Effectiveness of Factor V Leiden and Prothrombin Mutation Testing in Patients Presenting with Unprovoked First Thromboembolic Episode: Systematic Review and Economic Analysis
1. INTRODUCTION

Coagulation – or blood clotting – is mediated through a cascade of interactions between platelets, endothelium, and coagulation proteins to maintain a balance that prevents excessive bleeding or inappropriate clotting. Thrombophilias are a group of disorders that disturb the balance leading to a tendency for hypercoagulability, that increases the risk for thrombus formation and venous thromboembolism (VTE), including deep vein thrombosis (DVT) or pulmonary embolism (PE).\(^1\)

Thrombophilias can be inherited, acquired, or both. Inherited thrombophilias are due to mutations in the genes that encode coagulation proteins. The risk of developing a clinically significant blood clot is influenced by whether an individual is heterozygous for the condition (i.e., has one normal copy of the gene and one copy with a mutation), or is homozygous (i.e., both copies of the genes are mutated). The risk is increased if the person is homozygous for the condition. It is estimated that nearly 10% of the world’s population has an underlying thrombophilia, the two most common being factor V Leiden (FVL) thrombophilia and prothrombin (PM) thrombophilia.\(^2\)\(^4\) FVL thrombophilia and PM thrombophilia are associated with an increased risk of venous thrombosis and, in pregnant women, increased risk of miscarriage, pregnancy-induced high blood pressure (preeclampsia), slow fetal growth, and early separation of the placenta from the uterine wall (placental abruption). FVL and PM thrombophilia are typically low risk thrombophilias, in that the presence of these mutations confers a small increased risk of abnormal clots.\(^2\)\(^5\) A number of acquired conditions also increase the risk of thrombophilia, including trauma, pregnancy, use of estrogen as an oral contraceptive or as replacement therapy, cancer, autoimmune diseases, inflammatory diseases, hematologic conditions, and immobilization.\(^1\) Acquired thrombophilias can be referred to as provoked thrombophilias, as opposed to unprovoked or idiopathic thrombophilias in which thrombophilias are not triggered by a known acquired conditions. The annual incidence of VTE is between 1 and 2 events per 1,000 people.\(^6\)\(^7\) 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 for thrombophilia.\(^8\)

FVL thrombophilia is caused by a mutation in the gene for factor V (FVR506Q gene mutation), a coagulation factor. The mutation renders factor V resistant to cleavage by activated protein C (APC), leading to a reduced rate of factor V inactivation, and resulting in a hypercoagulable state. Being heterozygous for the condition increases the risk of hypercoagulability from 1 in 1,000 to 3 to 8 in 1,000 and being homozygous for the condition increases the risk to 80 in 1,000.\(^5\) Between 3% and 8% of people with European ancestry carry one copy of the factor V Leiden (heterozygous), and about 1 in 5,000 people have two copies of the mutation (homozygous).\(^3\) European populations have the highest prevalence of the mutation. Extrapolated to the full Canadian population, an estimated 1.76 million Canadians (5 per cent) are heterozygous for Factor V Leiden, and approximately 7,000 Canadians are homozygous.\(^3\)

Prothrombin thrombophilia is caused by a mutation in the coagulation factor II (F2) gene (F2G20210A gene mutation). The mutation results in an overactive F2 gene that causes too much prothrombin to be produced, initiating the coagulation cascade to promote the formation of blood clots. This genetic mutation increases the risk of developing an abnormal blood clot from 1 in 1,000 individuals per year for the normal population to 2 to 3 in 1,000 for heterozygous individuals, and to 20 in 1,000 for homozygous individuals.\(^2\) In the US and Europe, it is estimated that 1 in 50 Caucasians have prothrombin thrombophilia; prevalence is lower in Asian, African American, and Native American populations. This would amount to about 703,000 Canadians.\(^9\)
Commercial tests available in Canada to detect FVL R506Q and prothrombin G20210A mutations include the Factor V Leiden Kit for Light Cycler v2.0 and Factor II (Prothrombin) G20210A Kit for Light Cycler v2.0 (Roche Molecular Diagnostics, CA, USA), and Xpert Hemosil FII & FV (Instrumentation Laboratory, MA, USA). Using polymerase chain reaction restriction fragment (PCR-RFLP) or allele-specific polymerase chain reaction (AS-PCR) as reference standards, these kits were found to have excellent analytical validity with high accuracy in detecting the mutations. A systematic review of methods to identify FVL or PM mutations reported > 99% concordance with reference methods, with discordance resolved by test repetition in most cases, suggesting operator or administrative errors. Furthermore, in quality assurance studies, over 98% of laboratories were able to diagnose a sample with a known mutation with high, or in some cases, perfect accuracy, with the majority of errors coming from a small number of labs.

Use of the tests in clinical practice varies across Canada. Tests for FVL and PM mutations may be ordered individually, together, or as part of a panel including tests for protein S deficiency, protein C deficiency, or antithrombin deficiency. In some cases testing for FVL or PM mutations will follow an initial protein C resistance test which is an indicator of a hypercoagulable state which may be inherited or acquired. Tests may be ordered by a number of different medical specialties, including hematologists, obstetricians, general internists, and family doctors. A study of ordering practices at Vancouver General Hospital in British Columbia indicated that the majority (36.8%) of testing for hereditary thrombophilia was ordered by general practitioners followed by general internists (16.3%).

FVL and PM tests are often ordered after a first-time VTE, particularly 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 women with repeat miscarriages. Positive tests may also lead to testing of children and other family members; the genes are inherited in an incomplete autosomal dominant manner, so children of a parent heterozygous for one allele have a 50% chance of inheriting the mutation.

Upon presentation with a VTE, initial treatment with parenteral anticoagulation followed by long-term therapy is recommended. In most situations, a course of three months of anticoagulation therapy is recommended for unprovoked VTE, though longer treatment durations may be considered depending on the nature of the thromboembolic event and bleeding risk. Although practice varies, patients carrying FVL or PM mutations may receive extended anticoagulation therapy beyond three months (e.g., six months or in some cases indefinitely), particularly carriers of both FVL and PM alleles, or those homozygous for one of the mutations. However, the evidence to support extended anticoagulation for patients with FVL or PM mutations but no other risk factors is unclear.

2. ISSUE

There is a lack of clarity regarding when the tests for FVL and PM mutations should be ordered and how the tests impact patient management or improve patient health outcomes. Canadian laboratory managers surveyed by CADTH have identified FVL and PM as tests that are potentially over-utilized. 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 VTE event without a clear reason to suspect inherited thrombophilia, resulting in potential overutilization.
In addition to the resource use associated with overutilization, inappropriate use of FVL and PM genetic testing may lead to over-treatment with anticoagulation therapy, which is associated with an increased risk of bleeding. Additionally, due to the hereditary and irreversible nature of FVL and PM thrombophilias, testing may lead to increased anxiety and present other psychosocial challenges for patients and their families.

3. OBJECTIVES

Given the potentially low risk to patient health associated with FVL and PM thrombophilia, and the potential overutilization of FVL and PM testing, there is a need to assess the clinical and cost effectiveness of testing for these mutations in patients with an unprovoked first VTE event. The objective of this assessment is to review the available evidence on the accuracy with which these tests identify a patient’s clinical status (association with a first, unprovoked VTE), and the risks and benefits resulting from test use (clinical utility). The report focuses on patients presenting with a first episode of unprovoked VTE. The cost implications of FVL and PM testing in Canada are also assessed. The report addresses the following research questions:

1. What is the clinical validity of factor V Leiden and prothrombin mutation tests in patients presenting with a first episode of unprovoked (i.e., idiopathic) VTE?

2. What is the clinical utility of testing for factor V Leiden and prothrombin mutations compared to no testing of patients presenting with a first episode of unprovoked (i.e., idiopathic) VTE?

3. What is the cost-effectiveness of testing for factor V Leiden and prothrombin mutation compared to no testing of patients presenting with a first episode of unprovoked (i.e., idiopathic) VTE?

Additional considerations, such as the influence of these tests on clinical management, physician ordering practices, and social, ethical, and legal issues associated with these tests were also of interest.

4. CLINICAL REVIEW

4.1 Methods

4.1.1 Literature Search Strategy

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946- ) with in-process records & daily updates via Ovid; Embase (1980- ) via Ovid; The Cochrane Library (2014, Issue 3) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine’s MeSH (Medical Subject Headings), and keywords. The main search concepts were Factor V Leiden and prothrombin mutation. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was limited to English language documents published between January 1, 2004 and March, 2014. Conference abstracts were
excluded from the search results. See Appendix 1 for the detailed search strategies. The initial search was completed in March, 2014. Regular alerts were established to update the search until publication of the final report. Regular search updates were performed on databases that do not provide alert services. Grey literature (literature that is not commercially published) was identified by searching the Grey Matters checklist (http://www.cadth.ca/resources/grey-matters), which includes the websites of regulatory agencies, health technology assessment agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry. See Appendix 1 for more information on the grey literature search strategy.

4.1.2 Selection Criteria and Methods

Two reviewers independently screened the titles and abstracts of all citations retrieved from the literature search and, based on the selection criteria (Table 1), ordered the full text of any articles that appeared to meet those criteria. The reviewers independently reviewed the full text of the selected articles, applied the selection criteria to them, and compared the independently chosen studies. Disagreements were resolved through discussion until consensus was reached. Multiple publications of the same trial were excluded unless they provided additional outcome information of interest.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients presenting with unprovoked (idiopathic) first episode of VTE (i.e., without prior history of VTE)*</th>
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<tbody>
<tr>
<td>Intervention</td>
<td>Factor V Leiden or prothrombin mutation assays available in Canada</td>
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<tr>
<td>Comparator</td>
<td>Non-testing (for clinical utility outcomes)</td>
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| Outcomes | • Clinical validity of the assays (association between factor V Leiden and prothrombin mutation and first VTE, clinical sensitivity, specificity, positive predictive value, negative predictive value for detecting unprovoked VTE)  
• Clinical utility of hereditary thrombophilia testing (benefits and risks of thrombophilia testing including prevention of recurrence) |
| Study design | Randomized controlled trials (RCTs), observational studies, evidence-based guidelines |

* Based on the Wells Criteria and Pulmonary Embolism Rule-Out Criteria (PERC) for diagnosing DVT/PE and expert consultation, VTE was considered unprovoked if patients had no prior history of DVT/PE, had not recently (within four weeks) undergone surgery or trauma, were not receiving exogenous estrogen, did not have active malignancy, and had not been immobilized for more than 3 days. Studies conducted in pregnant women were also excluded.

Studies were excluded if they did not meet the selection criteria, or presented preliminary results in abstract form. Duplicate publications, narrative reviews, and editorials were also excluded.

4.1.3 Data Extraction

A data extraction form for the clinical effectiveness review was designed a priori to document and tabulate relevant study characteristics (e.g., study design, inclusion criteria, patient characteristics, setting, and measures of clinical effectiveness) (Appendix 2). Data were extracted by one reviewer, and independently checked by a second reviewer. Any disagreements were resolved through discussion until consensus was reached.

4.1.4 Critical Appraisal Methods
The methodological quality of the included clinical trials was assessed independently by two reviewers, using the Downs and Black checklist. Disagreements were resolved through consensus. The quality of the included guidelines was assessed using the AGREE checklist. Generalizability to the Canadian setting was also considered.

4.1.5 Data Analysis and Synthesis Methods

Clinical validity was based on the accuracy with which the test identifies a patient's clinical status. The relationship between the mutations and thrombophilia was determined. Findings on identification of patients who have hereditary thrombophilia (sensitivity), those who do not have the condition (specificity), those who truly have the condition from among those who tested positive (positive predictive value), and those who do not truly have the condition from among those who tested negative (negative predictive value) were of interest.

Clinical utility of thrombophilia testing was based on findings about the benefits (how testing influences management of thrombophilia and whether or not the choice of treatment based on test results alters clinical outcomes) and risks resulting from test use.

Existing evidence-based guidelines and recommendations for the use of thrombophilia mutation testing and subsequent management of patients were reviewed. While guidelines do not themselves constitute evidence for clinical utility of thrombophilia testing, they may provide an indication of how testing might be expected to influence clinical practice.

In addition to a systematic review of information related to clinical validity, clinical utility, and practice guidelines, behaviour and treatment patterns of physicians regarding hereditary thrombophilia testing and other aspects associated with testing, including availability and cost of testing, interest of and acceptability to the clients, ethical, and legal and social implications of thrombophilia testing, were also examined. This information was summarized but not systematically reviewed.

4.2 Results

All included studies on the clinical validity and clinical utility of FVL and PM testing in patients with a first unprovoked episode of VTE were observational studies. A narrative summary of study findings is presented.

4.2.1 Quantity of research available

The literature search identified 2,028 citations, from which 1,935 were excluded based on screening of title and abstract; 92 studies and one guideline were ordered for further examination. Upon full-text review, 88 studies were excluded; two guidelines were added from an additional search. Four studies and three evidence-based guidelines were included in the report. A list of included and excluded studies for the systematic review is provided in Appendix 3 and the PRISMA flow chart (Appendix 4) shows the selection process in detail.

4.2.2 Study and patient characteristics

Details of the characteristics of the included studies and patients are summarized in Appendices 5 and 6, respectively.

Study design
A total of four studies were included in this report.\textsuperscript{16-19} The included studies were prospective case-control studies conducted in the Netherlands (Coppens et al., 2008),\textsuperscript{16} the US (Kruse et al., 2006),\textsuperscript{17} Portugal (Mansilha et al., 2006),\textsuperscript{18} and Jordan (Obeidat et al., 2009).\textsuperscript{19} Coppens’ study provided some evidence on the clinical utility of FVL and PM testing; the remaining three studies provided information on the association of FVL and PM with first unprovoked VTE.

Coppens et al.\textsuperscript{16} studied patients that had recurrent venous thrombosis and patients who had venous thrombosis without recurrence during follow-up. A comparison was made between those patients who had been tested for either FVL or PM mutations, and those who were not tested for the mutations. The goal of the study was to determine if changes to the management of patients who were positive for these genetic mutations reduced the risk of recurrent venous thrombosis. The study did not specify what commercial cycler was used to determine mutation status.

The Kruse et al. study\textsuperscript{17} enrolled patients presenting with idiopathic PE in the emergency department, and blood samples were tested for FVL and PM mutations using a Perkin-Elmer DNA thermal cycler. Idiopathic PE was considered to include the absence of recent pregnancy or recent postpartum, no use of exogenous estrogen or estrogenic drug treatment, no history of malignancy, no recent surgery, limb or body immobilization for more than 48 hours, no transatlantic air travel within the previous week, and no previous VTE. The purpose of the study was to compare the frequency of the genotypes in patients with idiopathic PE to patients with PE who had overt risk factors.

The study by Mansilha et al.\textsuperscript{18} tested young patients (ages 16 to 40 years) with a first DVT for FVL and PM mutations using the Roche LightCycler, and compared the results to unrelated, asymptomatic, and healthy blood donors from the same geographical region. The study’s objective was to evaluate the association between FVL or PM mutations and DVT in this age group.

Obeidat et al.\textsuperscript{19} conducted a study on patients presenting with idiopathic PE, comparing them with healthy controls from the same hospital. Testing for FVL and PM mutations was performed, but the commercial instrument used to determine the mutation status was not specified in the publication. The study aimed to determine the frequency of FVL and PM mutations in patients with idiopathic PE compared to those with obvious risk factors (including age greater than 60 years, pregnancy, malignancy, surgery, limb immobilization for more than 48 hours, and previous history of VTE).

Population

The study by Coppens et al.\textsuperscript{16} was based on a large case-control study of patients with a first VTE, selecting patients who had a recurrence during the follow-up period (n = 197; 106 with idiopathic VTE), then comparing with patients in the same study who did not have recurrence (n = 324; 130 with idiopathic VTE). Kruse et al.\textsuperscript{17} enrolled 49 patients with idiopathic PE and 436 controls (patients with non-idiopathic PE, diagnosis of PE excluded, and patients not suspected of having PE). Obeidat et al.\textsuperscript{19} enrolled 92 patients with acute PE and 99 healthy controls. The Mansilha et al. trial\textsuperscript{18} was comprised of 99 patients less than 40 years old with a first DVT, compared with 100 healthy controls.

Funding status

None of the included studies were funded by industry.
Guidelines

Three evidence-based guidelines were included in this report. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group in the US published recommendations in 2011 regarding routine testing for FVL and PM mutations in adults with idiopathic VTE, and their family members. The recommendations assessed analytic validity, clinical validity, and clinical utility, but the publication did not provide detail on the quality of evidence used to inform the guidelines. The authors stated that Agency for Healthcare Research and Quality Evidence-based Practice Center (AHRQ) methods were followed when conducting the review upon which the recommendations were based.

Guidelines for testing for heritable thrombophilia were published by the British Society for Haematology in 2010, and were assessed for quality of evidence using the GRADE system. The guidelines were produced for the management of patients and families with venous thrombosis and pregnancy morbidity, and were not restricted to idiopathic VTE.

The American College of Chest Physicians produced guidelines in 2012 for antithrombotic therapy and prevention of thrombosis, of which the section on antithrombotic therapy for VTE disease was relevant to this report. The guidelines provided a detailed methodology which incorporated a systematic review of the evidence and the use of GRADE to evaluate the quality of evidence. These guidelines were not specific to patients with idiopathic VTE.

4.2.3 Results of Critical Appraisal

Details of the quality appraisal of individual clinical studies are provided in Appendix 7. None of the studies on clinical outcomes were randomized controlled studies. The method of patient selection, patient characteristics, and outcomes were clearly described, with the exception of one study, which provided very little detail on patient characteristics. Although all four studies identified potential confounders, the method of reporting some outcomes was not detailed enough with respect to those confounders to identify idiopathic events when extracting data from these publications. One study on clinical utility did not report clinical management decisions based on mutation status, making it unclear whether observations were due to changes in management or other factors and limiting the ability to interpret the findings. One of the studies indicated that the patient population may not have been representative of the general population, since there was a large proportion of African-American patients enrolled. Two studies reported that technicians performing the genetic tests were blinded. All studies were adequately powered to detect a clinically important effect. The testing methods used in the included studies appeared to be generalizable to Canadian practice. All studies focused on adults with VTE; no studies in children were identified.

The guidelines had clear scope and purpose, clear methods for searching for and selecting the evidence, and clear methods for formulating the recommendations. They provided specific and unambiguous recommendations, with health benefits, side effects, and risks stated in the recommendations, and target users of the guideline were clearly defined. It was unclear whether patients' views and preferences were sought. The UK guideline and the ACCP guideline provided grading of evidence quality for their recommendations. The EGAPP guideline was unclear regarding whether the guideline was piloted among target users; a procedure for updating the guidelines was not provided and level of evidence was not graded. The UK guideline was unclear regarding whether the guideline was piloted among target users,
whether potential cost implications of applying the recommendation were considered, and a procedure for updating the guidelines was not provided.

4.2.4 Clinical validity

Association between FVL and PM and unprovoked VTE in patients without prior history of DVT/PE

Three studies examined the relationship between FVL or PM and unprovoked VTE in patients presenting with a first episode of DVT/PE.\(^\text{17-19}\)

The Mansilha et al. investigation\(^\text{18}\) was an observational prospective case-control study of 99 young patients (under 40 years old; mean age 27 years) who presented with a first episode of DVT. Among them, 38 had no risk factors (unprovoked). Compared to the control group of 100 healthy subjects of whom 2% carried FVL and 5% carried PM (all carriers were heterozygous), 20.6% and 10.1% of patients as a whole carried FVL and PM, respectively. All PM carriers and 95% of FVL carriers were heterozygous (5% of FVL carriers were homozygous). No patients carried both FVL and PM. In the subset of patients with an unprovoked DVT, compared to healthy subjects, there was an increased risk of DVT in carriers of FVL (OR 15.9) and the difference was statistically significant (95% confidence interval [CI] 3.2 to 77.9; \(P < 0.0001\)), while in carriers of PM, there was no statistically significant association (OR 1.6, 95% CI 0.4 to 7.2; \(P = 0.68\)). Heterozygosity status was not reported for population subsets.

The Kruse et al. study\(^\text{17}\) was a prospective case-control study that included a case group consisting of 49 patients (mean age 56 years) who presented with unprovoked first episodes of PE (without risk factors such as pregnancy or < 4 weeks post-partum, estrogen therapy, congestive heart failure, history of cancer, connective tissue disease, inflammatory bowel disease, surgery within four weeks requiring general anesthesia, immobilization > 48 hours, indwelling central venous catheter, previous VTE, family history of TE, or body mass index > 40 kg/m\(^2\)), and three control groups consisting of provoked PE (152 patients; mean age 53 years), patients for whom the diagnosis of PE was excluded (91 patients, mean age 46 years), and patients in whom PE was not suspected (193 patients, mean age 50 years). Ten per cent of patients in the unprovoked PE group had either FVL or PM, compared to 13% of patients in the provoked PE group, 7% of those in which PE was not suspected, and 2% in those in the PE-excluded group. A statistically significant difference was found only between the number of patients who had a mutation in the provoked PE group and the PE-excluded group (difference 11%; 95%CI 4% to18%; \(P = 0.003\)).

The Obeidat et al. study\(^\text{19}\) was a prospective case-control design that included 92 patients with a first episode of acute PE (mean age 47 years); among them 29 had no risk factors (unprovoked PE, risk factors including pregnancy or < 4 weeks post-partum, estrogen therapy, congestive heart failure, history of cancer, connective tissue disease, inflammatory bowel disease, surgery within four weeks requiring general anesthesia, immobilization > 48 hours, indwelling central venous catheter, previous VTE, family history of TE, or body mass index > 40 kg/m\(^2\)). Compared to the control group of 99 healthy subjects of whom 12.1% carried FVL and 0% carried PM, in the group of patients as a whole, 23.9% carried FVL (91% of carriers were heterozygous, 9% were homozygous) and 3.3% carried PM (heterozygosity not reported). Among the subset of the population who presented with unprovoked PE, 27.6% carried FVL and 6.9% carried PM, while the frequency was 22.2% and 1.6%, respectively, in the provoked PE population (the difference in mutation carriers between the two populations was not statistically significant). Heterozygosity status was not reported in population subsets.
In summary, there was evidence that the presence of PM or FVL mutations represents a significant risk factor in the development of unprovoked first episode DVT in young patients. The frequency of either FVL or PM in the unprovoked PE population is not different from the provoked PE population.

### 4.2.5 Clinical utility

**Risk of recurrence following FVL and PM test use**

A case-control study by Coppens et al. examined the effect of FVL and PM testing on recurrence rates of VTE. Data from a registry of 197 patients with VTE recurrence after the first VTE episode (mean age 50 years) and 324 patients without recurrence (mean age 49 years) were analyzed, with stratification into provoked and unprovoked VTE populations. In the population as a whole, the risk of recurrence was similar between tested and non-tested patients: OR 1.2 (95% CI 0.8 to 1.8). Odds ratios for recurrence between tested and non-tested patients were 0.8 (95% CI 0.5 to 1.6) in patients with unprovoked VTE, 1.2 (95% CI 0.5 to 3.1) in patients with surgery/trauma/immobilization-provoked VTE, 3.4 (95% CI 1.3 to 8.6) in patients with oral contraceptive/hormone replacement therapy-provoked VTE. The odds ratio for recurrence was 0.8 (95% CI 0.3 to 2.6) in those who tested positive for FVL or PM, and 1.3 (95% CI 0.8 to 2.1) in those who tested negative. Except in patients taking oral contraceptive/hormone therapy, none of the observed effect estimates were statistically significant. The authors concluded that thrombophilia testing in patients presenting with a first episode of VTE does not reduce the incidence of recurrence. While the overall duration of treatment for the initial VTE appeared similar between the groups experiencing a recurrence (similar proportions in each group received treatment of 1 to 3, 4 to 7, 7 to 12, and greater than 12 months, with the majority receiving 4 to 7 months of treatment), the study did not report the number of patients whose clinical management was changed due to test results. Given that treatment duration was not available based on mutation status, it’s unclear whether the similarity in recurrence risk was due to management differences or lack of difference in baseline risk.

**Evidence-based guidelines**

Three evidence-based guidelines published since 2004 address genetic testing or clinical management for thrombophilia in patients with idiopathic VTE; The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (2010), a UK guideline group selected on behalf of the British Committee for Standards in Haematology (2010), and the 2012 guidelines for the prevention of thrombosis from the American College of Chest Physicians (ACCP).

The EGAPP guidelines state that mutation status does not affect the treatment patients receive to avoid recurrence, and there is convincing evidence that longer-term anticoagulation treatment (greater than three months) reduces the recurrence of VTE in all patients regardless of mutation status. The guideline states that the same consideration of harms and benefits for longer-term warfarin therapy should be applied to all VTE patients, regardless of mutation status. The UK guidelines also state that treatment of acute VTE, lower limb DVT, or PE should not be dependent on mutation status, based on moderate quality of evidence. The guidelines were not able to provide a validated recommendation regarding the selection of patients who should be tested for heritable thrombophilia.
The guidelines produced by the ACCP advise that, based on moderate quality evidence, unprovoked VTE is a primary factor for estimating the risk of VTE recurrence after stopping vitamin K antagonist therapy. They also state that, although hereditary thrombophilia is an additional factor for estimating recurrence risk, there is not enough strong or consistent evidence on the risk contribution to affect the recommendations regarding duration of therapy on the basis of this factor alone.

**4.2.6 Additional Considerations**

In addition to information on the clinical validity and clinical utility of Factor V Leiden and prothrombin mutation testing, other aspects related to their use was considered. Published information on physician ordering practices and psychosocial issues was retrieved and summarized. This information was not systematically reviewed.

**Physician practice patterns**

Physicians’ ordering practices are another issue surrounding testing for thrombophilia. A 2008 study conducted in the US found that tests for FVL were ordered much more often than the less costly and faster functional assay for activated protein C (APC) resistance. This was inconsistent with recommendations by the College of American Pathologists (CAP) 2002 consensus conference, which considered the APC test to be the appropriate first-line test in most cases. Another US study on physician ordering of FVL and test impact on clinical management found that physicians adhered to CAP guidelines 46% of the time, and to American College of Medical Genetics (ACMG) guidelines (published in 2001 and updated in 2005) 61% of the time. The main divergence from CAP guidelines for ordering of FVL tests was for the indications of first event VTE, abnormal pregnancy outcome (excluding fetal loss), arterial thrombosis (including stroke), and family history of VTE. The main divergence from ACMG guidelines was for the indications of arterial thrombosis (including stroke). Physicians modified clinical management for 20.2% of patients who were positive for FVL. These modifications were most often in length or type of anticoagulation treatment, recommendations for other medications (e.g., oral contraceptives), or recommendations for addressing additional risk factors such as surgery or long-distance travel.

**Psychosocial issues**

Testing for thrombophilia has become very common practice, and there is controversy surrounding the appropriateness of screening for the common genetic mutations associated with thrombophilia. There is concern also that screening often occurs without sufficient counselling for the patient regarding the risks, benefits, and potential limitations of testing. Testing for thrombophilia could provide a positive benefit by allowing the patient to make informed decisions for potential lifestyle changes and medical management. Negative psychosocial effects of a positive result could include patient anxiety and problems with obtaining insurance or employee discrimination. As well, positive results could raise questions regarding family testing (offspring of a carrier have a 50% chance of inheriting the mutation) and could lead to unnecessary anticoagulation therapy and the associated risks of overtreatment, such as bleeding, as well as increased costs. Testing may also influence a woman’s choices about exogenous hormone therapy, a known risk factor for thrombosis.
A systematic review published in 2008 studied the psychological impact of testing for thrombophilia.²⁶ The review included six studies, and was not able to reach a conclusion on the psychological impact of the testing, due to the large heterogeneity between studies. The authors stated that testing for thrombophilia did not seem to have any major adverse effects. The review reported on one study that found that approximately 90% of the participants were satisfied with the knowledge of being a carrier, despite increased worry in 43% of participants upon a positive FVL test. The same study reported that 79% of participants incorrectly estimated the associated risk, and that over 60% felt they were not provided sufficient information and had additional questions, highlighting the need for appropriate counselling. None of the included studies took the methods for counselling or provision of information to patients into consideration. The authors indicated a need for more uniformity in the assessment of psychological impact of testing for thrombophilia.

5 PRIMARY ECONOMIC EVALUATION

5.1 Background

The objective of the economic analysis was to determine the cost-effectiveness of testing for factor V Leiden (FVL) and prothrombin (PM) mutations compared to no testing of patients presenting with a first episode of unprovoked (i.e., idiopathic) VTE. This was predicated on the availability of clinical utility information to support the use of the FVL and PM tests.

5.1.1 Literature search

To identify existing economic evaluations of FVL and PM testing, a literature search was performed by searching the EMBASE and MEDLINE databases. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine’s MeSH (Medical Subject Headings), and keywords. The main search concepts were factor V Leiden and prothrombin mutation. A peer-reviewed set of broad health economic filter terms were applied. No filters were applied to limit the retrieval by study type. Retrieval was limited by publication year (2004-2014) and to English language articles. Conference abstracts were not excluded from the search results. The initial search was completed on May 14, 2014, which returned 280 references.

The reference titles and abstracts (where available) were reviewed to determine whether the articles fulfilled the criteria for inclusion:

- economic evaluation or reported the results of an economic evaluation; and,
- undertaken in patients with unprovoked VTE; and
- compared testing for FVL and PM mutations with not testing for these mutations.

Articles that looked at unprovoked VTE in populations who were excluded in the clinical review were also excluded from the economic review (e.g. patients using oral contraceptives, patients undergoing HRT).

Ten articles were retrieved for full review.²⁷-²⁹ No articles fulfilled the requirements for inclusion: three were not in the relevant patient population;²⁷-²⁹ two were not economic evaluations;²⁰,²¹ two were conference abstracts that did not provide enough information;²²,²³ and three were hypothetical cohorts that were not informed by clinical data from an appropriate population.²⁴-²⁶ A further two articles were retrieved for review from a bibliographic search.²⁷,²⁸ Both
were excluded as they were not in the relevant population. These articles did not show up in the primary literature search due to their date of publication.

Although there were no appropriate economic evaluations, several of those retrieved that were in different population, or used hypothetical information, concluded that testing for FVL and PM was not cost-effective.

5.1.2 Review of the clinical information

As noted in the review of the clinical information, three studies examined the clinical validity of the tests, concluding that there was evidence that the FVL and PM mutations are a significant risk factor in the development of unprovoked first DVT, and that there was no difference in the frequency of FVL or PM mutations in the provoked and unprovoked PE populations.

The clinical review found one case-control study that examined the recurrence rates (determined to be a proxy for assessing the clinical utility of the tests) of VTE after the first occurrence from a data registry. The authors concluded that thrombophilia testing in patients presenting with an initial VTE did not reduce the incidence of recurrence.

Three evidence-based guidelines have been published since 2004 addressing genetic testing or clinical management for thrombophilia in patients with idiopathic VTE. While these guidelines do not constitute evidence for clinical utility, they suggest that mutation status does not affect any subsequent treatment patients receive and that although hereditary thrombophilia is a factor for assessing risk of recurrence, there is no strong or consistent evidence to impact recommendations regarding subsequent therapy. The guidelines generally indicate that standard treatment should be anticoagulation for three months, upon which time the patient’s physician should determine whether further treatment is necessary, although the EGAPP guidelines state that there is convincing evidence that longer-term (greater than 3 months) anticoagulation treatment reduces recurrence, regardless of mutation status. While this may be the case, this is discussed as part of the standard management of these patients, regardless of mutation status, and has no bearing on the base case analysis being undertaken. Any increased use of anticoagulants will be associated with different benefits and risks that have not yet been assessed.

As noted in the clinical review, there are no relevant studies that report the clinical sensitivity, specificity, positive predictive value or negative predictive value. Thus, these have not been taken into account in the base case analysis, which focuses purely on the cost of the test.

5.1.3 Reframing the scope of the economics

Given the lack of appropriate economic evaluations, and the paucity of clinical information to support the benefit of either the FVL or prothrombin mutation test in the population of interest, a cost-effectiveness analysis was not undertaken. However, the economic impact of the project was of interest, and so the project was re-scoped as a cost analysis was undertaken.
5.2 Methods

5.2.1 Type of economic evaluation

A cost analysis was undertaken to assess the economic impact associated with testing for FVL and prothrombin mutations compared with not testing, in adult patients presenting with a first episode of unprovoked (i.e. idiopathic) VTE.

In the base case, it was assumed that there is no clinical utility of undertaking testing compared with not undertaking testing, the analysis focuses on a Canadian ministry of health perspective. The payer perspective incorporates only direct costs for healthcare products and services allowed or reimbursed by the payer, which does not normally indicate the inclusion of patient costs.

5.2.2 Clinical scenarios and assumptions

Cost of testing
The published clinical evidence for the relevant population indicates that treatment will not be altered based on the results of genetic testing. Thus, the primary analysis is based on the assumption that the only difference will be the cost of the test.

Scenario analyses
Although the evidence-based guidelines indicate that there is no clinical utility associated with testing, anecdotal evidence and clinical expert opinion suggests that this may not apply in all cases, such as where both FVL and prothrombin mutation tests are positive (double heterozygosity), and where patients are homozygous for either the FVL or prothrombin mutation. In these cases, patients are more likely to receive an extended length of anticoagulation treatment. While this strategy may alter the risk/benefit profile for patients, given the paucity of outcome evidence for this indication, the assumption was made that any change in treatment would not have an impact on patient outcomes for these scenario analyses. As such, a set of secondary analyses were undertaken in which patients testing positive to both the FVL and prothrombin mutations, or homozygous for either the FVL or prothrombin mutation, received alternative treatment regimens. Scenario analyses 1 through 3 were undertaken based partly on guidelines, and clinical expert opinion that indicated that three months of anticoagulation treatment was standard management, but that would be extended for patients with certain mutations. The fourth scenario analysis assumed a standard treatment of six months, which may be reduced to three months if the results of the test came back negative to both mutations. Table 1 reports the details of the four scenarios.

Table 1 Scenarios for the set of scenario analyses

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Patient is tested</th>
<th>Patient is not tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>If test results are negative or heterozygous positive to one of either the FVL or prothrombin mutation tests, patient receives 3 months of anticoagulation. If the patient tests positive to both the FVL or prothrombin mutation tests, or homozygous positive for either the FVL or prothrombin mutations, the patient receives 6 months of anticoagulation</td>
<td>Patient was not tested and received 3 months of anticoagulation (standard treatment)</td>
</tr>
<tr>
<td>2</td>
<td>If test results are negative or heterozygous positive to one of either the FVL or prothrombin mutation tests, patient receives 3 months of anticoagulation. If the patient tests positive to both the FVL or prothrombin mutation tests, or homozygous positive</td>
<td>Patient was not tested and received 3 months of anticoagulation (standard treatment)</td>
</tr>
</tbody>
</table>
for either the FVL or prothrombin mutations, patient receives 12 months of anticoagulation

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>If test results are negative or heterozygous positive to one of either the FVL or prothrombin mutation tests, patient receives 3 months of anticoagulation. If the patient tests positive to both the FVL or prothrombin mutation tests, or homozygous positive for either the FVL or prothrombin mutations, the patient receives anticoagulation for the remainder of their lives (assumed to be 40 years)</td>
<td>Patient was not tested and received 3 months of anticoagulation (standard treatment)</td>
</tr>
<tr>
<td>4</td>
<td>If test results are negative for both the FVL and prothrombin mutations, patient receives only 3 months of anticoagulation. If the patient tests heterozygous positive to either one or both of FVL or PM, or homozygous positive for either FVL or PM, the patient receives 6 months of anticoagulation (assumed standard treatment)</td>
<td>Patient was not tested and received 6 months of anticoagulation (assumed standard treatment)</td>
</tr>
</tbody>
</table>

FVL = Factor V Leiden; PM = prothrombin mutation

This set of scenario analyses also incorporates epidemiological data to provide an estimate of the proportion of patients whose treatment strategy would be altered according to test results based on the scenarios described above, as these would be the patients impacted by the absence of testing.

5.2.3 Data inputs and assumptions

a) Test Costs

There is limited information regarding the cost of these tests. Only one province reports the cost of FVL and/or PM testing in Canada – British Columbia (BC). The schedule of fees provides a price for a 1st and 2nd gene of what appears to be a combined FVL/PM test, however the document does not clarify what is meant by the first and second gene within the document, or what is included within the price (e.g. test, technician time, consumables), and any test sequencing that is required (e.g. 1st gene, 2nd gene).

Based on initial solicitation from lab managers, there appears to be some variation in the cost of the tests based on geographic location. To better understand the variation in cost of tests, a survey was created to solicit information from lab managers across Canada. The responses reflect variation in the provincially set fees for the tests and how they are administered (as individual tests or panel). Panel testing in this section refers only to the FVL and PM tests as a combined test, as opposed to the larger panel tests (which may include other tests such as protein C, protein S, and APC) that are available in some jurisdictions which have not been taken into account in this analysis. The cost of the test was reported to differ based upon the expertise of the person running the test, which may explain differences in responses. A test kit is available that requires no technical skill, but is priced higher than a test that requires a level of technical expertise. Combination or panel testing was reported to be priced at between $15 and $125. While single tests were offered in some provinces, these were not commonly recommended. Single tests were reported to cost between $13 and $77.

A full list of costs for FVL and prothrombin mutation testing are reported in Table 2. The base case analysis presented results based on both the upper and lower costs of testing either FVL and PM as singular tests, or as a combined test. The scenario analyses used the median cost reported in Table 2 – $60 – as the base test cost.
Table 2 Cost of FVL and Prothrombin mutation testing

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Province 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Province 3&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of FVL test</td>
<td>$13.35</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; test: $76.53</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; test: $48.53</td>
</tr>
<tr>
<td></td>
<td>Reagent cost only. Other costs not included</td>
<td>DNA extraction, test kit, capillaries/ tubes/ tips, labour</td>
</tr>
<tr>
<td>Cost of PM test</td>
<td>$13.35</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; test: $76.53</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; test: $48.53</td>
</tr>
<tr>
<td></td>
<td>Reagent cost only. Other costs not included</td>
<td>DNA extraction, test kit, capillaries/ tubes/ tips, labour</td>
</tr>
<tr>
<td>Cost of combined test</td>
<td>$15.19</td>
<td>$60.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$125.45</td>
</tr>
<tr>
<td></td>
<td>Reagent cost only. Other costs not included</td>
<td>Test kit cost. No technical expertise required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DNA extraction, test kit, capillaries/ tubes/ tips, labour</td>
</tr>
</tbody>
</table>

<sup>a</sup>Expert opinion (2014).<br><sup>b</sup>BC Lab Formulary

b) Treatment costs

Clinician feedback from hematopathologists, internists and general physicians was targeted for information pertaining to the clinical management of patients pre- and post-test. Expert opinion was split on whether longer term anticoagulation treatment was appropriate in certain patients, depending on their test results.

Scenario analyses assumed differing lengths of anticoagulation medication use. The anticoagulant used in the analysis was warfarin, based on clinical guidance regarding first-line anticoagulation management. Cost estimates of anticoagulation medication (warfarin) and associated monitoring costs were included. Although these costs can be obtained from the Schedule of Medical Benefits for various jurisdictions, this report undertook the base case analysis using Ontario data (Table 3). The daily dose of warfarin was assumed to be 5 mg, based on a CADTH report of New Oral Anticoagulants compared with warfarin in patients with atrial fibrillation.8 The monitoring costs were based upon this dose of warfarin.

Table 3 Cost of anticoagulation treatment

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Cost</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg warfarin tablet</td>
<td>$0.0675</td>
<td>Ontario provincial drug formulary</td>
</tr>
<tr>
<td>3 months of 5 mg warfarin</td>
<td>$6.16</td>
<td></td>
</tr>
<tr>
<td>6 months of 5 mg warfarin</td>
<td>$12.33</td>
<td></td>
</tr>
<tr>
<td>12 months of 5 mg warfarin</td>
<td>$24.65</td>
<td></td>
</tr>
<tr>
<td>Monitoring costs (annual)</td>
<td>$240.69</td>
<td>CADTH Therapeutic Review (2012)&lt;sup&gt;38&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

c) Epidemiologic information and assumptions

Epidemiologic data was used to inform the cost analysis to determine the economic impact in the cases that there is a difference in usage of anticoagulants, allowing an assessment of the explicit opportunity cost of testing versus not testing. These data were sourced from non-Canadian sources, as no Canadian-specific sources could be identified. The prevalence rates used to inform the secondary cost analysis are reported in Table 4.

Table 4 Epidemiology data

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Value&lt;sup&gt;+&lt;/sup&gt; (range)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterozygous FVL mutation in</td>
<td>NR (15 to 20)</td>
<td>No mean or median prevalence was reported.</td>
</tr>
</tbody>
</table>
patients with a first DVT episode (%) | Thus, the upper rate was used as a proxy. The lower rate was tested in sensitivity analyses.
--- | ---
Heterozygous PM in patients with a first DVT or VTE episode (%)<sup>12,39-41</sup> | 6 (NR) | No ranges were reported.
Homozygosity for FVL (%)<sup>12,42,43</sup> | 0.02 (NR) | No ranges were reported. No clarity was provided regarding the population, thus it was assumed this was in the general population.
Homozygosity for PM (%) | NR | No prevalence rate is reported. The mutation is extremely rare, and as of 2005, only 70 cases had been reported in the literature.<sup>44</sup>
Both FVL and PM in patients with VTE (%) | NR (1 to 5) | No mean or median prevalence was reported. Thus, the upper rate was used as a proxy. The lower rate was tested in sensitivity analyses.

* all values are expressed as percentages (e.g. 0.02% is equivalent to 1 in 5000)
DVT = deep vein thrombosis; FVL = factor V leiden; NR = not reported; VTE = venous thromboembolism

**Epidemiologic assumptions and calculations**

Several assumptions have been made with regards to the prevalence of the mutations and their occurrence in patients presenting with a first episode of VTE:

- prevalence rates of DVT and VTE are similar enough that the rates can be used interchangeably in the absence of better information (see heterozygous PM results);
- prevalence of heterozygosity on either FVL or PM is equal to the sum the upper prevalence rates of FVL (0.20) and PM individually (0.06), minus the prevalence rate of patients having both the FVL and prothrombin mutations (0.05), resulting in a prevalence of at least one mutation of 0.21;
- the prevalence of homozygosity in all patients with FVL is 1 in 5,000 (0.0002). While this is likely to be lower than the prevalence in this population, it is considered a conservative estimate to be applied in this analysis.

Given the prior assumption that only patients with both mutations, or patients who are homozygous will receive lifetime anticoagulation if the mutations are detected, based on the upper prevalence rates, this covers approximately 5% of the population. Thus, 95% of those tested are not going to receive a different treatment based upon the test result – a number needed to test of 20. Using the lower prevalence rates, the number needed to test increases to 100.

### 5.2.6 Sensitivity analyses

A series of one-way sensitivity analyses were undertaken to assess some of the uncertainty with the cost analysis. Ranges were used based on either literature or assumption. Sensitivity analyses were undertaken on the secondary scenario analyses only, as the base case analysis was based purely on the cost of the test.

### 5.3 Results

#### 5.3.1 Base-case analysis

The results of the cost analysis indicate that testing is associated with an increased cost per patient of between $13 and $125 per episode compared to not testing, depending upon the tests run and the province in which the patient is located.
5.3.2 Scenario analyses

The results of a simple cost analysis of the four scenarios indicate that testing is associated with an increased cost per patient, in line with the results reported in the base case (Table 5).

However, the first three scenarios supported by clinical expert opinion that assume an extension to standard management in patients who were double heterozygous or single or double homozygous, the incremental cost per patient of testing compared to not testing can be seen to increase in a linear fashion based upon the amount of anticoagulation received by patients. As noted in the epidemiology section, based on the assumptions made, only 5% of patients in these three scenarios would have their treatment changed based on the results of the tests.

In the one scenario that assumed standard management was six months, and that all patients received six months’ anticoagulation unless they tested negative to both tests, the increased cost per patient to provinces associated with testing was minimal. Were the standard management period longer than six months, it is likely that testing would be cost saving to the province compared with no testing.

Table 5 Scenario analysis results (per patient)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Cost of testing</th>
<th>Cost of not testing</th>
<th>Incremental costs/savings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$129.67</td>
<td>$66.34</td>
<td>$63.33</td>
</tr>
<tr>
<td>2</td>
<td>$136.33</td>
<td>$69.99</td>
<td>$66.33</td>
</tr>
<tr>
<td>3</td>
<td>$655.82</td>
<td>$589.48</td>
<td>$589.48</td>
</tr>
<tr>
<td>4</td>
<td>$143.60</td>
<td>$132.67</td>
<td>$10.92</td>
</tr>
</tbody>
</table>

5.3.3 Sensitivity analyses

The results of the first three scenarios which had similar premises, were robust to changes in the sensitivity analyses, with testing resulting in an increased cost per patient compared to not testing, in areas where testing is currently being conducted (Table 6). The parameters that had the largest effect on the incremental cost of testing for all scenarios were the cost of the test, and the prevalence of patients with homozygous mutations. In the sole scenario that assumed a longer standard treatment, and that standard treatment could be shortened but not increased, the alteration of the parameters changed the results from testing to having an incremental cost per patient to plans, to being cost saving in certain circumstances.
### Table 6 Sensitivity analysis inputs (incremental cost of testing reported per patient per episode)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Base case value</th>
<th>Incremental cost of testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scenario 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost of the test</td>
<td>Lower: $13.35 Upper: $125.45</td>
<td>$60.00</td>
<td>$63.33</td>
</tr>
<tr>
<td>Cost of warfarin</td>
<td>2.5 mg: $0.0674 7.5 mg: $0.1349</td>
<td>5 mg: $0.0675</td>
<td>$63.33 $69.64</td>
</tr>
<tr>
<td>Lifetime horizon</td>
<td>NA</td>
<td>40 years</td>
<td>NA</td>
</tr>
<tr>
<td>Altered prevalence of having both FVL and prothrombin mutations in patients with VTE (%)</td>
<td>1%</td>
<td>5%</td>
<td>$60.68</td>
</tr>
<tr>
<td><strong>Scenario 2</strong></td>
<td></td>
<td></td>
<td>$69.99</td>
</tr>
<tr>
<td>Cost of the test</td>
<td>Lower: $13.35 Upper: $125.45</td>
<td>$60.00</td>
<td>$23.34 $135.44</td>
</tr>
<tr>
<td>Cost of warfarin</td>
<td>2.5 mg: $0.0674 7.5 mg: $0.1349</td>
<td>5 mg: $0.0675</td>
<td>$69.99 $70.92</td>
</tr>
<tr>
<td>Lifetime horizon</td>
<td>NA</td>
<td>40 years</td>
<td>NA</td>
</tr>
<tr>
<td>Altered prevalence of having both FVL and prothrombin mutations in patients with VTE (%)</td>
<td>1%</td>
<td>5%</td>
<td>$62.03</td>
</tr>
<tr>
<td><strong>Scenario 3</strong></td>
<td></td>
<td></td>
<td>$589.48</td>
</tr>
<tr>
<td>Cost of the test</td>
<td>Lower: $13.35 Upper: $125.45</td>
<td>$60.00</td>
<td>$541.45 $653.55</td>
</tr>
<tr>
<td>Cost of warfarin</td>
<td>2.5 mg: $0.0674 7.5 mg: $0.1349</td>
<td>5 mg: $0.0675</td>
<td>$589.41 $638.61</td>
</tr>
<tr>
<td>Lifetime horizon</td>
<td>10 years 20 years 30 years 50 years</td>
<td>40 years</td>
<td>$189.87 $323.08 $456.28 $722.68</td>
</tr>
<tr>
<td>Altered prevalence of having both FVL and prothrombin mutations in patients with VTE (%)</td>
<td>1%</td>
<td>5%</td>
<td>$167.58</td>
</tr>
<tr>
<td><strong>Scenario 4</strong></td>
<td></td>
<td></td>
<td>$10.92</td>
</tr>
<tr>
<td>Cost of the test</td>
<td>Lower: $13.35 Upper: $125.45</td>
<td>$60.00</td>
<td>$(35.73) $76.37</td>
</tr>
<tr>
<td>Cost of warfarin</td>
<td>2.5 mg: $0.0674 7.5 mg: $0.1349</td>
<td>5 mg: $0.0675</td>
<td>$10.93 $6.37</td>
</tr>
<tr>
<td>Lifetime horizon</td>
<td>NA</td>
<td>40 years</td>
<td>NA</td>
</tr>
<tr>
<td>Altered prevalence of FVL mutation in patients with a first DVT episode (%)</td>
<td>15%</td>
<td>20%</td>
<td>$7.61</td>
</tr>
</tbody>
</table>

DVT = deep vein thrombosis; FVL = factor V leiden; NA = not applicable; VTE = venous thromboembolism

## 6 DISCUSSION

### 6.1 Summary of Findings From the Systematic Review

This review examined the use of FVL and PM testing for thrombophilia in patients with a first, unprovoked VTE. Findings on the clinical validity of FVL and PM testing in patients presenting with unprovoked VTE/PE without prior history of VTE/PE are limited. This review did not identify any studies that met our criteria for examining the use of FVL or PM testing in children with idiopathic VTE. The association between FVL and PM mutations and unprovoked first VTE/PE was reported only in a small number of studies that showed that carriers of these mutations had a significantly increased risk, with FVL carrying a stronger association. Our findings are in agreement with other systematic reviews that found that FVL and PM increased the odds of recurrent VTE.45-48 There were no data found on clinical sensitivity, clinical specificity, PPV, or
NPV of FVL and PM tests. A systematic review\textsuperscript{48} reported clinical sensitivity of FVL between 20\% and 50\%, based on a 2003 study,\textsuperscript{49} as well as FVL clinical sensitivity of 28\% (95\% CI 12.9 to 34.6\%) and PM clinical sensitivity of 11\% (95\% CI 6.2 to 21.1\%) to detect recurrent events, based on CDC guidelines.\textsuperscript{50}

Clinical utility refers to the risks and benefits that result from test use. Data on the clinical utility in patients presenting with unprovoked VTE/PE without prior history of VTE/PE are limited. Our report determined clinical utility using the risk of recurrence following FVL and PM testing, recommendations from evidence-based guidelines regarding whether FVL and PM test results should alter the length of anticoagulant use, as well as the test result impact on physician use pattern and potential patient psychosocial outcomes. Our report found that limited data from one study showed thrombophilia testing in patients presenting with a first episode of VTE does not reduce the incidence of recurrence. However this study did not report on specific management decisions for patients with or without a mutation, so results should be interpreted with caution. However, in agreement with the findings on the limited clinical utility of FVL and PM tests, evidence-based guidelines on thrombophilia testing stated that mutation status should not affect the treatment patients receive to avoid recurrence, and that anticoagulation treatment greater than three months reduces the recurrence of VTE in all patients regardless of mutation status. Recognizing the clinical relevance of the ability to predict individual risk of recurrence of VTE, Meijer and Schulman performed a systematic review of the literature on various factors that have been studied in relation to recurrence of VTE, and determined the predictive value of the absence of individual factors on recurrence rate.\textsuperscript{51} The authors found that factors such as negative D-dimer result, non-elevated thrombin generation after discontinuation of anticoagulant therapy, non-elevated factor VIII level, female gender, and distal location of VTE may be indicative of a low risk of recurrence. Absence of FVL and PM mutations, on the other hand, was found to be unhelpful in guiding the duration of therapy in patients presenting with first event of provoked or unprovoked thrombophilia (negative likelihood ratio for unprovoked VTE of 1.02 for FVL heterozygotes and 0.97 for PM heterozygotes). Negative predictive values and likelihood ratios for recurrence of VTE in the absence of FVL and PM based on recurrence-free survival showed that absence of FVL and PM mutations does not lead to a clinically significant change in recurrence-free survival.

A review in 2007 on the implications of testing for thrombophilia and VTE listed the reasons to test and the reasons to not test for genetic mutations.\textsuperscript{52} The list of reasons to test included the probability that patients and their doctors would like to have an explanation for the episode and the possibility to adjust management based on test results. The reasons not to test included the cost of testing and the psychosocial impact of knowing that one is carrier of the defect. The limited findings from our review on the populations who presented with an unprovoked first DVT/PE showed that testing did not reduce the incidence of recurrence (based on a study with significant limitations), therefore the intention of adjusting management based on test results no longer seems to be a valid reason to test. On the other hand, limited evidence from our review found that testing did not result in major psychological adverse effects to patients, although a positive test did result in an increased worry, thus alleviating the role of psychosocial impact as a reason to not test, especially with sufficient genetic counselling.

### 6.2 Summary of Findings From the Cost Analysis

Based on findings from the clinical and economic reviews, there is no published evidence to indicate that testing for FVL and/or prothrombin mutation is likely to improve the overall clinical outcomes compared with not testing in patients with an unprovoked initial episode of VTE.
The results of the base case cost analysis, which looked solely at the cost of the FVL and PM tests singularly and as a 2-test panel, indicated that public and private plans that currently fund FVL and PM testing should expect a cost saving associated with not undertaking FVL and prothrombin mutation testing. The results of these analyses cannot be extrapolated to larger 3-, 4- or 5-test panels, as the other tests that are included in those panels have not been reviewed for clinical utility or costing information.

The scenario analyses informed by clinical expert opinion, which suggest that treatment may be extended for patients that test positive as double heterozygous, or as homozygous to either FVL or PM mutations, indicates that exclusive of any difference in clinical outcome, testing is associated with an increased cost per patient to plans. One-way sensitivity analyses reported that variances in the costs associated with the treatments and the ranges in prevalence of the mutations did not result in any differences in the direction of the incremental costs, just in the magnitude of the incremental costs.

In the scenario analysis that assumed that treatment may be reduced in patients that test negative to the FVL and prothrombin mutations, the base case indicated that testing was associated with a small incremental cost per patient to plans compared with not testing. However, a series of one-way sensitivity analyses indicated that this result was uncertain and highly dependent upon cost of the test, cost of the subsequent treatment, and prevalence of the various mutations in patients with VTE.

The results of the economic analysis must be interpreted with caution given the assumptions that had to be made as a result of limited clinical evidence for the tests, epidemiology data and variations in costs. Based on the previously identified limitations, the largest uncertainty related to the assumption that testing would result in a change in medical management, however, in most cases testing led to an incremental cost per patient compared to not testing for jurisdictions who are currently funding FVL or prothrombin mutation tests. Only in settings where there is the potential for reduced treatment with anticoagulants based on tests that are negative for both the FVL and prothrombin mutations is there a potential for cost savings to the plan to continue testing. Were information on clinical utility in this population to become available, the analysis should be re-evaluated.

7 CONCLUSIONS

Taken together, findings from the systematic review showed that, despite a significant association between FVL and PM mutations and first unprovoked VTE, there was limited evidence to determine whether FVL or PM mutations increase the risk of future VTE recurrence. Previous reviews that have assessed a broader population of patients with VTE indicate that FVL or PM mutation status may, at best, represent a minor risk factor for recurrent VTE. Evidence on whether FVL or PM testing influences patient management or clinical outcomes was sparse and of insufficient methodological quality to make a meaningful assessment of clinical utility. Furthermore, the available clinical practice guidelines suggest that there is insufficient evidence to warrant differential treatment based on FVL or PM mutation status, and the available data on physician practice outside of Canada indicated that treatment modification based on mutation status may occur relatively infrequently. Taken together, it appears that routine testing for FVL and PM mutations in patients with unprovoked first VTE may have limited clinical effectiveness.
The results of the cost analysis indicate that given the lack of clinical utility associated with FVL and PT mutation testing in patients with an initial unprovoked VTE episode, the incremental costs associated with testing suggest that stopping funding of these tests in jurisdictions that are currently funding these tests would lead to cost savings for the jurisdictions. The results were robust to changes in assumptions based on feedback from clinical experts, as epidemiologic data indicate that the probability that results of tests would affect medical management is low. Only in the situation where negative test results would lead to a reduction in treatment, would testing be cost-saving for plans. Were further information made available that suggested different clinical outcomes for patients, the current analysis may need to be revised.
REFERENCES


## Appendix 1: Literature search strategy

### OVERVIEW

**Interface:** Ovid  
**Databases:** Embase 1974 to 2014 March 13  
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present  
**Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.  
**Date of Search:** March 13, 2014  
**Study Types:** No filters were applied to limit the retrieval by study type. Conference abstracts, comments, editorials, letters, case reports and caase studies were removed.  
**Limits:** Humans  
English language  
**Publication years:** 2004-2014

### SYNTAX GUIDE

<table>
<thead>
<tr>
<th>Syntax</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>/</td>
<td>At the end of a phrase, searches the phrase as a subject heading</td>
</tr>
<tr>
<td>.sh</td>
<td>At the end of a phrase, searches the phrase as a subject heading</td>
</tr>
<tr>
<td>MeSH</td>
<td>Medical Subject Heading</td>
</tr>
<tr>
<td>exp</td>
<td>Explode a subject heading</td>
</tr>
<tr>
<td>*</td>
<td>Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings</td>
</tr>
<tr>
<td>ADJ</td>
<td>Requires words are adjacent to each other (in any order)</td>
</tr>
<tr>
<td>ADJ#</td>
<td>Adjacency within # number of words (in any order)</td>
</tr>
<tr>
<td>.ti</td>
<td>Title</td>
</tr>
<tr>
<td>.ab</td>
<td>Abstract</td>
</tr>
<tr>
<td>.jn</td>
<td>Journal name</td>
</tr>
<tr>
<td>.pt</td>
<td>Publication type</td>
</tr>
<tr>
<td>.po</td>
<td>Population group [PsychInfo only]</td>
</tr>
<tr>
<td>.nm</td>
<td>Name of substance word</td>
</tr>
<tr>
<td>Pmez</td>
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</tr>
<tr>
<td>oemezd</td>
<td>Ovid database code; Embase 1974 to present, updated daily</td>
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## Multi-database Strategy

<table>
<thead>
<tr>
<th>#</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Factor V Leiden.nm.</td>
</tr>
<tr>
<td>2</td>
<td>exp Factor V/ and (exp mutation/ or (Leiden or G1691A or R506Q or ARG506 or (ARG adj3 &quot;506&quot;) or mutation*).ti,ab.)</td>
</tr>
<tr>
<td>3</td>
<td>(FV Leiden or FVL).ti,ab.</td>
</tr>
<tr>
<td>4</td>
<td>(&quot;Factor V&quot; adj3 (Leiden or G1691A or R506Q or ARG506 or (ARG adj3 &quot;506&quot;) or mutation*)).ti,ab.</td>
</tr>
<tr>
<td>5</td>
<td>or/1-4</td>
</tr>
<tr>
<td>6</td>
<td>prothrombin/ and (exp mutation/ or (G20210A or &quot;20210&quot; or 20210A or 20210GA or mutation*).ti,ab.)</td>
</tr>
<tr>
<td>7</td>
<td>(&quot;factor II&quot; or FII or &quot;factor 2&quot; or &quot;factor ii&quot; or prothrombin) adj3 (G20210A or &quot;20210&quot; or 20210A or 20210GA or mutation*)).ti,ab.</td>
</tr>
<tr>
<td>8</td>
<td>((G20210A adj2 mutation*) or &quot;PT mutation&quot; or &quot;PT 20210&quot; or PT20210).ti,ab.</td>
</tr>
<tr>
<td>9</td>
<td>or/6-8</td>
</tr>
<tr>
<td>10</td>
<td>5 or 9</td>
</tr>
<tr>
<td>11</td>
<td>Genetic testing/ or molecular diagnostic techniques/ or exp Mass screening/ or early diagnosis/ or *diagnosis/</td>
</tr>
<tr>
<td>12</td>
<td>(test or tests or tested or testing* or screen or screening* or screened or assay or assays).ti,ab.</td>
</tr>
<tr>
<td>13</td>
<td>(detect or detection or detecting* or detected or diagnos*).ti.</td>
</tr>
<tr>
<td>14</td>
<td>Genetic test*.jn.</td>
</tr>
<tr>
<td>15</td>
<td>or/11-14</td>
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</table>
10 and 15
16 use pmez
18 blood clotting factor v leiden/
19 (FV Leiden or FVL).ti,ab.
   ("Factor V" adj3 (Leiden or G1691A or R506Q or ARG506 or (ARG adj3 "506") or mutation*)).ti,ab.
21 or/18-20
   prothrombin/ and (exp gene mutation/ or (G20210A or "20210" or 20210A or 20210GA or mutation*).ti,ab.
   ("factor II" or FII or "factor 2" or "factor ii" or prothrombin) adj3 (G20210A or "20210" or 20210A or 20210GA or mutation*).ti,ab.
24 ((G20210A adj2 mutation*) or "PT mutation" or "PT 20210" or PT20210).ti,ab.
25 or/22-24
26 or 21 or 25
   Genetic screening/ or molecular diagnosis/ or early diagnosis/ or *diagnosis/ or exp diagnostic test/ or exp laboratory diagnosis/ or diagnostic accuracy/ or screening test/
   (test or tests or tested or testing* or screen or screening* or screened or assay or assays).ti,ab.
29 (detect or detection or detecting* or detected or diagnos*).ti.
30 Genetic test*.jn.
31 or/27-30
32 or 26 and 31
33 32 use oemezd
34 conference abstract.pt.
35 33 not 34
36 17 or 35
37 exp animals/
38 exp animal experimentation/ or exp animal experiment/
39 exp models animal/
40 nonhuman/
41 exp vertebrate/ or exp vertebrates/
42 animal.po.
43 or/37-42
44 exp humans/
45 exp human experimentation/ or exp human experiment/
46 human.po.
47 or/44-46
48 43 not 47
49 36 not 48
50 (comment or newspaper article or editorial or letter or note).pt.
51 49 not 50
52 case reports.pt.
53 case report/
54 case study/
55 or/52-54
56 51 not 55
57 limit 56 to english language

58 limit 57 to yr="2004 -Current"

59 remove duplicates from 58

### OTHER DATABASES

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<thead>
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</tr>
<tr>
<td>Cochrane Library</td>
<td>Same MeSH, keywords, and date limits used as per Medline search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.</td>
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</table>

### Grey Literature

- **Dates for Search:** March 2014
- **Keywords:** Factor V Leiden, FVL, FV Leiden, R506Q, G1691A, ARG506 , prothrombin mutation, factor II mutation, G20210A, 20210GA
- **Limits:** Publication years 2004-2014

Relevant websites from the following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based searching” ([http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters](http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters)) was searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search
- Open Access Journals
APPENDIX 2: Data Extraction Form for Accuracy and Clinical Effectiveness Review

<table>
<thead>
<tr>
<th>Reviewer</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>RefID</td>
<td></td>
</tr>
<tr>
<td>Author, Date</td>
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</tr>
<tr>
<td>Country of origin</td>
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**Study characteristics**

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<thead>
<tr>
<th>Study design</th>
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<td>Study duration</td>
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<tr>
<td>Eligibility criteria</td>
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</tr>
<tr>
<td>Type of assay</td>
<td></td>
</tr>
<tr>
<td>Conflict of interests (yes, no, none declared, not mentioned)</td>
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</tbody>
</table>

**Other**

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<tr>
<th>Patient characteristics</th>
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<th>Control</th>
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<tr>
<td>Number enrolled</td>
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<td></td>
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<tr>
<td>Number completing study</td>
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<td>Age, Gender</td>
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**Other**

**Outcomes**

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<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
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<table>
<thead>
<tr>
<th>NPV</th>
<th>Clinical utility</th>
<th>Benefits</th>
<th>Risks</th>
<th>Costs</th>
<th>Availability</th>
<th>Acceptability</th>
<th>Interest</th>
<th>Ethical, legal, social implications</th>
<th>Other</th>
<th>Other</th>
<th>Thrombophilia testing</th>
<th>Non-testing</th>
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<tbody>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Notes</td>
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</tbody>
</table>
APPENDIX 3: Included and Excluded Studies

Included studies

Included clinical studies


Included guidelines


Excluded studies

Inappropriate comparator


**Inappropriate intervention**


**Inappropriate outcomes**


Inappropriate population


Koshy A, Jeyakumari M. Factor V Leiden is not commonly associated with idiopathic portal vein thrombosis in Southern India. Indian J Gastroenterol [Internet]. 2006 [cited 2014 Jun


Inappropriate study type (e.g., review, letter)


Other (not published in English)

APPENDIX 4: Selection of Included Studies

2,028 citations identified from electronic literature search and screened

1,935 citations excluded

93 potentially relevant articles retrieved for scrutiny (full text, if available)

2 potentially relevant reports retrieved from other sources (grey literature, hand search)

95 potentially relevant reports

88 reports excluded:
- inappropriate study design or review, letter, etc. (8)
- inappropriate comparator (5)
- inappropriate intervention (1)
- inappropriate population (63)
- inappropriate outcomes (10)
- not published in English (1)

4 clinical studies and 3 evidence-based guidelines
## APPENDIX 5: Study Characteristics

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Study Design; Duration</th>
<th>Country</th>
<th>Study Objective</th>
<th>Eligibility Criteria</th>
<th>Author Conflicts of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coppens, 2008&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Prospective case-control; 8 years</td>
<td>The Netherlands</td>
<td>“To investigate whether thrombophilia testing reduces the risk of recurrent VT by virtue of these management alterations.” p. 1474</td>
<td>Patients aged 18-70 years with 2nd VT (controls had only 1st VT)</td>
<td>No</td>
</tr>
<tr>
<td>Kruse, 2006&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Prospective case-control; 32 months</td>
<td>US</td>
<td>“…to measure the frequency of the thrombophilic genotypes…in patients with idiopathic PE (cases) compared with control patients diagnosed with PE in the presence of overt risk factors.” p. 1027</td>
<td>Patients with idiopathic PE</td>
<td>Not declared</td>
</tr>
<tr>
<td>Mansilha, 2006&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Prospective case-control; Duration not reported</td>
<td>Portugal</td>
<td>“To evaluate the association between the Factor V Leiden (FV R506Q) and prothrombin gene (FII G20210A) mutations and deep venous thrombosis (DVT) in young people.” p. 24</td>
<td>Patient &lt; 40 years old with 1st episode of DVT</td>
<td>Not declared</td>
</tr>
<tr>
<td>Obeidat, 2009&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Prospective case-control; 2 years</td>
<td>Jordan</td>
<td>“To study the frequency of Factor V Leiden (FVL), prothrombin gene mutation G20210A… in patients with acute pulmonary embolism (PE); and to investigate whether these factors are more frequent in patients who have no obvious risk factors for venous thromboembolism compared to those with obvious risk factors.” p. 921</td>
<td>Patients ≤ 60 years old, with confirmed idiopathic PE</td>
<td>Not declared</td>
</tr>
</tbody>
</table>

DVT = deep vein thrombosis; PE = pulmonary embolism; VT = venous thromboembolism
## APPENDIX 6: Patient Characteristics

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Study arms</th>
<th>Number enrolled</th>
<th>Gender (Male/Female)</th>
<th>Age (mean years)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coppens, 2008</strong>&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Patients with a 2&lt;sup&gt;nd&lt;/sup&gt; VTE</td>
<td>197 (106 had idiopathic VTE)</td>
<td>120(60%) / 77(40%)</td>
<td>50 ± 13 SD</td>
</tr>
<tr>
<td></td>
<td>Control: Patients with 1&lt;sup&gt;st&lt;/sup&gt; VTE only</td>
<td>324 (130 had idiopathic VTE)</td>
<td>179(55%) / 145(45%)</td>
<td>49 ± 13 SD</td>
</tr>
<tr>
<td><strong>Kruse, 2006</strong>&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Patients with idiopathic PE</td>
<td>49</td>
<td>32(65%) / 17(35%)</td>
<td>56 ± 16 SD</td>
</tr>
<tr>
<td></td>
<td>Control: Patients with a) non-idiopathic PE; b) patients with PE excluded; and c) patients not suspected of having PE</td>
<td>Total: 436 a)152; b) 91; c) 193</td>
<td>a) 55(36%) / 97(64%); b) 30(33%) / 61(67%); c) 77(40%) / 116(60%)</td>
<td>a) 53 ± 17 SD; b) 46 ± 10 SD; c) 50 ± 10 SD</td>
</tr>
<tr>
<td><strong>Mansilha, 2006</strong>&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Patients &lt; 40 years old, with 1&lt;sup&gt;st&lt;/sup&gt; DVT</td>
<td>99</td>
<td>31(31%) / 68 (69%)</td>
<td>27 (range 16-40)</td>
</tr>
<tr>
<td></td>
<td>Healthy controls</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Obeidat, 2009</strong>&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Patients with acute PE</td>
<td>92</td>
<td>34(37%) / 58(63%)</td>
<td>49.5 ± 16.7 SD</td>
</tr>
<tr>
<td></td>
<td>Healthy controls</td>
<td>99</td>
<td>38(38%) / 61(62%)</td>
<td>31.0 ± 10.1 SD</td>
</tr>
</tbody>
</table>

*VTE = venous thromboembolism; PE = pulmonary embolism; SD = standard deviation*

---

DVT = deep vein thrombosis; NR = not reported; PE = pulmonary embolism; SD = standard deviation; VTE = venous thromboembolism
APPENDIX 7: Summary of Critical Appraisal of Included Studies

Table A3: Critical Appraisal of Clinical Studies (Downs and Black Checklist) 

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coppens, 2008</td>
<td>• The hypothesis/aim/objective of the study is clearly described.</td>
<td>• The distributions of principal confounders in each group of subjects to be compared is described, however they are not presented in a clear enough manner for use of some data.</td>
</tr>
<tr>
<td></td>
<td>• The main outcomes to be measured, patient characteristics, interventions of interest, and main findings of the study are clearly described.</td>
<td>• Other important adverse events that may be a consequence of the intervention were not reported.</td>
</tr>
<tr>
<td></td>
<td>• The study provides estimates of the random variability in the data for the main outcomes.</td>
<td>• Actual probability values were not reported.</td>
</tr>
<tr>
<td></td>
<td>• The included subjects are representative of the entire population from which they were recruited.</td>
<td>• It is not apparent that an attempt was made to blind those measuring the main outcomes of the intervention.</td>
</tr>
<tr>
<td></td>
<td>• The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The time period between the intervention and outcome is the same for cases and controls.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Statistical tests used to assess the main outcomes were appropriate.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The main outcome measures used were accurate (valid and reliable).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The cases and controls were recruited from the same population and over the same time.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance &lt;5%.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The distributions of principal confounders in each group of subjects to be compared is described, however they are not presented in a clear enough manner for use of some data.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The subjects comprised a high proportion of African-Americans, so may not be representative of the entire population from which they were recruited.</td>
<td></td>
</tr>
<tr>
<td>Kruse, 2006</td>
<td>• The hypothesis/aim/objective of the study is clearly described.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The main outcomes to be measured are clearly described.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The characteristics of the patients included in the study are clearly described.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The interventions of interest are clearly described.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The main findings of the study are clearly described.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The study provides estimates of the random variability in the data for the main outcomes.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Actual probability values were reported (except where $P$ is less than 0.001).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• An attempt was made to blind those measuring the main outcomes of the intervention.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The time period between the intervention and outcome is the same for cases and controls.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Statistical tests used to assess the main outcomes were appropriate.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The main outcome measures used were accurate (valid and reliable).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The cases and controls were recruited from the same population.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The cases and controls were recruited over the same time.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• There was adequate adjustment for confounding in the analyses from which the main findings were</td>
<td></td>
</tr>
<tr>
<td>First author, year</td>
<td>Strengths</td>
<td>Limitations</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------</td>
<td>-------------</td>
</tr>
</tbody>
</table>
| Mansilha, 2006³⁸  | • The hypothesis/aim/objective of the study is clearly described.  
• The main outcomes to be measured are clearly described.  
• The interventions of interest are clearly described.  
• The distributions of principal confounders in each group of subjects to be compared is clearly described.  
• The main findings of the study are clearly described.  
• The study provides estimates of the random variability in the data for the main outcomes.  
• Actual probability values were reported (except where \( P \) is less than 0.001).  
• The subjects asked to participate in the study are representative of the entire population from which they were recruited.  
• An attempt was made to blind those measuring the main outcomes of the intervention.  
• The time period between the intervention and outcome is the same for cases and controls.  
• Statistical tests used to assess the main outcomes were appropriate.  
• The main outcome measures used were accurate (valid and reliable).  
• The cases and controls were recruited from the same population.  
• The study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance <5%. | • The characteristics of the patients included in the study are not clearly described; little detail is provided.  
• Two failed reactions occurred in laboratory measurements, but the characteristics of those patients were not described.  
• The time frames for selection of patients and controls are not reported.  
• It is not apparent if there was adequate adjustment for confounding in the analyses from which the main findings were drawn.  
• The distributions of principal confounders in each group of subjects to be compared is clearly described.  
• The main findings of the study are clearly described.  
• The characteristics of the patients included in the study are clearly described.  
• The interventions of interest are clearly described.  
• The main findings of the study are clearly described.  
• Actual probability values were reported  
• The subjects asked to participate in the study are representative of the entire population from which they were recruited.  
• The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.  
• The time period between the intervention and outcome is the same for cases and controls. |
### Table A3: Critical Appraisal of Clinical Studies (Downs and Black Checklist)"

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
|                    | - Statistical tests used to assess the main outcomes were appropriate.  
- The main outcome measures used were accurate (valid and reliable).  
- The cases and controls were recruited from the same population.  
- The cases and controls were recruited over the same time.  
- The study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance <5%. | |
### APPENDIX 8: Summary of Critical Appraisal of Included Guidelines

<table>
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<tr>
<th>Guideline Producer, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Evaluation of Genomic Applications in Practice and Prevention (EQAPP) Working Group, 2011 | • scope and purpose of the guidelines are clear  
• the recommendations are specific and unambiguous  
• the method for searching for and selecting the evidence are clear  
• methods used for formulating the recommendations are clearly described  
• health benefits, side effects and risks were stated in the recommendations  
• target users of the guideline are clearly defined  
• potential cost implications of applying the recommendation was considered | • unclear whether patients’ views and preferences were sought  
• unclear whether the guideline was piloted among target users  
• procedure for updating the guidelines not provided  
• level of evidence not graded |
| British Committee for Standards in Haematology, 2010 | • scope and purpose of the guidelines are clear  
• the recommendations are specific and unambiguous  
• the method for searching for and selecting the evidence are clear  
• methods used for formulating the recommendations are clearly described  
• health benefits, side effects and risks were stated in the recommendations  
• target users of the guideline are clearly defined  
• the guideline was piloted among target users  
• procedure for updating the guidelines provided  
• potential cost implications of applying the recommendation was considered  
• level of evidence graded | • unclear whether patients’ views and preferences were sought  
• unclear whether the guideline was piloted among target users  
• procedure for updating the guidelines not provided  
• unclear whether potential cost implications of applying the recommendation was considered |
| American College of Chest Physicians (ACCP), 2012 | • scope and purpose of the guidelines are clear  
• the recommendations are specific and unambiguous  
• the method for searching for and selecting the evidence are clear  
• methods used for formulating the recommendations are clearly described  
• health benefits, side effects and risks were stated in the recommendations  
• target users of the guideline are clearly defined  
• the guideline was piloted among target users  
• procedure for updating the guidelines provided  
• potential cost implications of applying the recommendation was considered  
• level of evidence graded | • unclear whether patients’ views and preferences were sought |
APPENDIX 9: SUMMARY OF CRITICAL APPRAISAL OF EXCLUDED STUDIES

<table>
<thead>
<tr>
<th>First year, author</th>
<th>Country</th>
<th>Reason for exclusion</th>
<th>Summary</th>
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<tbody>
<tr>
<td>Compagni (2013)(^{27})</td>
<td>Italy</td>
<td>Not in the relevant patient population</td>
<td>Two decision models were undertaken to screening for FVL and PM in women who requested oral contraception.</td>
</tr>
<tr>
<td>Smith (2008)(^{26})</td>
<td>NR</td>
<td>Not in the relevant patient population</td>
<td>This economic evaluation focused on female relative of FVL carriers being screened prior to oral contraceptive use.</td>
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<tr>
<td>Wu (2006)(^{23})</td>
<td>Review</td>
<td>Not in the relevant patient population</td>
<td>The authors undertook a systematic review and cost-effectiveness analysis of universal and selective VTE in of women receiving oral contraceptives, HRT, at onset of pregnancy, or in patients undergoing major orthopaedic surgery. Thus, these were not patients with idiopathic VTE.</td>
</tr>
<tr>
<td>Donadini (2011)(^{30})</td>
<td>Review</td>
<td>Not in economic evaluations</td>
<td>This paper reviews the available information regarding the treatment of patients with unprovoked VTE. The authors conclude that there is currently no evidence to support extended AC after the initial 3 or 6 month treatment period. While costs associated with risk of bleeding were discussed in the abstract, there was no explicit discussion of costs of testing or treatment.</td>
</tr>
<tr>
<td>Paci (2009)(^{31})</td>
<td>Review</td>
<td>Not in economic evaluations</td>
<td>This paper provided a synthesis of past and emerging literature on cost-effectiveness studies that evaluate pharmacogenomics (PGx) tests – including FVL and PM, noting that the scarcity of evidence creates a barrier to testing in this era of personalized medicine. The authors noted a large clinical evidence gap associated with several of the PGx tests</td>
</tr>
<tr>
<td>Smith (2013)(^{32})</td>
<td>US</td>
<td>Conference abstract – not enough information</td>
<td>The authors developed a clinical decision tool a cost component, on the basis of the assumption that the presence of heritable thrombophilia does not have any impact on patient management. The authors looked at a larger panel of tests that included FVL and PM. The tool recommended that patients with recent prior incidences of thrombosis or those already on AC treatment should not be tested. This reduced the mean annual costs associated with testing from $13,700 to $3,600. The authors note that patient outcome should be assessed in future studies.</td>
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<tr>
<td>Mahajerin (2012)(^{33})</td>
<td>US</td>
<td>Conference abstract – not enough information</td>
<td>Evaluated the cost of thrombophilia testing in children (aged 0 to 20) at a single hospital over a 7 year period. A series of test were done to confirm the presence of thrombophilia, including FVL and PM. The costs associated with</td>
</tr>
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thrombophilia testing were sourced from hospital charge and US Medicaid rates. It isn’t stated, but the assumption is that patients underwent panel testing for various mutations. The authors identified no benefits to testing, and due to the low prevalence of positive tests, concluded that Medicaid could save up to $365 per patient by eliminating routine thrombophilia testing in hospitalized children with VTE.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study Design</th>
<th>Study Details</th>
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</thead>
<tbody>
<tr>
<td>Auerbach (2004)</td>
<td>US</td>
<td>Hypothetical cohort, not informed by relevant clinical data</td>
<td>Markov model assessing strategies of not testing followed by 6 to 36 months of AC in a hypothetical cohort of patients. Five primary health states were identified: Alive and well, alive with AC, postphlebitic syndrome, alive after bleeding sequelae, death. Relative risk of subsequent event alters based on test result, age, year in the model. Risk of event based on health treatment, health states included. Mortality, based on age and event included. Utility values based on health state included. Costs included. Lifetime time horizon, age at entry to model was 40 years. Results indicated that based on the reference strategy (no test, 24 months AC), only testing, and treating positives with 24 months AC followed by observation was represented marginal cost-effectiveness ($11,000/QALY).</td>
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<tr>
<td>Simpson (2009)</td>
<td>UK</td>
<td>Hypothetical cohort, not informed by relevant clinical data</td>
<td>A literature search was undertaken to identify clinical and cost-effectiveness literature comparing thrombophilia testing of patients with thrombosis with no testing, and the resulting long-term AC management and outcomes. No trials were identified that met the inclusion criteria for the clinical effectiveness review. Several papers were identified that investigated CE of interventions for thrombophilia, but none were appropriate. However, based on various assumptions around prevalence of thrombophilia, efficacy and risks of warfarin, clinical outcomes, and costs and utilities, a cost-effectiveness model was undertaken. The results indicate that testing is associated with a cost per QALY of less than £20,000 in patients with PE, and some subgroups of patients with DVT, but there is substantial uncertainty around these values.</td>
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<tr>
<td>O’Brien (2009)</td>
<td>US</td>
<td>Hypothetical cohort, not informed by relevant clinical data</td>
<td>Markov model was developed to evaluate the cost-utility of 3 strategies: (1) no testing and 3 months AC, (2) no testing and 6 months AC, and (3) testing and 3 or 6 months AC; in children with a first episode of thrombosis. A 2 year time horizon was used, and results reported from a societal perspective. The hypothetical cohort was assumed to survive the first event and that testing included not only FVL and PM tests, but also Protein C, Protein</td>
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S, and antithrombin activity levels. Clinical data were limited and based on retrospective surveys, other populations, or assumptions. Utility values were sourced from the Gold et al (1998) paper to provide proxy values. The results indicated a cost per QALY of between $4,500 and $7,000 for all strategies, with no test and 3 months’ AC dominating the other strategies.

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Country</th>
<th>Relevant Population</th>
<th>Description</th>
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<tbody>
<tr>
<td>Eckman (2002)(35233)</td>
<td>US</td>
<td>Not in the relevant patient population</td>
<td>A markov model was used to model FVL testing in VTE survivors from a societal perspective. The analysis looked at 3 hypothetical cohorts of women who suffered an initial episode of VTE, assessing no testing and 6 months’ AC, compared with 3 testing strategies (test positive and get 3 years AC; test positive and get lifelong AC; test negative, no treatment). Further testing (APC-resistance, PCR) was undertaken to assess AC treatment. Several assumptions were made in the model structure. The authors found little agreement in medical literature regarding risk of recurrence in patients with the FVL mutation. Various sources of clinical data used did not assess utility of the test, but with the subsequent treatment efficacy. The results indicated that testing and treating for 3 years was associated with the lowest cost per QALY, dominating the other strategies. The authors did note that the results were highly dependent upon the assumptions made.</td>
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<tr>
<td>Marchetti (2001)(35235)</td>
<td>Italy</td>
<td>Not in the relevant patient population</td>
<td>Undertook a Markov model using a hypothetical cohort of Italian patients with an initial DVT to compare standard AC prophylaxis to screening for FVL and PM and extending AC for patients with double heterozygous mutations. Clinical data for risks and rates of events, and utility values were sourced from similar populations. Cost data was sourced specific to the Italian perspective. The results of the analysis indicated that the cohort that was tested received an incremental 1 quality adjusted life day, at an incremental cost of $40 over the reported lifetime time horizon (model entry age was 60 years).</td>
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</tbody>
</table>

NR = not reported; US = United States of America; UK = United Kingdom