylactic treatment in asymptomatic patients is unknown.
- HTERP considered the potential impact of reduced testing for FVL and PG mutations on existing patient care pathways and clinician-patient interactions. It was noted that such impacts would likely be minimal, as most patients with VTE are unlikely to be aware of the specific laboratory investigations performed as part of their care.

### Other Discussion Points:

- Although there was no evidence of harms unique to FVL and PG mutation testing, HTERP considered an increased risk of bleeding complications as a potential harm to patients who are treated with prolonged anticoagulation therapy as a result of a positive test. Other potential harms of genetic tests, more generally — such as increased anxiety, pressure to test family members, implications for insurance coverage, and employee discrimination — were also discussed by HTERP.
- HTERP acknowledged that a small number of patients who could potentially benefit from testing (e.g., those homozygous for FVL or PG mutations) may be missed if routine testing for FVL and PG mutations among patients with a first episode VTE is reduced or eliminated. However, there was no evidence available to identify subgroups which could potentially benefit from testing.
- As a general issue, HTERP discussed the importance of informed consent should patients be offered genetic testing, as the results may have significant implications for patients and their families. HTERP also discussed the need for appropriate genetic counselling before and after testing is performed.

## 2 BACKGROUND

VTE is a condition that includes DVT and PE. DVT refers to the formation of a blood clot in a deep vein, typically in the leg. These clots can dislodge and travel to the lung, resulting in PE. In patients with a first, unprovoked VTE, the 30-day case-fatality rate is 4% and the one-year case-fatality rate is 14.5%.<sup>11</sup> The annual incidence of VTE is between one and two events per 1,000 in the general population.<sup>1,2</sup> Approximately 50% of all patients with a first DVT are considered to have an unprovoked event, in that there are no known acquired risk factors such as recent surgery, trauma, malignancy, pregnancy, or use of exogenous estrogen.<sup>12</sup> Upon presentation with a VTE, treatment with parenteral anticoagulation or an oral direct inhibitor of coagulation is recommended, followed by long-term oral anticoagulation therapy with warfarin or one of the

newer oral anticoagulant agents to prevent VTE recurrence. Longer treatment durations are generally given to patients with unprovoked VTE.<sup>3</sup>

Thrombophilias are a group of disorders that disturb the balance of the coagulation cascade, leading to an increased risk of VTE.<sup>4</sup> Thrombophilias can be inherited, acquired, or due to a combination of inherited and acquired factors. Inherited thrombophilias are due to mutations in one or more genes that encode coagulation proteins. It is estimated that nearly 10% of the world's population has an inherited thrombophilia, the two most common being FVL thrombophilia and prothrombin (PG; also known as factor II) thrombophilia.<sup>5-7,13</sup>

FVL thrombophilia is caused by a mutation in the gene for factor V (F5G1691A mutation resulting in the amino acid substitution FVR506Q). Being heterozygous for the allele increases the annual risk of VTE from 1 in 1,000 to 3 to 8 in 1,000, and being homozygous for the allele increases the annual risk to 80 in 1,000.<sup>14</sup> European populations have the highest prevalence of the mutation; between 3% and 8% of people with European ancestry are heterozygous for the FVL mutation and about 1 in 5,000 are homozygous.<sup>6</sup> Extrapolated to the Canadian population, over one million Canadians are heterozygous for the FVL mutation, and over 4,000 Canadians are homozygous.<sup>6</sup>

Prothrombin thrombophilia is caused by a mutation in the factor II gene (*F2G20210A* mutation in an untranslated region). This genetic mutation increases the risk of developing VTE from 1 in 1,000 individuals per year for the general population to 2 to 3 in 1,000 for heterozygous individuals, and to 20 in 1,000 for homozygous individuals.<sup>5</sup> In the US and Europe, it is estimated that 1 in 50 Caucasians have PG thrombophilia; this would amount to about 703,000 Canadians.<sup>15</sup> Prevalence is much lower in Asian, African-American, and Native American populations.

Commercial tests are available in Canada to detect factor V G1691A and prothrombin G20210A mutations. These tests have been found to have high analytical validity for detecting the mutations; a systematic review of methods to identify FVL or PG mutations reported greater than 99% concordance with reference methods.<sup>8</sup> Furthermore, in quality assurance studies, over 98% of laboratories were able to detect a known mutation with high — or in some cases perfect — accuracy, with the majority of errors coming from a small number of labs.<sup>8</sup>

FVL and PG tests are often ordered after a first-time VTE when other provoking factors, such as trauma or malignancy, are absent. They may also be ordered in other situations; for example, in patients with a history of recurrent VTE or in women with repeat miscarriages. Positive tests may also lead to testing of children and other family members; the genes are inherited in an autosomal dominant manner, so children of a heterozygous parent have a 50% chance of inheriting the mutation.<sup>16</sup> It should be noted that negative test results for FVL and PG only exclude these specific mutations, not the clinical condition of thrombophilia.

Although practice varies, patients carrying FVL or PG mutations may receive extended anticoagulation therapy beyond the standard duration of three to six months, particularly carriers of both FVL and PG alleles or those homozygous for one of the mutations.

There is a lack of clarity regarding when the tests for FVL and PG mutations should be ordered and how the tests impact patient management or improve patient health outcomes. Input from internal medicine specialists and general practitioners indicates that genetic testing for these two mutations typically occurs as part of batch testing and is often performed following a first

unprovoked VTE event without a clear rationale for how test results will influence patient management, resulting in potential overutilization.

To assist decision-makers considering implementation or reassessment of FVL and PG mutation testing practices, HTERP developed evidence-informed guidance on the optimal use of these tests for patients with unprovoked VTE. The clinical and economic evidence used for developing guidance was derived from the following CADTH report:<sup>10</sup>

- The CADTH Optimal Use report: *Effectiveness of Factor V Leiden and Prothrombin Mutation Testing in Patients Presenting with Unprovoked First Thromboembolic Episode*, consisting of a systematic review of the clinical evidence and an economic analysis.

HTERP considered the evidence and its limitations from a population-based perspective.

## 3 SUMMARY OF THE EVIDENCE

### 3.1 Clinical Evidence

HTERP considered the results of a systematic review, which assessed the validity and utility of FVL and PG mutation testing in patients presenting with a first, unprovoked VTE. The clinical review included five studies and three evidence-based guidelines. Additionally, information on physician practice patterns and psychosocial issues was summarized.

All included studies were non-randomized designs; four were case-controlled studies and a fifth was a prospective cohort study. Although all studies identified potential confounders, not all considered these in their analyses. Three studies examined the association between FVL and PG mutations and unprovoked VTE, and two studies reported on the risk of recurrence of VTE following FVL or PG mutation testing. One of these did not report clinical management decisions made as a result of testing, making it unclear whether observations were due to changes in management or other factors, thereby limiting the ability to interpret the findings. Nearly all studies enrolled a sufficient sample size to detect clinically important effects. The testing methods used in the included studies appeared to be generalizable to Canadian practice. All studies focused on adults presenting with VTE; no studies in children were identified.

#### **Association between FVL or PG mutations and unprovoked VTE**

Three studies examined the relationship between FVL or PG mutations and unprovoked VTE in patients presenting with a first episode of DVT/PE. There was evidence that the presence of FVL or PG mutations represents a risk factor in the development of unprovoked first episode DVT based on studies conducted in younger patients (mean age in each study was less than 60-years-old). The frequency of either FVL or PG mutations in the unprovoked PE population was not different from the provoked PE population.

#### **Risk of VTE recurrence following FVL and PG mutation testing**

Two studies reported on the risk of VTE recurrence following FVL and PG mutation testing. One case-control study found that the risk of recurrence was similar between tested and non-tested patients. The study also reported that the risk of recurrence was similar for patients who tested positive or negative for either FVL or PG mutations, compared with no testing. However, this study did not report on clinical management decisions made as a result of testing; hence, the finding of similar recurrence risk is difficult to interpret. One prospective cohort study found that there was

no statistical association between heterozygous status for FVL or PG mutations and risk of VTE recurrence.

### **Evidence-based guidelines and physician practice patterns**

Three evidence-based guidelines addressing genetic testing or clinical management of patients with VTE were identified. While these guidelines describe the management of unprovoked VTE or testing for thrombophilia separately, the issue of thrombophilia in this population is not specifically addressed. These guidelines stated that mutation status should not affect the treatment patients receive to avoid recurrence and that anticoagulation treatment for greater than three months reduces the recurrence of VTE in all patients regardless of mutation status. However, a study of physician practice patterns found that rates of adherence to practice guidelines were as low as 46%. Another study reported that physicians modified clinical management for only 20% of patients who tested positive for FVL.

### **Psychosocial issues**

One systematic review on the psychological impact of testing for inherited thrombophilia concluded that testing did not seem to have any major adverse effects but noted that, despite approximately 90% of patients being satisfied with the knowledge of being a carrier of the FVL mutation, 43% of participants experienced increased worry. In addition, one study reported that 79% of participants incorrectly estimated the associated risk of a positive test, and over 60% felt they were not provided sufficient information. Studies have also suggested that testing for thrombophilia can influence potential lifestyle or health choices (e.g., taking precautions during long flights, decisions to use oral contraceptives or hormone therapy), which may be perceived by patients as beneficial.

## **3.2 Economic Evidence**

HTERP considered the results of a cost analysis comparing testing for FVL and PG mutations with no testing in adult patients presenting with a first episode of unprovoked VTE. A cost-effectiveness analysis was not performed, as there was insufficient information regarding clinical outcomes associated with testing. In the absence of clinical evidence supporting the utility of thrombophilia testing, a cost analysis was deemed most appropriate. Inputs for the analysis included costs of the tests, estimated prevalence of the mutations, and cost of subsequent anticoagulation treatment. Test costs were obtained from various jurisdictions through a combination of published information and a survey of senior laboratory administrators. The prevalence of the mutations was sourced from published information where available, or inferred from the available data, and applied to the Canadian population, if needed. Anticoagulation treatment was assumed to be warfarin-based, the cost of which was obtained from the Ontario Drug Benefit Formulary, and the cost of warfarin monitoring was taken from CADTH's Therapeutic Review of the new oral anticoagulant agents. The analysis was based on a Canadian ministry of health perspective and only included direct costs for health care products and services allowed or reimbursed by the payer.

A series of four hypothetical scenario analyses were undertaken based upon anecdotal evidence and clinical feedback that certain subsets of patients that test positive for FVL and/or PG mutations may receive extended anticoagulation treatment. Three of the scenarios assumed standard anticoagulation treatment of three months' duration for all patients except those testing compound heterozygous (i.e., heterozygous for *both* FVL and PG mutations) or homozygous for either FVL or PG mutations who were assumed to have received extended duration anticoagulation (six months, 12 months, and lifetime [40 years] in scenarios 1, 2, and 3, respectively). The fourth scenario assumed that standard anticoagulation therapy (in the absence



of testing, or if a patient was found to be heterozygous or homozygous for FVL and/or PG mutations) was six months in duration. Patients without any FVL or PG mutations upon testing were assumed to receive a reduced duration of anticoagulation treatment (three months) in this scenario. One-way sensitivity analyses were undertaken around the costs of the tests, prevalence of the mutations, and duration of anticoagulation treatment.

Key findings of the cost analysis were, as follows:

- Thrombophilia testing was associated with a higher cost to the payer in the base-case analysis (incremental cost of \$13 to \$125 per patient) and all four scenario analyses (incremental cost of \$10 to \$590 per patient). Thrombophilia testing was most costly to the payer if patients had received lifetime anticoagulation therapy subsequent to testing.
- The one-way sensitivity analyses did not greatly alter the magnitude of the incremental cost to the payer associated with thrombophilia testing in three of the four scenarios.
- The sensitivity analyses suggested that the direction and magnitude of the results were substantially affected by the cost of the test. When altering the test cost to the upper and lower ranges, the results changed from an incremental cost to the payer of \$76 per patient (when the higher test cost was used) to an incremental savings of \$36 per patient (when the lower range of the test costs were used).

There were several caveats with the analysis:

- The results of these analyses cannot be extrapolated to larger panels of tests, as the other tests that are included in those panels were not reviewed for clinical utility or costing information.
- The duration of standard anticoagulation management in routine clinical practice was discussed by HTERP. It was acknowledged that it is typically longer than the three months assumed in the cost analysis. However, changes in this assumption will not affect the direction of the results as long as the detection of FVL and/or PG mutations leads to extended anticoagulation treatment beyond the standard duration.
- HTERP discussed the importance of appropriate counselling for patients offered genetic testing. The costs of counselling were not included in the economic analysis for two reasons: first, a lack of information exists on the extent to which counselling is offered in clinical practice; and second, uncertainty exists as to whether counselling influences the decision to perform testing.
- The results of the economic analysis must be interpreted with caution given the assumptions that were made as a result of limited clinical evidence for the tests, epidemiology data, and variations in costs for different jurisdictions in Canada.

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# APPENDIX 1: HEALTH TECHNOLOGY EXPERT REVIEW PANEL (HTERP)

HTERP consists of up to seven Core Members appointed to serve for all topics under consideration during their terms of office, and up to five Expert Members appointed to provide their expertise for a specific topic. For this project, five Expert Members were appointed; their expertise included hematology, pathology and laboratory medicine, internal medicine, and family medicine. The Core Members include health care practitioners and other individuals with expertise and experience in evidence-based medicine, critical appraisal, health technology assessment, bioethics, and health economics. One Public Member is also appointed to the Core Panel to represent the broad public interest.

HTERP is an advisory body to CADTH and is convened to develop guidance or recommendations on non-drug health technologies to inform a range of stakeholders within the Canadian health care system. More information regarding HTERP is available at [www.cadth.ca/en/advisory-bodies/health-technology-expert-review-panel](http://www.cadth.ca/en/advisory-bodies/health-technology-expert-review-panel).

## HTERP Core Members

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Dr. Stirling Bryan (Chair)  
Dr. Leslie Anne Campbell  
Dr. Jenny Basran  
Ms. Anita Fineberg  
Dr. Hilary Jaeger  
Dr. Charlotte Moore  
Dr. Lisa Schwartz

## Expert Members

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Dr. Ron Booth  
Dr. Narmin Kassam  
Dr. Michael O'Connor  
Dr. Paul Salomon  
Dr. Sam Schulman

## Conflict of Interest

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No members declared any conflicts of interest. *Conflict of Interest Guidelines* are posted on the CADTH website.

## APPENDIX 2: ABBREVIATIONS

<b>DVT</b>	deep vein thrombosis
<b>FVL</b>	factor V Leiden
<b>HTERP</b>	Health Technology Expert Review Panel
<b>PE</b>	pulmonary embolism
<b>PG</b>	prothrombin gene
<b>VTE</b>	venous thromboembolism