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Effectiveness of Factor V Leiden and Prothrombin Mutation Testing in Patients Presenting With a First Unprovoked Venous Thromboembolic Episode: A Systematic Review and Economic Analysis

Supporting Informed Decisions

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

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ACRONYMS AND ABBREVIATIONS

ACCP	American College of Chest Physicians
APC	activated protein C
APCR	activated protein C resistance
CAP	College of American Pathologists
CI	confidence interval
DVT	deep vein thrombosis
EGAPP	Evaluation of Genomic Applications in Practice and Prevention (Working Group)
F2	factor II
FVL	factor V Leiden
NPV	negative predictive value
OR	odds ratio
PE	pulmonary embolism
PG	prothrombin gene
PPV	positive predictive value
VTE	venous thromboembolism

EXECUTIVE SUMMARY

The Issue

There is a lack of clarity regarding when the tests for factor V Leiden (FVL) and prothrombin gene (PG) mutations should be ordered, and how the test results affect patient management or improve patient health outcomes. Input from internal medicine specialists and general practitioners indicates that genetic testing for these two mutations is included in batch testing and is often performed following a first venous thromboembolism (VTE) event without a clear reason to suspect inherited thrombophilia, resulting in potential overutilization.

Objectives

The objective of this report was to systematically review the available evidence on the association of a positive FVL or PG test with a first, unprovoked VTE (suspected thrombophilia), and the risks and benefits resulting from test use. The report focused on patients presenting with a first episode of unprovoked VTE. The cost implications of FVL and PG testing in Canada were also assessed. The following research questions were addressed:

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?

Methods

A peer-reviewed literature search strategy was employed to identify published literature in the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Library via Wiley; and PubMed. The search strategy comprised both a controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were factor V Leiden, prothrombin mutation, and thrombophilia (for randomized and non-randomized studies). Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic studies, and guidelines. Where possible, retrieval was limited to the human population, and to English language documents published between January 1, 2004 and April 28, 2014. Conference abstracts were excluded from the search results. Supplemental searches were conducted for health technology assessments, systematic reviews, meta-analyses, guidelines, and economic studies. The search was completed on April 28, 2014 and 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 was 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.

Clinical Effectiveness

The literature search identified 2,028 citations. After exclusion of articles with irrelevant study designs, populations, interventions, or outcomes, five studies and three evidence-based guidelines were included in the clinical report. A systematic review of the clinical evidence found that the association between FVL and PG mutations and unprovoked first VTE or pulmonary embolism (PE) was reported only in a small number of studies and showed that carriers of these mutations had a significantly increased risk for VTE, with FVL carrying a stronger association. There were no data found on clinical sensitivity, clinical specificity, positive predictive value (PPV), or negative predictive value (NPV) of FVL and PG tests.

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 were limited. Our report determined clinical utility using the risk of recurrence following FVL and PG testing, recommendations from evidence-based guidelines regarding whether FVL and PG 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. We found that limited data from one study indicated that 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. That being said, in agreement with the findings on the limited clinical utility of FVL and PG tests, evidence-based guidelines on thrombophilia testing state 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. The available data on physician practice outside of Canada indicated that treatment modification based on mutation status may occur relatively infrequently.

Economic Evaluation

In the absence of clinical evidence supporting the utility of thrombophilia testing, a cost analysis was deemed the most appropriate form of economic evaluation to compare testing for FVL and prothrombin mutations with no testing in adult patients presenting with a first episode of unprovoked VTE. The analysis was undertaken from a Canadian ministry of health perspective and included only direct costs for health care products and services allowed or reimbursed by the payer, such as the cost of the tests and the cost of subsequent anticoagulation treatment. Estimated prevalence of the mutations was also factored in. The base case compared only the cost of the tests, while a series of four hypothetical scenario analyses were undertaken based upon anecdotal evidence and clinical feedback that certain subsets of patients that test positive for FVL and/or prothrombin mutations may receive extended anticoagulation treatment. One-way sensitivity analyses were undertaken around the input parameters.

The results of the cost analysis found thrombophilia testing to be associated with a higher cost to the payer in the base case and scenario analyses; however, the magnitude of the cost was dependent upon the duration of anticoagulation treatment (incremental cost of $10 to $590 per patient). One-way sensitivity analyses did not greatly alter the magnitude of the incremental cost to the payer associated with thrombophilia testing in three of the four scenarios. However, in the fourth scenario, altering the cost of the test affected the direction of the results — from an incremental cost to a slight incremental saving. Several caveats with the analysis were identified, such that 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 for different jurisdictions in Canada.

Conclusions

Findings from the systematic review showed that, despite a significant association between FVL and PG mutations and first unprovoked VTE, there was limited evidence to determine whether FVL or PG mutations increase the risk of future VTE recurrence. Evidence on whether FVL or PG 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 PG 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 PG 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 PG 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 payers. If further information was to be made available that suggested different clinical outcomes for patients, the current analysis might need to be revised.

1 INTRODUCTION

Venous thromboembolism (VTE) is a condition that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT refers to the formation of a blood clot in a deep vein, typically in the leg. These clots can dislodge and travel to the lung, resulting in PE. In patients with a first, unprovoked VTE, the 30-day case fatality rate is 4% and the one-year case fatality rate is 14.5%.[1] The annual incidence of VTE is between one and two events per 1,000 in the general population.[2,3] Approximately 50% of all patients with a first DVT are considered to have an unprovoked event, in that there are no known acquired risk factors such as recent surgery, trauma, malignancy, pregnancy, immobilization, or use of exogenous estrogen.[4] Upon presentation with a VTE, treatment with parenteral anticoagulation or an oral direct inhibitor of coagulation is recommended, followed by long-term oral anticoagulation therapy with warfarin or one of the newer oral anticoagulant agents to prevent VTE recurrence.[5]

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 an increased risk of VTE.[6] Thrombophilias can be inherited, acquired, or due to a combination of inherited and acquired factors. Inherited thrombophilias are due to mutations in one or more genes that encode coagulation proteins. The risk of developing a clinically significant blood clot is higher if an individual is homozygous for an inherited thrombophilia (i.e., both copies of the genes are mutated) rather than heterozygous (i.e., one copy of the gene is normal and one copy has a mutation). It is estimated that nearly 10% of the population has an underlying thrombophilia, the two most common being factor V Leiden (FVL) thrombophilia and prothrombin gene (PG, also known as factor II) thrombophilia.[7-9] FVL thrombophilia and PG thrombophilia are associated with an increased risk of venous thrombosis, as well as a higher risk for a number of complications in pregnancy.[10-13] FVL and PG thrombophilias are typically low-risk thrombophilias, in that the presence of either of these mutations confers a small increased risk of abnormal clots.[7,14]

FVL thrombophilia is caused by a mutation in the gene for factor V (*F5G1691A* mutation resulting in an R506Q amino acid substitution), a coagulation protein. 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 mutation increases the risk of VTE from 1 in 1,000 to 3 to 8 in 1,000 and being homozygous increases the risk to 80 in 1,000.[14] Between 3% and 8% of people with European ancestry carry one copy of the FVL mutation (heterozygous) and about 1 in 5,000 people have two copies of the mutation (homozygous).[8] European populations have the highest prevalence of the mutation. Extrapolated to the full Canadian population, an estimated 1.76 million Canadians (5%) are heterozygous for the FVL mutation and approximately 7,000 Canadians are homozygous.[8]

Prothrombin thrombophilia is caused by a mutation in the factor II (*F2*) gene (*F2G20210A* mutation in an untranslated region). The mutation results in an overactive *F2* gene that causes too much prothrombin to be produced, increasing the risk of thrombosis. This 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.[7] In the US and Europe, it is estimated that 1 in 50 Caucasians have prothrombin thrombophilia; this would amount to 703,000 individuals in Canada.[15] The prevalence is lower in Asian, African-American, and Native-American populations.

Commercial tests available in Canada to detect FVL G1691A mutations and prothrombin G20210A mutations include the Factor V Leiden Kit and Factor II (Prothrombin) G20210A Kit (Roche Molecular Diagnostics, California, US), and the Xpert HemosIL FII & FV Assay (Instrumentation Laboratory, Massachusetts, US). Using polymerase chain reaction restriction fragment length polymorphism or allele-specific polymerase chain reaction as reference standards, these kits were found to have excellent analytical validity in detecting the mutations. A systematic review of methods to identify FVL or PG mutations reported a greater than 99% concordance with reference methods; discordance was resolved by test repetition in most cases, suggesting operator or administrative errors.[16] 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 arising from a small number of labs.[16]

Use of the tests in clinical practice varies across Canada. Tests for FVL and PG mutations may be ordered individually, together, or as part of a panel of tests, including tests for protein S deficiency, protein C deficiency, or antithrombin deficiency.[17] In some cases, investigations for FVL mutations begin with testing for APC resistance (APCR). Most, but not all, patients who have APCR have FVL mutations. Tests may be ordered by a number of different medical specialties, including internists, neurologists, and family doctors. A study of ordering practices at Vancouver General Hospital in British Columbia indicated that the majority of testing for heritable thrombophilia was ordered by general practitioners (36.8%), followed by general internists (16.3%).[17]

FVL and PG tests are often ordered after a first-time VTE when other provoking factors, such as trauma or malignancy, are absent. They may also be ordered in other situations; for example, in patients with a history of recurrent VTE or women with repeat miscarriages. Positive tests may also lead to testing of children and other family members; as the mutations are inherited in an autosomal dominant manner, children of a heterozygous parent have a 50% chance of inheriting the mutation.[18]

Upon presentation with a VTE, treatment consists of parenteral anticoagulation or an oral direct inhibitor of coagulation, followed by long-term therapy to prevent recurrence. In most situations, a course of at least three months of anticoagulation therapy is recommended. Longer treatment durations are generally prescribed for unprovoked VTE.[5] Although practice varies, patients carrying FVL or PG mutations may receive extended anticoagulation therapy beyond three months (e.g., six months or in some cases indefinitely), particularly carriers of both FVL and PG mutations or those homozygous for one of the mutations.

2 ISSUE

There is a lack of clarity regarding when the tests for FVL and PG mutations should be ordered and how the tests impact patient management or improve patient health outcomes. Canadian laboratory managers surveyed by CADTH have identified FVL and PG testing as tests that are potentially overutilized. 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.

In addition to the costs associated with potential overutilization, inappropriate use of FVL and PG testing may lead to over-treatment with anticoagulation therapy, which is associated with an

increased risk of bleeding. Other potential adverse consequences of testing are over-investigation of patients who test positive, subsequent difficulties in obtaining life and disability insurance, and, if the findings are negative, false reassurance regarding the risk of recurrence. Testing may also lead to increased anxiety and present other psychosocial challenges for patients and their families.

3 OBJECTIVES

Given the relatively low risk to patient health associated with FVL and PG thrombophilias, and the potential overutilization of FVL and PG 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 association of a positive FVL or PG test with a first unprovoked VTE, the association between a positive FVL or PG test and VTE recurrence after unprovoked VTE, and the risks and benefits resulting from the use of the tests. The cost implications of FVL and PG testing in Canada are also assessed. The report addresses the following research questions:

1. What is the clinical validity of FVL and PG mutation tests in patients presenting with a first episode of unprovoked VTE?
2. What is the clinical utility of FVL and PG mutation tests compared to no testing in patients presenting with a first episode of unprovoked VTE?
3. What is the cost-effectiveness of FVL and PG mutation tests compared to no testing in patients presenting with a first episode of unprovoked 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 (1974-) via Ovid; The Cochrane Library via Wiley; and PubMed. The search strategy comprised 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 (FVL), prothrombin mutation, and thrombophilia (for randomized and non-randomized studies).

The search was completed on April 28, 2014. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic studies, and guidelines. Where possible, retrieval was limited to the human population. Retrieval was limited to English language documents published between January 1, 2004 and April 28, 2014. Conference abstracts were excluded from the search results. (See Appendix 1 for the detailed search strategies.) Supplemental searches were conducted for health technology assessments, systematic reviews, meta-analyses, guidelines, and economic studies.

Grey literature (literature that is not commercially published) was identified by searching selected sections of the *Grey Matters* checklist (http://www.cadth.ca/resources/grey-matters): health technology assessments, health economics, clinical practice guidelines, databases, and Internet search. Google was 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. (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 information on outcomes of interest.

Table 1: Selection Criteria

Population	Patients presenting with unprovoked (idiopathic) first episode of VTE [a]
Intervention	FVL or prothrombin mutation assays available in Canada
Comparator	Non-testing (for clinical utility outcomes)
Outcomes	• Clinical validity of the assays (association between FVL and prothrombin mutation and first unprovoked VTE; clinical sensitivity, specificity, PPV, NPV for detecting unprovoked VTE; clinical sensitivity, specificity, PPV, NPV for detecting VTE) • Clinical utility of hereditary thrombophilia testing (benefits and risks of FVL and PG mutation testing including prevention of recurrence)
Study design	RCTs, observational studies, evidence-based guidelines

FVL = factor V Leiden; NPV = negative predictive value; PG = prothrombin gene; PPV = positive predictive value; RCT = randomized controlled trials; VTE = venous thromboembolism.
[a] Based on Well's Criteria[19] and pulmonary embolism rule-out criteria (PERC)[20] for diagnosing deep vein thrombosis/pulmonary embolism, and input from HTERP (Health Technology Expert Review Panel, HTERP, Ottawa: 2014), VTE was considered unprovoked if patients 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 three days.

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. Studies conducted in pregnant women 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.[21] Disagreements were resolved through consensus. The quality of the included guidelines was assessed using the AGREE II checklist.[22] 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 FVL and PG mutation tests identify unprovoked VTE (i.e., the association between a positive test and a first, unprovoked thromboembolic event). The relationship between the mutations and unprovoked VTE was determined. Outcomes of interest included measures of association such as odds ratios (ORs), as well as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Clinical utility of FVL and PG mutation testing was based on findings about the benefits (how testing influences management of thrombophilia, and whether or not treatment that is guided by test results alters clinical outcomes) and risks resulting from test use.

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

In addition to the systematic review of clinical validity, clinical utility, and practice guidelines, the available literature on the following issues related to genetic testing for thrombophilia was reviewed: physician behaviour and treatment patterns surrounding hereditary thrombophilia testing; availability and cost of testing; interest of and acceptability of testing to patients; and ethical, legal, and social implications of thrombophilia testing. This information was summarized but not systematically reviewed.

4.2 Results

All included studies on the clinical validity and clinical utility of FVL and PG testing in patients with a first unprovoked episode of VTE were observational studies. A narrative summary of study findings is presented, as the data were not amenable to quantitative synthesis.

4.2.1 Quantity of research available

The literature search identified 2,028 citations, from which 1,935 were excluded based on the screening of the 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; and one study, from an external source, was added. Five studies and three evidence-based guidelines were included in the report. A list of included and excluded studies 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.

a) Study designs

A total of five studies were included in this report.[23-27] Four of the included studies were case-control studies conducted in the Netherlands (Coppens et al.),[23] the US (Kruse et al.),[24] Portugal (Mansilha et al.),[25] and Jordan (Obeidat et al.).[26] A fifth study (Rodger et al.)[27] was a prospective cohort study conducted in Canada, Switzerland, the US, and France. Three studies provided information on the association of FVL and PG mutations with first unprovoked VTE;[24-26] and the

Rodger et al. study[27] identified risk factors (including the presence of FVL and PG mutations) for VTE recurrence following oral anticoagulation therapy discontinuation in patients with a first, unprovoked VTE. The Coppens et al. study provided some evidence on the clinical utility of FVL and PG testing.[23]

The Kruse et al. study[24] enrolled patients presenting with idiopathic PE in the emergency department, and blood samples were tested for FVL and PG mutations using a Perkin-Elmer DNA thermal cycler. Idiopathic PE was considered to include the *absence* of:

- recent pregnancy or post-partum, and if there was no use of exogenous estrogen or estrogenic drugs
- a history of malignancy
- recent surgery
- limb or body immobilization for more than 48 hours
- transatlantic air travel within the previous week
- previous VTE.

The purpose of the study was to compare the frequency of FVL and PG mutations in patients with idiopathic PE with patients with PE who had overt risk factors.

The study by Mansilha et al.[25] tested young patients (ages 16 years to 40 years) with a first DVT, for FVL and PG 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 PG mutations and DVT.

Obeidat et al.[26] conducted a study on patients presenting with idiopathic PE, comparing them with healthy controls from the same hospital. Testing for FVL and PG 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 PG mutations in patients with idiopathic PE compared with those with obvious risk factors (including age greater than 60 years, pregnancy, malignancy, surgery, limb immobilization for more than 48 hours, and a previous history of VTE).

Rodger et al.[27] conducted a multi-centre, multi-country study on adult patients with a first unprovoked VTE who were treated with oral anticoagulation therapy for five to seven months, then followed for up to four years for recurrence. Genetic mutations (including FVL and PG mutations) were determined using the ABI PRISM 3100 Genetic Analyzer (Applied Biosystems). The study's objective was to determine what patient characteristics could be used as predictors for risk of VTE recurrence following unprovoked VTE.

Coppens et al.[23] studied patients who had recurrent venous thrombosis and those who did not have recurrence after a first unprovoked VTE. Patients who had been tested for either FVL or PG mutations were compared with those who were not to determine the effect of testing on VTE recurrence. The goal of the study was to determine if changes to the management of patients who were positive for FVL or PG mutations reduced the risk of recurrent VTE. The study did not specify what commercial thermal cycler was used to determine mutation status.

b) Populations

Kruse et al.[24] 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.[26] enrolled 92 patients with acute PE and 99 healthy controls. The Mansilha et al. trial[25] was comprised of 99 patients less than 40 years old with a first DVT, and 100 healthy controls. The Rodger et al. study[27] included 646 patients; 91 patients experienced recurrent VTE during the study period, and 555 patients had no recurrent VTE. The study by Coppens et al.[23] was based on a large case-control study of patients with a first VTE; patients who had a recurrence during the follow-up period (n = 197; 106 with idiopathic VTE) and who did not have a recurrence (n = 324; 130 with idiopathic VTE) were selected.

All studies enrolled adults with VTE; no studies in children were identified.

c) Funding status

One of the studies (Rodger et al.[27]) was partially funded by industry. Sources of funding for the other studies were combinations of foundation grants and federal government grants. Funding details for the included studies are provided in Appendix 5.

d) Guidelines

Three evidence-based guidelines were included in this report. Guidelines were considered to be evidence-based if they were based on a systematic review of evidence and described a literature search strategy.

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 PG mutations in adults with idiopathic VTE and their family members.[28] The recommendations assessed analytic validity, clinical validity, and clinical utility, but the publication did not provide details on the quality of evidence used to inform the guidelines. The authors stated that Agency for Healthcare Research and Quality Evidence-based Practice Center methods were followed in 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; the authors employed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the quality of the available evidence.[9] The guidelines were produced to guide the management of patients and families with venous thrombosis, as well as patients who had experienced pregnancy morbidity, and were not restricted to patients with idiopathic VTE.

The American College of Chest Physicians (ACCP) produced guidelines in 2012 for antithrombotic therapy and the prevention of thrombosis,[5] of which the section on antithrombotic therapy for VTE 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 critical appraisal of individual clinical studies are provided in Appendix 7. The methods for patient selection, patient characteristics, and outcomes were clearly described, with the exception of the Mansilha study, which provided very little detail on patient characteristics.[25] Although all five studies identified potential confounders, reporting was not detailed enough regarding these confounders to determine whether they could have biased study results. Lack of detail in the publications also made it difficult to identify if thrombotic events were idiopathic or provoked.

Two studies, Coppens et al.[23] and Kruse et al.,[24] stated that they performed power calculations to determine the sample size necessary to detect a clinically important effect. Coppens et al.[23] required 200 patients per arm, but they were able to collect data from only 197 patients in the recurrence arm of the study; the Kruse study achieved the necessary sample size. Mansilha et al.,[25] Obeidat et al.,[26] and Rodger et al.[27] did not report if they performed power calculations to determine the minimum sample sizes required.

In the Kruse et al. and Mansilha et al. studies,[24,25] it was reported that technicians performing the genetic tests were blinded. Rodger et al.[27] incorporated physicians who were blinded to the predictor data for adjudication of suspected recurrent VTE and deaths. The remaining two studies did not report on blinding.

The Coppens et al. study[23] did not report clinical management decisions based on mutation status, making it unclear whether the observed associations (or lack thereof) between FVL and PG mutation testing and VTE recurrence were due to changes in management or other factors, and thereby limiting the ability to interpret the findings. Regarding the generalizability of the included studies, Kruse et al. [24] indicated that the patient population in their study may not have been representative of the general US population, as there was a large proportion of African-American patients enrolled. Rodger et al.[27] reported that the patient population in their study was limited to mainly Caucasian patients and did not include patients with known high-risk thrombophilia. The testing methods used in the included studies appeared to be generalizable to Canadian practice.

The guidelines[5,9,28] had clear scope and purpose, clear methods for searching and selecting 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 guidelines were clearly defined. It was unclear whether patients' views and preferences were sought. The UK guideline[9] and the ACCP guideline[5] provided grading of evidence quality for their recommendations. The EGAPP guideline[28] was unclear as to whether the guideline was piloted among target users, a procedure for updating the guidelines was not provided, and the level of evidence was not graded. The UK guideline[9] was unclear as to whether it was piloted among target users and whether potential cost implications of applying the recommendation were considered. A procedure for updating these guidelines was not provided.

4.2.4 Association between FVL and PG mutations and first unprovoked VTE

Three studies examined the relationship between FVL or PG mutations and first unprovoked VTE.[24-26]

The Mansilha et al. investigation[25] 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). In the control group of 100 healthy subjects, 2% carried FVL mutations and 5% carried PG mutations (all carriers were heterozygous). In the DVT patient group, 20.6% and 10.1% of patients carried FVL mutations and PG mutations, respectively. All PG mutation carriers and 95% of FVL mutation carriers in the DVT group were heterozygous (5% of FVL mutation carriers were homozygous). No patients carried both FVL and PG mutations. In the subset of patients with an unprovoked DVT, compared with healthy subjects, there was a significantly increased risk of DVT in carriers of FVL mutations (OR 15.9, 95% confidence interval [CI] 3.2 to 77.9; $P < 0.0001$), while in carriers of PG mutations, 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 the subgroup of patients with unprovoked DVT.

The Kruse et al. study[24] was a prospective case-control study that included a case group consisting of 49 patients (mean age 56 years) who presented with an unprovoked first episode of PE (without risk factors such as pregnancy or less than four 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 for more than 48 hours, indwelling central venous catheter, previous VTE, a family history of thromboembolism, or a body mass index of greater than 40 kg/m^2), and three control groups consisting of patients with 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). In the unprovoked PE group, 10% of patients had either FVL or PG mutations compared with 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[26] 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 (such as unprovoked PE, risk factors including pregnancy or less than four 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 for more than 48 hours, indwelling central venous catheter, previous VTE, a family history of thromboembolism, or a body mass index of greater than 40 kg/m^2). Compared with the control group of 99 healthy subjects, of whom 12.1% carried FVL mutations and 0% carried PG mutations, 23.9% carried FVL mutations in the case group as a whole (91% of carriers were heterozygous, 9% were homozygous) and 3.3% carried PG mutations (heterozygosity not reported). Among the subset of the population who presented with unprovoked PE, 27.6% carried FVL mutations and 6.9% carried PG mutations, 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 from one study that the presence of PG or FVL mutations represents a significant risk factor for experiencing a first unprovoked first DVT in young patients. The frequency of either FVL or PG mutations in the unprovoked PE population is not different from the provoked PE population.

4.2.5 Association between FVL and PG mutations and recurrent VTE

A Canadian prospective cohort study by Rodger et al. sought to determine clinical predictors that can identify patients at low risk of recurrent VTE who could safely discontinue anticoagulant therapy.[27] A total of 646 participants (mean age 53.6 years) with a first, unprovoked VTE were enrolled over a four-year period. The study found that there was no statistically significant association between the risk of recurrence and positive PG or FVL mutation status. Among patients who experienced a recurrent VTE (n = 91), 2 (2.2%) were heterozygous for the PG mutation and 19 (20.9%) carried the FVL mutations. In contrast, among those who did not experience a recurrent VTE (n = 555), 35 (6.3%) were heterozygous for the PG mutation and 81 (14.6%) had an FVL mutation. There was no statistically significant difference in the proportion

of patients heterozygous for PG mutations experiencing recurrence and those who did not (*P* = 0.12). A similar observation was made for FVL mutations (*P* = 0.13).

4.2.6 Risk of VTE recurrence following FVL and PG test use

A case-control study by Coppens et al. examined the effect of FVL and PG testing on recurrence rates of VTE.[23] 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). OR 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, and 3.4 (95% CI 1.3 to 8.6) in patients with oral contraceptive/hormone replacement therapy-provoked VTE. When test result was considered, the OR for recurrence was 0.8 (95% CI 0.3 to 2.6) in those who tested positive for FVL or PG mutations, and 1.3 (95% CI 0.8 to 2.1) in those who tested negative, compared to no testing. Except in patients taking oral contraceptive/hormone therapy, none of the observed effect estimates were statistically significant. The authors concluded that FVL and PG mutation 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 based on test results. Hence, it is unclear from this study whether the observed similarity in recurrence risk between tested and non-tested patients was due to differences in management or the lack of an association between FVL or PG mutation status and recurrence risk.

4.2.7 Evidence-based guidelines

Three evidence-based guidelines published since 2004 addressed genetic testing for, or clinical management of, thrombophilia in patients with VTE; the EGAPP Working Group (2010),[28] a UK guideline group selected on behalf of the British Committee for Standards in Haematology (2010),[9] and the 2012 guidelines for the prevention of thrombosis from the ACCP.[5]

The EGAPP guidelines[28] stated that FVL or PG mutation status does not affect the treatment patients receive to avoid recurrence, and that 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 stated 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[9] also stated that treatment of acute VTE, lower limb DVT, or PE should not be dependent on mutation status, based on moderate quality evidence. Neither guideline was able to provide a validated recommendation regarding the selection of patients who should be tested for heritable thrombophilia.

The guidelines produced by the ACCP[5] advised, based on moderate quality evidence, that unprovoked VTE is the primary factor for estimating the risk of VTE recurrence after stopping vitamin K antagonist therapy. They also stated that, although hereditary thrombophilia is an additional factor for estimating recurrence risk, there is insufficient evidence on the risk contribution to affect the recommendations regarding duration of therapy.

4.2.8 Additional considerations

In addition to information on the clinical validity and clinical utility of FVL and PG mutation testing, other aspects related to their use were considered. Published information on physician ordering practices and psychosocial issues was retrieved and summarized. This information was not systematically reviewed. No literature pertaining to the ethical or legal issues associated with genetic testing for thrombophilia was identified.

a) Physician practice patterns

A 2008 study conducted in the US found that tests for FVL mutations were ordered more often than the less costly and faster functional assay for APCR. This was inconsistent with recommendations from the College of American Pathologists (CAP) 2002 Consensus Conference, which considered the APCR test to be the appropriate first-line test in most cases.[29] Another US study on physician ordering of FVL tests and test impact on clinical management found that physicians adhered to CAP guidelines 46% of the time, and to American College of Medical Genetics guidelines (published in 2001 and updated in 2005) 61% of the time.[30] The main divergence from CAP guidelines for the ordering of FVL tests was for the indications of first event VTE, abnormal pregnancy outcome (excluding fetal loss), arterial thrombosis (including stroke), and a family history of VTE. The main divergence from the American College of Medical Genetics guidelines was for the indications of arterial thrombosis (including stroke). Physicians modified clinical management for 20% of patients who were positive for FVL mutations. 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.[30]

b) Psychosocial issues

There is concern that screening for genetic mutations underlying thrombophilia often occurs without sufficient counselling for the patient regarding the risks, benefits, and potential limitations of testing.[31] According to the authors of a 2008 paper,[31] potential benefits of testing for thrombophilia include patient empowerment to make informed decisions regarding potential lifestyle changes (e.g., taking precautions during long flights) and medical management (e.g., use of extended oral anticoagulation therapy following surgery). 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 over-treatment, such as bleeding, as well as increased costs.[32] Testing may also influence a woman's choices about exogenous hormone therapy, a known risk factor for thrombosis.[32]

A systematic review published in 2008 studied the psychological impact of genetic testing for thrombophilia.[33] Six studies were included in the review, and there was considerable heterogeneity across studies. The review reported on one study that found that approximately 90% of 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 risk associated with being a carrier, and that over 60% felt that 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 the psychological impact of genetic 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 FVL and PG mutations compared to no testing of patients presenting with a first episode of unprovoked VTE. This was predicated on the availability of clinical utility information to support the use of the FVL and PG mutation tests.

5.1.1 Literature search

To identify existing economic evaluations of FVL and PG mutation 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 FVL and prothrombin mutation. The initial search was filtered using a narrow set of health economic terms and undertaken on April 28, 2014. Retrieval was limited by publication year (2004 to 2014) and to English language articles. A total of 29 references were returned. Given the paucity of citations returned, a supplemental search was undertaken using the same main search concepts, and a peer-reviewed set of broad health economic filter terms were applied. Retrieval was limited by publication year (2004 to 2014) and to English language articles. Conference abstracts were not excluded from the search results. This supplemental search was completed on May 12, 2014 and returned 280 references.

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

- economic evaluation, or the results of an economic evaluation reported
- testing for FVL and PG mutations undertaken in patients with unprovoked VTE
- compared testing for FVL and PG mutations with no testing.

Articles that looked at unprovoked VTE in populations that were excluded from the clinical review were also excluded from the economic review (e.g., patients using oral contraceptives or hormone replacement therapy).

Ten articles were retrieved for full review.[34-43] No articles fulfilled the requirements for inclusion. Three were not in the relevant patient population,[34-36] two were not economic evaluations,[37,38] two were conference abstracts that did not provide enough information,[39,40] and three were hypothetical cohorts that were not informed by clinical data from an appropriate population.[41-43] An additional two articles were retrieved for review from a bibliographic search; they did not appear in the primary literature search because of their date of publication.[44,45] Both were excluded, as they were not in the relevant population.

Although there were no relevant economic evaluations, several of the retrieved economic studies that were undertaken in a different population, or used hypothetical information, concluded that testing for FVL and PG mutations was not cost-effective.

5.1.2 Review of the clinical evidence

As noted in the systematic review, three studies examined the clinical validity of FVL and PG mutation testing,[24-26] concluding that there was evidence that these mutations are a significant risk factor in the development of first unprovoked DVT and that there was no difference in the frequency of FVL or PG mutations in the provoked and unprovoked PE populations. A

prospective cohort study was also identified that sought to determine clinical predictors of VTE recurrence.[27] The authors found the presence of FVL or PG mutations did not confer an increased risk of VTE recurrence.

The clinical review also found one case-control study that examined VTE recurrence rates after the first occurrence from a data registry.[23] The authors concluded that thrombophilia testing in patients presenting with an initial VTE did not reduce the incidence of recurrence, although the lack of information on how clinical management was altered based on test results makes it difficult to interpret this conclusion.

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 subsequent treatment that patients receive.[28] Although hereditary thrombophilia is a potential risk factor for recurrence, the guidelines stated that there was insufficient evidence to have an impact on recommendations regarding subsequent therapy.[5] The guidelines generally indicated that standard treatment should be anticoagulation for a minimum of three months, upon which time the patient's physician should determine whether further treatment is necessary.[5,9,28] The EGAPP guidelines stated that there is convincing evidence that longer-term (greater than three months) anticoagulation treatment reduces recurrence, regardless of mutation status.[28] 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 systematic review, there were no relevant studies that reported the clinical sensitivity, specificity, PPV or NPV of FVL and PG mutation testing. 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 economic analysis

Given the paucity of clinical information to support the benefit of either the FVL or PG mutation test in the population of interest, a cost-effectiveness analysis was not undertaken. Based on the review of published literature, no existing economic evaluations could be used to inform the research question. As such, the project was re-scoped and 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 PG mutations compared to no testing in adult patients presenting with a first episode of unprovoked VTE. In the base case, it was assumed that the duration of anticoagulation therapy was not altered based on test results. The analysis focused on a Canadian ministry of health perspective. This payer perspective incorporates only direct costs for health care 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

a) Cost of testing

The published clinical evidence for the relevant population indicates that treatment is not altered based on the results of FVL or PG mutation testing. Thus, the base-case analysis is based on the assumption that the only difference between the test and no test strategies is the cost of the tests.

b) Scenario analyses

Although the available evidence-based guidelines indicated that there is no clinical utility associated with testing, anecdotal evidence and clinicians' survey results suggests that subsequent treatment may be altered in certain cases, such as when both FVL and prothrombin mutation tests are positive (double heterozygosity), or when 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 any change to the subsequent treatment strategy may alter the risk/benefit profile for patients, given the paucity of outcome evidence for this indication, an assumption was made that any change in duration of subsequent treatment modelled as part of scenario analyses would not have an impact on patient outcomes. Thus, only impacts on total costs were assessed. As such, a set of secondary (scenario) analyses were undertaken under hypothetical situations 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 the 2012 ACCP guidelines,[46] and clinicians' survey results that indicated that three months of anticoagulation treatment was standard management, but that this may 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 were negative for both mutations. Table 2 reports the details of the four scenarios.

Epidemiological data related to the prevalence of FVL and PG mutations were incorporated in the scenario analyses to provide an estimate of the proportion of patients whose treatment strategy would be altered according to test results, as per the description of each scenario presented in Table 2.

Testing of family members and the potential increase in the number of specialist consultations required as a result of testing positive for FVL or PG mutations are not captured in any of the economic scenarios. Had the scenarios been extended to include hereditary testing, the costs to the payer for FVL and PG testing would have increased further.

Table 2: Description of Scenario Analyses		
Scenario	**Patient is Tested**	**Patient is Not Tested**
1	If test results are negative or heterozygous positive to one of either the FVL or prothrombin mutation tests, the 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.	The patient was not tested and received 3 months of anticoagulation (standard treatment).
2	If test results are negative or heterozygous positive to one of either the FVL or prothrombin mutation tests, the 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 12 months of anticoagulation.	The patient was not tested and received 3 months of anticoagulation (standard treatment).
3	If test results are negative or heterozygous positive to one of either the FVL or prothrombin mutation tests, the 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 his or her life (assumed to be 40 years).	The patient was not tested and received 3 months of anticoagulation (standard treatment).
4	If test results are negative for both the FVL and prothrombin mutations, the patient receives only 3 months of anticoagulation. If the patient tests positive for a mutation in either FVL or PG (heterozygous or homozygous), the patient receives 6 months of anticoagulation (assumed standard treatment).	The patient was not tested and received 6 months of anticoagulation (assumed standard treatment).

FVL = factor V Leiden; PG = prothrombin gene.

5.2.3 Data inputs and assumptions

a) Test costs

There is limited information regarding the cost of FVL and PG mutation tests in Canada, with only British Columbia (BC) reporting the cost. The BC schedule of fees[47] provides a price for a first and second gene of what appears to be a combined FVL/PG mutation 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 listed cost (e.g., test, technician time, consumables). The first and second gene descriptions imply a sequence of tests; however, it is not clear whether there is a requirement for test sequencing.

Based on initial consultation with laboratory managers, there appeared to be some variation in the cost of the FVL and PG mutation tests based on geographic location. To better understand this variation, a survey was created to solicit additional information from laboratory managers across Canada. The responses reflect variation in the provincially set fees for the tests and how they are administered (as individual tests or part of a test panel). Panel testing in this section refers only to the FVL and PG mutation 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 tests was reported to differ based on the different components included and the expertise of the person running the test, which may explain some of the variation in responses. A test kit is available that requires little technical skill but is more costly than in-house approaches to

performing the test, which require a greater level of technical expertise. However, there are also likely to be other costs associated with running the tests in the latter circumstance that may not be captured in the responses received from laboratory managers.

Combination or panel testing was reported to cost between $15 and $125. Whereas 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 estimated costs for FVL and PG mutation testing is presented in Table 3. The base-case analysis was based on both the upper and lower costs of testing either FVL or PG mutation as single tests, or as a combined test. The scenario analyses used the median cost of the combined test reported in Table 3 — $60 — as the base test cost.

Table 3: Estimated Cost of FVL and Prothrombin Mutation Testing

Descriptor	Price	Comment
Cost of FVL test		
Province 1[a]	$13.35	Reagent cost only. Other costs not included
Province 3[a,b]	1st test: $76.92 2nd test: $48.53	DNA extraction, test kit, capillaries/ tubes/ tips, labour
Cost of PM test		
Province 1[a]	$13.35	Reagent cost only. Other costs not included
Province 3[a,b]	1st test: $76.92 2nd test: $48.53	DNA extraction, test kit, capillaries/ tubes/ tips, labour
Cost of combined test		
Province 1[a]	$15.19	Reagent cost only. Other costs not included
Province 2[a]	$60.00	Test kit cost. No technical expertise required
Province 3[a,b]	$125.45	DNA extraction, test kit, capillaries/ tubes/ tips, labour

FVL = factor V Leiden; PM = prothrombin mutation.
[a]Lab managers' survey results (2014).
[b]BC lab formulary.[47]

b) Treatment costs

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

Scenario analyses assumed differing durations of anticoagulation. As previously indicated, this was based on clinicians' survey results and ACCP guidelines.[46] The anticoagulant used in the analysis was warfarin, based on clinical guidance regarding first-line anticoagulation management. Cost estimates of anticoagulation medication (warfarin), daily dose (5 mg), and associated monitoring costs were based on an earlier CADTH report of new oral anticoagulants compared with warfarin in patients with atrial fibrillation.[48] 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 4). Warfarin costs were updated based upon prices listed on the Ontario Drug Benefit Formulary in July 2014. Monitoring costs may have increased since the CADTH report was published. The newer anticoagulants such as rivaroxaban or dabigatran are an alternative to warfarin for patients requiring anticoagulation after a VTE. If these agents were to be used instead of warfarin, the associated subsequent treatment costs would be substantially increased.[48]

Table 4: Cost of Anticoagulation Treatment		
Descriptor	**Cost**	**Source**
5 mg warfarin tablet	$0.0675	Ontario provincial drug formulary (2014)[a]
3 months of 5 mg warfarin	$6.16	
6 months of 5 mg warfarin	$12.33	
12 months of 5 mg warfarin	$24.65	
Monitoring costs (annual)	$240.69	CADTH Therapeutic Review (2012)[48]

[a] Ontario Drug Benefit Formulary/Comparative Drug Index: https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp.

c) Epidemiologic information and assumptions

Epidemiologic data related to FVL and PG mutation prevalence were used to inform the cost analysis for the scenarios in which the length of anticoagulation therapy was modified based on test results (Table 5). These data were sourced from non-Canadian sources, as no Canadian-specific sources could be identified.

Table 5: Epidemiology Data		
Prevalence	**Value[a] (Range)**	**Comment**
Heterozygous FVL mutation in patients with a first DVT episode (%)	NR (15 to 20)	No mean or median prevalence was reported. Thus, the upper rate was used as a proxy. The lower rate was tested in sensitivity analyses.
Heterozygous PG mutation in patients with a first DVT or VTE episode (%)[18,49-51]	6 (NR)	No ranges were reported.
Homozygosity for FVL (%)[18,52,53]	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 PG mutation (%)	NR	No prevalence rate is reported. The mutation is extremely rare and, as of 2005, only 70 cases had been reported in the literature.[54]
Both FVL and PG mutation 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.

DVT = deep vein thrombosis; FVL = factor V Leiden; NR = not reported; PG = prothrombin gene; VTE = venous thromboembolism.
[a] All values are expressed as percentages (e.g., 0.02% is equivalent to 1 in 5,000).

Several assumptions were made regarding the prevalence of the mutations in patients presenting with a first episode of VTE:

- Mutation prevalence rates among DVT and VTE patients are similar enough that the rates can be used interchangeably in the absence of better information (see heterozygous PG mutation results)
- The prevalence of heterozygosity for either FVL or PG mutation was estimated at 0.21, calculated as the sum of the upper prevalence rates of FVL (0.20) and PG mutation individually (0.06) minus the prevalence of mutation in both FVL and PG (0.05)
- The prevalence of homozygosity among all patients with FVL mutation is 1 in 5,000 (0.0002). As this is likely to be lower than the prevalence in the VTE population, it is considered a conservative estimate for the purposes of this analysis.

Based on these assumptions, 5% of patients with first unprovoked VTE would have the duration of anticoagulation therapy extended based on test results in scenarios 1 to 3; i.e., 5% would either have both FVL and PG mutations or be homozygous for at least one mutation. Thus, 95% of those tested would not receive a different treatment based upon the test result, corresponding to a number needed to test for a change in management of 20. Use of the lower individual prevalence rates for FVL and PG in the calculation of the percentage of patients that would qualify for extended anticoagulation in scenarios 1 to 3 results in a number needed to test of 100.

5.2.4 Sensitivity analyses

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

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 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 6).

In the first three scenarios that assume an extension to standard management in patients who were double heterozygous or single or double homozygous for FVL and PG mutations, the incremental cost per patient of testing compared to not testing can be seen to increase in a linear fashion based upon the duration of anticoagulation. As noted in the previous description of epidemiological assumptions, only 5% of patients in these three scenarios would have their treatment changed based on the results of the tests.

In the fourth scenario, where it was assumed that the standard duration of anticoagulation was six months, and that all patients received six months of anticoagulation unless they tested negative to both tests, the increased cost per patient to provinces associated with testing was minimal. If the relative difference between the standard management period and alternate management duration were longer than six months, it is likely that testing would be cost-saving compared to no testing.

Table 6: Scenario Analysis Results (Per Patient)

Scenario	Cost of Testing	Cost of Not Testing	Incremental Costs (Savings)
1	$129.67	$66.34	$63.33
2	$136.33		$69.99
3	$655.82		$589.48
4	$143.60	$132.67	$10.92

5.3.3 Sensitivity analyses

The results for the first three scenarios were robust to changes in the sensitivity analyses, with testing resulting in an increased cost per patient compared to not testing (Table 7). The

parameters that had the largest effects on the incremental costs of testing for all scenarios were the cost of the tests and the prevalence of patients with homozygous mutations. In scenario 4, where standard treatment could be shortened from the standard duration for patients with negative FVL and PG mutation tests but not increased for patients with positive tests, the alteration of parameters in the sensitivity analysis changed the results such that testing was cost-saving in certain circumstances.

Table 7: Sensitivity Analysis Inputs and Results (Per Patient)

Parameter	Value(s) for Sensitivity Analysis	Base-Case Value	Incremental Cost (Savings) of Testing
Scenario 1			**$63.33**
Cost of the test	Lower: $13.35 Upper: $125.45	$60.00	$16.68 $128.78
Cost of warfarin	2.5 mg: $0.0674 7.5 mg: $0.1349	5 mg: $0.0675	$63.33 $69.64
Lifetime horizon	NA	40 years	NA
Altered prevalence of having both FVL and prothrombin mutations in patients with VTE (%)	1%	5%	$60.68
Scenario 2			**$69.99**
Cost of the test	Lower: $13.35 Upper: $125.45	$60.00	$23.34 $135.44
Cost of warfarin	2.5 mg: $0.0674 7.5 mg: $0.1349	5 mg: $0.0675	$69.99 $70.92
Lifetime horizon	NA	40 years	NA
Altered prevalence of having both FVL and prothrombin mutations in patients with VTE (%)	1%	5%	$62.03
Scenario 3			**$589.48**
Cost of the test	Lower: $13.35 Upper: $125.45	$60.00	$541.45 $653.55
Cost of warfarin	2.5 mg: $0.0674 7.5 mg: $0.1349	5 mg: $0.0675	$589.41 $638.61
Lifetime horizon	10 years 20 years 30 years 50 years	40 years	$189.87 $323.08 $456.28 $722.68
Altered prevalence of having both FVL and prothrombin mutations in patients with VTE (%)	1%	5%	$167.58
Scenario 4			**$10.92**
Cost of the test	Lower: $13.35 Upper: $125.45	$60.00	$(35.73) $76.37
Cost of warfarin	2.5 mg: $0.0674 7.5 mg: $0.1349	5 mg: $0.0675	$10.93 $6.37
Lifetime horizon	NA	40 years	NA
Altered prevalence of FVL mutation in patients with a first DVT episode (%)	15%	20%	$7.61

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 PG mutation testing in patients with a first, unprovoked VTE. Evidence on the clinical validity of FVL and PG testing in patients presenting with unprovoked VTE was limited. This review did not identify any studies that met our criteria for examining the use of FVL or PG mutation testing in children with unprovoked VTE. The association between FVL and PG mutations and unprovoked first VTE was reported only in a small number of studies, some of which 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 an association between FVL and PG mutations, and VTE.[55-58] There were no data reported in the included studies on clinical sensitivity, clinical specificity, PPV, or NPV of FVL and PG tests. A systematic review[58] reported clinical sensitivity for FVL mutation testing of between 20% and 50%, based on a 2003 study,[59] as well as FVL test clinical sensitivity of 28% (95% CI 12.9 to 34.6%) and PG test clinical sensitivity of 11% (95% CI 6.2 to 21.1%) to detect recurrent events, based on Centers for Disease Control and Prevention guidelines.[60]

Clinical utility refers to the risks and benefits that result from test use. Data on the clinical utility of FVL and PG mutation testing in patients presenting with a first unprovoked VTE were scant. Our report examined clinical utility using the risk of recurrence following FVL and PG testing, recommendations from evidence-based guidelines regarding whether FVL and PG 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 that FVL and PG mutation testing in patients presenting with a first unprovoked VTE did not reduce the incidence of recurrence. However, this study did not report whether and how treatment was modified based on test results; consequently, the finding of no apparent benefit of testing in this study is difficult to interpret. Nonetheless, in agreement with the findings on the limited clinical utility of FVL and PG tests, evidence-based guidelines on genetic testing for thrombophilia testing were consistent in stating 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 the recurrence of VTE, and determined the predictive value of the absence of individual factors on recurrence rate.[61] 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. The absence of FVL and PG 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 mutations heterozygotes and 0.97 for PG mutation heterozygotes). NPVs and likelihood ratios for the recurrence of VTE in the absence of FVL and PG mutations based on recurrence-free survival showed that the absence of FVL and PG mutations does not lead to a clinically significant change in recurrence-free survival.

A review in 2007 on the implications of genetic testing for thrombophilia listed the reasons to test and the reasons to not test for genetic mutations.[62] The list of reasons to test included the desire of patients and their doctors to have an explanation for the episode and the possibility to

adjust management based on test results. The reasons to not test included the cost of testing and the psychosocial impact of knowing that one is a carrier of the defect. The limited findings from our review indicated that testing did not predict or reduce the incidence of recurrence (based on a study with significant limitations) after a first unprovoked episode of VTE; therefore, testing for FVL and PG mutations with the intention of adjusting management based on the results may not 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 increased worry, thus potentially mitigating concerns that testing will produce adverse psychosocial impacts. The provision of appropriate genetic counselling can further reduce the risk of such harms. No literature pertaining to the ethical or legal issues surrounding genetic testing for thrombophilia was found.

6.2 Summary of Findings From the Cost Analysis

Based on findings from the clinical and economic literature reviews, there was no published evidence to indicate that testing for FVL and/or PG mutations is likely to improve clinical outcomes compared to not testing in patients with an unprovoked initial episode of VTE. Hence, a cost analysis, rather than a cost-effectiveness analysis, was performed to assess the economic impact of FVL and PG mutation testing.

The results of the base-case cost analysis, which looked solely at the cost of the FVL and PG mutation tests singularly and as a two-test panel, indicated that health care payers who currently fund FVL and PG mutation testing should realize cost savings from reduced testing in patients with an unprovoked first episode of VTE. 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, which were informed by clinical guidelines and clinicians' survey results suggesting that anticoagulation treatment may be extended for patients that are double heterozygous or homozygous for either FVL or PG mutations, indicated that testing is associated with an increased cost to payers. Clinicians' survey results also indicated that standard anticoagulation therapy after a first unprovoked VTE may be six months in duration rather than three months, as modelled in the base-case analysis based on guideline recommendations. However, even if the duration of standard management with anticoagulation therapy was extended beyond three months, there would be no change in the direction of the results — testing would still be more costly to the payer than not testing in the first three scenarios, as they all assume extended anticoagulation beyond the standard duration for patients who are double heterozygous for FVL and PG mutations, or homozygous for either mutation. However, there may be a change in the magnitude of the incremental costs associated with testing. One-way sensitivity analyses showed that variation in the costs associated with the tests and anticoagulation treatment, and in the prevalence of FVL and PG mutations, only affected the magnitude and not the direction of results for scenarios 1 to 3 (i.e., testing remained more costly than not testing).

In scenario 4, where treatment duration was reduced in patients who tested negative for both FVL and PG mutations, the base-case analysis indicated that testing was associated with an incremental cost to payers compared with not testing. However, a series of one-way sensitivity analyses indicated that this result was uncertain and highly dependent upon the cost of the test, the duration of anticoagulation treatment, and the prevalence of mutations in patients with VTE. Under some assumptions regarding these inputs, testing was cost-saving for the payer.

The results of the economic analysis must be interpreted with caution given the assumptions required as a result of limited clinical evidence, epidemiology data, and variations in costs. The largest source of uncertainty related to the assumption in the scenario analysis that testing would result in a change in medical management. Nevertheless, testing led to an incremental cost per patient compared to not testing for jurisdictions that are currently funding FVL or PG mutation tests, as long as the duration of anticoagulation therapy was either the same or longer than standard anticoagulation therapy. Only in settings where there is the potential for a reduced treatment duration compared with standard therapy upon a negative test for both FVL and PG mutations is testing associated with potential cost savings to the payer.

The available data on the clinical validity and clinical utility of FVL and PG mutation testing for patients with first unprovoked VTE supports the assumption in the cost analysis that testing is not associated with incremental benefits or risks compared to not testing. However, should information become available in the future to suggest otherwise, the cost analysis should be re-evaluated.

7 CONCLUSIONS

The limited evidence identified in this systematic review showed that FVL and PG mutations are associated with first unprovoked VTE in adults; however, the presence of mutations did not predict VTE recurrence in this population. This aligns with the findings of previous reviews that have assessed a broader population of patients with VTE, in which FVL or PG mutation status were at best minor risk factors for recurrent VTE. There was insufficient evidence to assess whether FVL or PG mutation testing influences patient management or clinical outcomes, although the fact that the presence of these mutations does not appreciably influence the risk of VTE recurrence makes it unlikely that the tests have clinical utility in patients with a first unprovoked VTE. The available clinical practice guidelines support this, in that they were consistent in highlighting the lack of sufficient evidence to warrant differential treatment based on FVL or PG mutation status. There was no evidence available regarding the clinical validity and utility of FVL and PG mutation testing in children with a first VTE.

The results of the cost analysis indicated that reduced or eliminated FVL and PG mutation testing in patients with a first unprovoked VTE is likely to result in cost savings for jurisdictions that currently fund these tests. The magnitude of savings is dependent on a number of factors that may vary across jurisdictions including test costs and the extent to which clinicians modify the duration of anticoagulation therapy after VTE based on test results in current clinical practice.

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APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to 2014 April 25 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:	April 28, 2014
Study Types:	Health technology assessments, systematic reviews, meta-analyses, randomized clinical trials, non-randomized studies, economic studies, and guidelines Conference abstracts were removed
Limits:	Humans English language Publication years: 2004-April 2014

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	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
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.pt	Publication type
.po	Population group [PsychInfo only]
.hw	Heading word; usually includes subject headings and controlled vocabulary
.nm	Name of substance word
.mp	Mapped term
.jw	Journal word
pmez	Ovid database code; MEDLINE(R) In-Process & Other Non-Indexed Citations MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	Factor V Leiden.nm.
2	exp Factor V/ and (exp mutation/ or (Leiden or G1691A or R506Q or ARG506 or (ARG adj3 "506") or mutation*).ti,ab.)
3	(FV Leiden or FVL).ti,ab.
4	("Factor V" adj3 (Leiden or G1691A or R506Q or ARG506 or (ARG adj3 "506") or mutation*)).ti,ab.
5	or/1-4
6	prothrombin/ and (exp mutation/ or (G20210A or "20210" or 20210A or 20210GA or mutation*).ti,ab.)
7	(("factor II" or FII or "factor 2" or "factor ii" or prothrombin) adj3 (G20210A or "20210" or 20210A or 20210GA or mutation*)).ti,ab.
8	((G20210A adj2 mutation*) or "PT mutation" or "PT 20210" or PT20210).ti,ab.
9	or/6-8
10	5 or 9
11	10 use pmez
12	blood clotting factor v leiden/
13	(FV Leiden or FVL).ti,ab.
14	("Factor V" adj3 (Leiden or G1691A or R506Q or ARG506 or (ARG adj3 "506") or mutation*)).ti,ab.
15	or/12-14
16	prothrombin/ and (exp gene mutation/ or (G20210A or "20210" or 20210A or 20210GA or mutation*).ti,ab.)
17	(("factor II" or FII or "factor 2" or "factor ii" or prothrombin) adj3 (G20210A or "20210" or 20210A or 20210GA or mutation*)).ti,ab.
18	((G20210A adj2 mutation*) or "PT mutation" or "PT 20210" or PT20210).ti,ab.
19	or/16-18
20	15 or 19
21	20 use oemezd
22	11 or 21
23	meta-analysis.pt.
24	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
25	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
26	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
27	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
28	(data synthes* or data extraction* or data abstraction*).ti,ab.
29	(handsearch* or hand search*).ti,ab.
30	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
31	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab.
32	(meta regression* or metaregression*).ti,ab.
33	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.

MULTI-DATABASE STRATEGY	
#	**Searches**
34	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
35	(cochrane or (health adj2 technology assessment) or evidence report).jw.
36	(meta-analysis or systematic review).md.
37	(comparative adj3 (efficacy or effectiveness)).ti,ab.
38	(outcomes research or relative effectiveness).ti,ab.
39	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab.
40	or/23-39
41	(guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.
42	(guideline* or standards or consensus* or recommendat*).ti.
43	(practice parameter* or position statement* or policy statement* or CPG or CPGs or best practice*).ti.
44	(care adj2 (path or paths or pathway or pathways or map or maps or plan or plans or standard)).ti.
45	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti.
46	(algorithm* and (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti.
47	(algorithm* and (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti.
48	or/41-47
49	22 and (40 or 48)
50	limit 49 to english language
51	limit 50 to yr="2004 -Current"
52	exp thrombophilia/ or exp thromboembolism/ or exp pulmonary embolism/ or exp thrombosis/
53	(thrombophil* or thrombofil* or hypercoagulabilit* or hyper-coagulabilit* or thrombos* or VTE or DVT or pulmonary embol* or lung embol* or thromboembol* or thrombo-embol* or thrombophlebit* or thrombo-phlebit*).ti,ab.
54	or/52-53
55	11 and 54
56	exp thromboembolism/
57	(thrombophil* or thrombofil* or hypercoagulabilit* or hyper-coagulabilit* or thrombos* or VTE or DVT or pulmonary embol* or lung embol* or thromboembol* or thrombo-embol* or thrombophlebit* or thrombo-phlebit*).ti,ab.
58	or/56-57
59	21 and 58
60	55 or 59
61	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
62	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
63	Multicenter Study.pt.
64	Randomized Controlled Trial/
65	Randomized Controlled Trials as Topic/
66	"Randomized Controlled Trial (topic)"/
67	Controlled Clinical Trial/
68	Controlled Clinical Trials as Topic/

MULTI-DATABASE STRATEGY	
#	**Searches**
69	"Controlled Clinical Trial (topic)"/
70	Clinical Trial/ or Phase 2 Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/
71	Clinical Trials as Topic/ or Clinical Trials, Phase II as Topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/
72	"Clinical Trial (topic)"/ or "Phase 2 Clinical Trial (topic)"/ or "Phase 3 Clinical Trial (topic)"/ or "Phase 4 Clinical Trial (topic)"/
73	Multicenter Study/ or Multicenter Study as Topic/ or "Multicenter Study (topic)"/
74	Randomization/
75	Random Allocation/
76	Double-Blind Method/
77	Double Blind Procedure/
78	Double-Blind Studies/
79	Single-Blind Method/
80	Single Blind Procedure/
81	Single-Blind Studies/
82	Placebos/
83	Placebo/
84	Control Groups/
85	Control Group/
86	Cross-Over Studies/ or Crossover Procedure/
87	(random* or sham or placebo*).ti,ab,hw.
88	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
89	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
90	(control* adj3 (study or studies or trial*)).ti,ab,hw.
91	(clinical adj3 (study or studies or trial*)).ti,ab,hw.
92	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
93	(phase adj3 (study or studies or trial*)).ti,ab,hw.
94	((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw.
95	((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw.
96	allocated.ti,ab,hw.
97	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
98	trial.ti.
99	or/61-98
100	exp animals/
101	exp animal experimentation/
102	exp models animal/
103	exp animal experiment/
104	nonhuman/
105	exp vertebrate/
106	animal.po.
107	or/100-106
108	exp humans/
109	exp human experiment/
110	human.po.

MULTI-DATABASE STRATEGY	
#	**Searches**
111	or/108-110
112	107 not 111
113	99 not 112
114	epidemiologic methods.sh.
115	epidemiologic studies.sh.
116	cohort studies/
117	cohort analysis/
118	longitudinal studies/
119	longitudinal study/
120	prospective studies/
121	prospective study/
122	follow-up studies/
123	follow up/
124	followup studies/
125	retrospective studies/
126	retrospective study/
127	case-control studies/
128	exp case control study/
129	cross-sectional study/
130	observational study/
131	quasi experimental methods/
132	quasi experimental study/
133	validation studies.pt.
134	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab.
135	cohort*.ti,ab.
136	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti,ab.
137	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab.
138	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti,ab.
139	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti,ab.
140	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab.
141	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab.
142	(population adj3 (study or studies or analysis or analyses)).ti,ab.
143	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab.
144	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab.
145	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab.
146	((natural adj experiment) or (natural adj experiments)).ti,ab.
147	(quasi adj (experiment or experiments or experimental)).ti,ab.
148	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab.
149	(prevalence adj3 (study or studies or analysis or analyses)).ti,ab.
150	or/114-149
151	exp animals/

MULTI-DATABASE STRATEGY	
#	**Searches**
152	exp animal experimentation/ or exp animal experiment/
153	exp models animal/
154	nonhuman/
155	exp vertebrate/ or exp vertebrates/
156	animal.po.
157	or/151-156
158	exp humans/
159	exp human experimentation/ or exp human experiment/
160	human.po.
161	or/158-160
162	157 not 161
163	150 not 162
164	60 and (113 or 163)
165	limit 164 to english language
166	limit 165 to yr="2004 -Current"
167	51 or 166
168	conference abstract.pt.
169	167 not 168
170	remove duplicates from 169
171	*economics/
172	exp *"costs and cost analysis"/
173	(economic adj2 model*).mp.
174	(cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab.
175	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti.
176	(life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab.
177	(cost or economic*).ti. and (costs or cost-effectiveness or markov).ab.
178	or/171-177
179	22 and 178
180	limit 179 to english language
181	limit 180 to yr="2004 -Current"
182	remove duplicates from 181

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library, 2014	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

Grey Literature

Dates for Search:	March 2014
Keywords:	Factor V Leiden, FVL, FV Leiden, 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 Deep-Web Search Tool for Evidence-Based Medicine* (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

APPENDIX 2: DATA EXTRACTION FORM FOR ACCURACY AND CLINICAL EFFECTIVENESS REVIEW

Reviewer		
RefID		
Author, Date		
Country of origin		
Study characteristics		
Study design		
Study duration		
Eligibility criteria		
Type of assay		
Conflict of interests (yes, no, none declared, not mentioned)		
Other		
Patient characteristics	**Intervention**	**Control**
Number enrolled Number completing study		
Age, Gender		
Conditions		
Other		
Outcomes		
Clinical validity Sensitivity Specificity Positive Predictive Value (PPV) Negative Predictive Value (NPV)		

Clinical utility Benefits Risks Costs Availability Acceptability Interest Ethical, legal, social implications Other	**Thrombophilia testing**	**Non-testing**
Other		
Notes		

APPENDIX 3: INCLUDED AND EXCLUDED STUDIES FOR CLINICAL REVIEW

Included studies

Included clinical studies

Coppens M, Reijnders JH, Middeldorp S, Doggen CJM, Rosendaal FR. Testing for inherited thrombophilia does not reduce the recurrence of venous thrombosis. J Thromb Haemost. 2008;6(9):1474-7.

Kruse L, Mitchell AM, Camargo CA, Jr., Hernandez J, Kline JA. Frequency of thrombophilia-related genetic variations in patients with idiopathic pulmonary embolism in an urban emergency department. Clin Chem [Internet]. 2006 Jun [cited 2014 Jun 19];52(6):1026-32. Available from: http://www.clinchem.org/content/52/6/1026.full.pdf+html

Mansilha A, Araújo F, Severo M, Sampaio SM, Toledo T, Albuquerque R. Combined factor V Leiden (R506Q) and prothrombin G20210A genotyping in young patients presenting with deep venous thrombosis. Phlebology. 2006;21(1):24-7.

Obeidat NM, Awidi A, Sulaiman NA, bu-Khader IB. Thrombophilia-related genetic variations in patients with pulmonary embolism in the main teaching hospital in Jordan. Saudi Med J. 2009 Jul;30(7):921-5.

Rodger MA, Kahn SR, Wells PS, Anderson DA, Chagnon I, Le GG, et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. CMAJ [Internet]. 2008 Aug 26 [cited 2014 Sep 3];179(5):417-26. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2518177

Included guidelines

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: routine testing for factor V Leiden (R506Q) and prothrombin (20210G>A) mutations in adults with a history of idiopathic venous thromboembolism and their adult family members. Genet Med. 2011 Jan;13(1):67-76.

Baglin T, Gray E, Greaves M, Hunt BJ, Keeling D, Machin S, et al. Clinical guidelines for testing for heritable thrombophilia. Br J Haematol. 2010 Apr;149(2):209-20.

Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest [Internet]. 2012 Feb [cited 2014 Sep 4];141(2 Suppl):e419S-e494S. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278049

Excluded studies

Inappropriate comparator

Sobol AB, Mochecka A, Loba J. Factor V Leiden G1691A and prothrombin gene G20210A mutations in patients with ischemic stroke and diabetes up to the age of 55. Diabetologia Doswiadczalna i Kliniczna. 2007;7(5):240-4.

Pezzini A, Grassi M, Del ZE, Archetti S, Spezi R, Vergani V, et al. Cumulative effect of predisposing genotypes and their interaction with modifiable factors on the risk of ischemic stroke in young adults. Stroke [Internet]. 2005 [cited 2014 Jun 19];36(3):533-9. Available from: http://stroke.ahajournals.org/content/36/3/533.full.pdf+html

Gonzalez-Porras JR, Garcia-Sanz R, Alberca I, Lopez ML, Balanzategui A, Gutierrez O, et al. Risk of recurrent venous thrombosis in patients with G20210A mutation in the prothrombin gene or factor V Leiden mutation. Blood Coagul Fibrinolysis. 2006 Jan;17(1):23-8.

Kalkanli S, Ayyildiz O, Tiftik N, Batun S, Isikdogan A, Ince H, et al. Factor V Leiden mutation in venous thrombosis in southeast Turkey. Angiology. 2006 Mar;57(2):193-6.

Eichinger S, Weltermann A, Minar E, Stain M, Schonauer V, Schneider B, et al. Symptomatic pulmonary embolism and the risk of recurrent venous thromboembolism. Arch Intern Med. 2004 Jan 12;164(1):92-6.

Inappropriate intervention

Prandoni P, Prins MH, Lensing AWA, Ghirarduzzi A, Ageno W, Imberti D, et al. Residual thrombosis on ultrasonography to guide the duration of anticoagulation in patients with deep venous thrombosis, a randomized trial. Ann Intern Med. 2009;150(9):577-85.

Inappropriate outcomes

Papay P, Miehsler W, Tilg H, Petritsch W, Reinisch W, Mayer A, et al. Clinical presentation of venous thromboembolism in inflammatory bowel disease. J Crohns Colitis. 2013;7(9):723-9.

Spiezia L, Campello E, Bon M, Tison T, Milan M, Simioni P, et al. ABO blood groups and the risk of venous thrombosis in patients with inherited thrombophilia. Blood Transfus [Internet]. 2013 [cited 2014 Jun 19];11(2):250-3. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3626477/pdf/blt-11-250.pdf

Hron G, Eichinger S, Weltermann A, Minar E, Bialonczyk C, Hirschl M, et al. Family history for venous thromboembolism and the risk for recurrence. Am J Med. 2006;119(1):50-3.

Chaireti R, Jennersjo C, Lindahl TL. Is thrombin generation at the time of an acute thromboembolic episode a predictor of recurrence? The LInkoping Study on Thrombosis (LIST)--a 7-year follow-up. Thromb Res. 2013 Feb;131(2):135-9.

Ringelstein M, Jung A, Berger K, Stoll M, Madlener K, Klötzsch C, et al. Promotor polymorphisms of plasminogen activator inhibitor-1 and other thrombophilic genotypes in cerebral venous thrombosis: a case-control study in adults. J Neurol. 2012 Nov;259(11):2287-92.

Delluc A, Gourhant L, Lacut K, Mercier B, Audrezet MP, Nowak E, et al. Association of common genetic variations and idiopathic venous thromboembolism. Results from EDITh, a hospital-based case-control study. Thromb Haemost. 2010 Jun;103(6):1161-9.

Eichinger S, Heinze G, Jandeck LM, Kyrle PA. Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: the Vienna prediction model. Circulation [Internet]. 2010 Apr 13 [cited 2014 Jun 19];121(14):1630-6. Available from: http://circ.ahajournals.org/content/121/14/1630.full.pdf+html

Van Stralen KJ, Doggen CJ, Bezemer ID, Pomp ER, Lisman T, Rosendaal FR. Mechanisms of the factor V Leiden paradox. Arterioscler Thromb Vasc Biol [Internet]. 2008 Oct [cited 2014 Jun 19];28(10):1872-7. Available from: http://atvb.ahajournals.org/content/28/10/1872.full.pdf+html

Wahlander K, Eriksson H, Lundstrom T, Billing CS, Wall U, Nystrom P, et al. Risk of recurrent venous thromboembolism or bleeding in relation to thrombophilic risk factors in patients receiving ximelagatran or placebo for long-term secondary prevention of venous thromboembolism. Br J Haematol. 2006 Apr;133(1):68-77.

De Paula Sabino A, Guimaraes DA, Ribeiro DD, Paiva SG, Sant'Ana Dusse LM, das Gracas CM, et al. Increased factor V Leiden frequency is associated with venous thrombotic events among young Brazilian patients. J Thromb Thrombolysis. 2007 Dec;24(3):261-6.

Inappropriate population

Supanc V, Sonicki Z, Vukasovic I, Solter VV, Zavoreo I, Kes VB. The role of classic risk factors and prothrombotic factor gene mutations in ischemic stroke risk development in young and middle-aged individuals. J Stroke Cerebrovasc Dis. 2014;23(3):e171-e176.

Siniarski A, Wypasek E, Fijorek K, Gajos G, Undas A. Association between thrombophilia and seated immobility venous thromboembolism. Blood Coagul Fibrinolysis. 2014;25(2):135-41.

Krleza JL, Duranovic V, Bronic A, Herak DC, Mejaski-Bosnjak V, Zadro R. Multiple presence of prothrombotic risk factors in Croatian children with arterial ischemic stroke and transient ischemic attack. Croat Med J [Internet]. 2013 [cited 2014 Jun 19];54(4):346-54. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3760658/pdf/CroatMedJ_54_0346.pdf

Pai N, Ghosh K, Shetty S. Hereditary thrombophilia in cerebral venous thrombosis: a study from India. Blood Coagul Fibrinolysis. 2013;24(5):540-3.

Pourgheysari B, Boroujeni HR, Hasheminia AM, Drees F. PLA2 polymorphism of platelet glycoprotein IIb/IIIa but not factor V Leiden and prothrombin G20210A polymorphisms is associated with venous thromboembolism and more recurrent events in central Iran. Blood Coagul Fibrinolysis. 2013;24(5):471-6.

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Alfirevic Z, Simundic AM, Nikolac N, Sobocan N, Alfirevic I, Stefanovic M, et al. Frequency of factor II G20210A, factor V Leiden, MTHFR C677T and PAI-15G/4G polymorphism in patients with venous thromboembolism: Croatian case-control study. Biochem Med. 2010;20(2):229-35.

Rahimi Z, Mozafari H, Shahriari-Ahmadi A, Alimogaddam K, Ghavamzadeh A, Aznab M, et al. Deep venous thrombosis and thrombophilic mutations in western Iran: association with factor V Leiden. Blood Coagul Fibrinolysis. 2010;21(5):385-8.

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Palko-Labuz A, Sadakierska-Chudy A, Pilecki W. The genetic background of thrombosis - the distributions of factor V Leiden, prothrombin G20210A, and MTHFR C677T polymorphisms. Adv Clin Exp Med [Internet]. 2010 [cited 2014 Jun 19];19(1):51-5. Available from: http://www.advances.am.wroc.pl/pdf/2010/19/1/51.pdf

Bolaman Z, Ozkul A, Kiylioglu N, Kadikoylu G, Erturk A, Batun S, et al. Hereditary thrombophilic factors in stroke due to cerebral infarct. Am J Med Sci. 2009;337(1):11-3.

Del Balzo F., Spalice A, Ruggieri M, Greco F, Properzi E, Iannetti P. Stroke in children: Inherited and acquired factors and age-related variations in the presentation of 48 paediatric patients. Acta Paediatr. 2009;98(7):1130-6.

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Balci YI, Unal S, Gumruk F, Cetin M, Ozkutlu S, Gurgey A. Nonstroke arterial thrombosis in children: Hacettepe experience. Blood Coagul Fibrinolysis. 2008;19(6):519-24.

Dutta AK, Chacko A, George B, Joseph JA, Nair SC, Mathews V. Risk factors of thrombosis in abdominal veins. World J Gastroenterol [Internet]. 2008 [cited 2014 Jun 19];14(28):4518-22. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2731279/pdf/WJG-14-4518.pdf

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Ozyurek E, Balta G, Degerliyurt A, Parlak H, Aysun S, Gurgey A. Significance of factor V, prothrombin, MTHFR, and PAI-1 genotypes in childhood cerebral thrombosis. Clin Appl Thromb Hemost. 2007;13(2):154-60.

Hasan NS, El Din HG, Abd El Kader AM, Aisha HA. Genetic mutation in thrombophilic Egyptian patients. J Med Sci. 2006;6(4):591-6.

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Bouaziz-Borgi L, Almawi WY, Mtiraoui N, Nsiri B, Keleshian SH, Kreidy R, et al. Distinct association of factor V-Leiden and prothrombin G20210A mutations with deep venous thrombosis in Tunisia and Lebanon. Am J Hematol. 2006;81(8):641-3.

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Kheradmand E, Pourhossein M, Amini G, Saadatnia M. Factor V Leiden does not have a role in cryptogenic ischemic stroke among Iranian young adults. Adv Biomed Res. 2014;3:80:80.

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Ocak G, Vossen CY, Verduijn M, Dekker FW, Rosendaal FR, Cannegieter SC, et al. Risk of venous thrombosis in patients with major illnesses: results from the MEGA study. J Thromb Haemost. 2013 Jan;11(1):116-23.

Djordjevic V, Stankovic M, Brankovic-Sreckovic V, Rakicevic L, Damnjanovic T, Antonijevic N, et al. Prothrombotic genetic risk factors in stroke: a possible different role in pediatric and adult patients. Clin Appl Thromb Hemost. 2012 Nov;18(6):658-61.

Kupeli E, Verdi H, Simsek A, Atac FB, Eyuboglu FO. Genetic mutations in Turkish population with pulmonary embolism and deep venous thrombosis. Clin Appl Thromb Hemost. 2011 Nov;17(6):E87-E94.

Rios DR, Fernandes AP, Carvalho MG, Figueiredo RC, Guimaraes DA, Reis DR, et al. Hemodialysis vascular access thrombosis: the role of factor V Leiden, prothrombin gene mutation and ABO blood groups. Clin Chim Acta. 2011 Feb 20;412(5-6):425-9.

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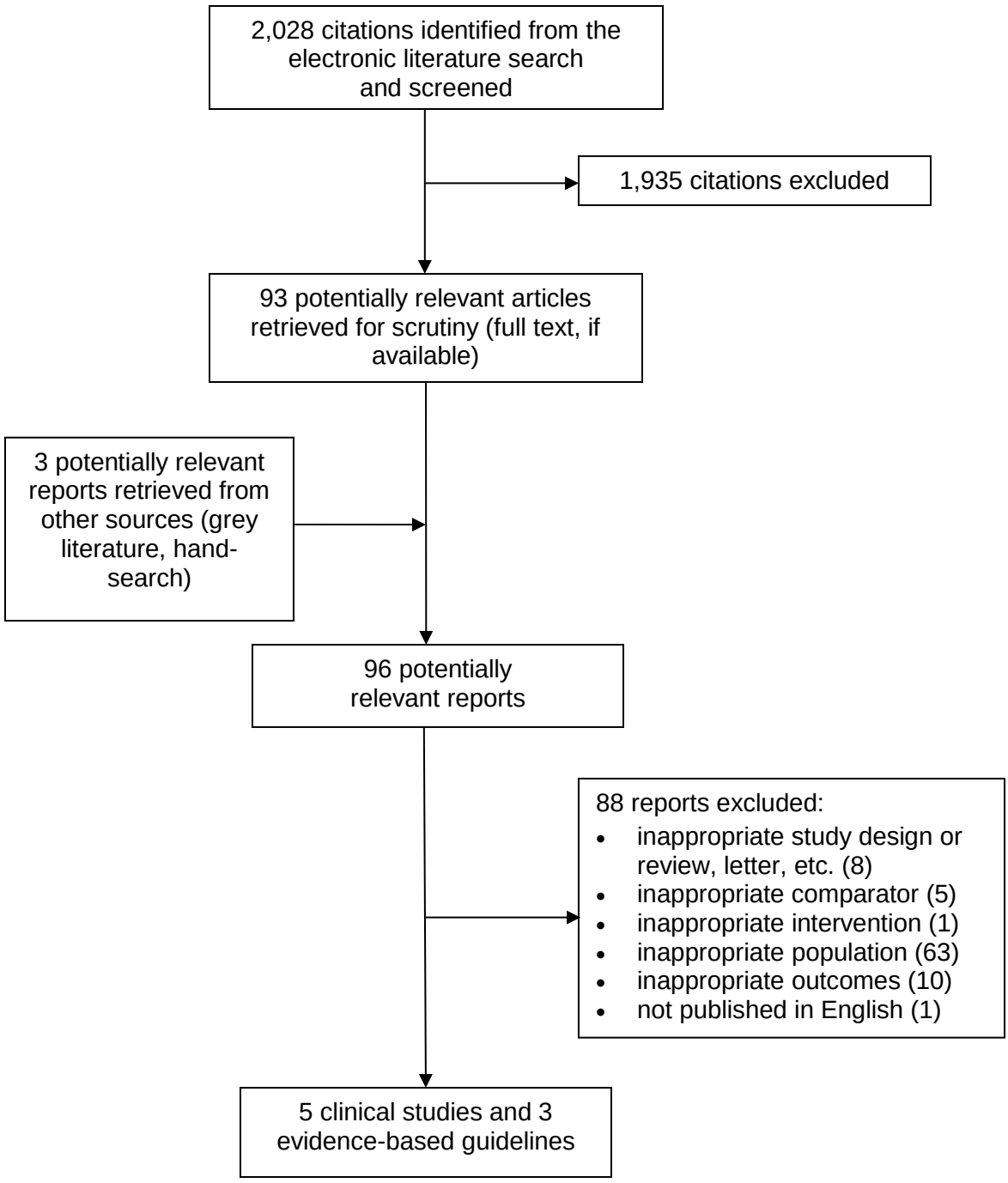
APPENDIX 4: SELECTION OF INCLUDED STUDIES



APPENDIX 5: CLINICAL STUDY CHARACTERISTICS

Table 8: Clinical Study Characteristics

First Author, Year; Funding Sources	Study Design; Duration	Country	Study Objective	Eligibility Criteria	Author Conflicts of Interest
Coppens et al., 2008;[23] Netherlands Heart Foundation; Dutch Cancer Foundation; Netherlands Organisation for Scientific Research	Prospective case-control; 8 years	The Netherlands	"To investigate whether thrombophilia testing reduces the risk of recurrent VT by virtue of these management alterations." p. 1474	Patients aged 18 to70 years with 2nd VTE (controls had only 1st VTE)	No
Kruse et al., 2006;[24] National Institutes of Health; National Heart, Lung, and Blood Institute; Emergency Medicine Foundation's Rigg's Family Heart Policy Award	Prospective case-control; 32 months	US	"…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	Patients with idiopathic PE	Not declared
Mansilha et al., 2006;[25] European Society for Vascular Surgery	Prospective case-control; duration not reported	Portugal	"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	Patient < 40 years old with a 1st episode of DVT	Not declared
Obeidat et al., 2009;[26] University of Jordan Faculty of Academic Research	Prospective case-control; 2 years	Jordan	"To study the frequency of Factor V Leiden (FVL), prothrombin gene mutation G20210A… in patients with acute pulmonary embolism (PE); and to investigate whether	Patients ≤ 60 years old, with confirmed idiopathic PE	Not declared

Table 8: Clinical Study Characteristics					
First Author, Year; Funding Sources	**Study Design; Duration**	**Country**	**Study Objective**	**Eligibility Criteria**	**Author Conflicts of Interest**
			these factors are more frequent in patients who have no obvious risk factors for venous thrombo-embolism compared to those with obvious risk factors." p. 921		
Rodger, 2008 et al.;[27] Canadian Institutes of Health Research; bioMérieux	Prospective cohort; 4 years	Canada, Switzerland, US, France	"…to determine the clinical predictors or combinations of predictors that identify patients with an annual risk of venous thromboembolism of less than 3% after taking an oral anticoagulant for 5-7 months after a first unprovoked event." p. 418	Patients > 17-years-old with 1st unprovoked VTE, who received heparin or LMW heparin for ≥ 5 days and oral anticoagulation therapy for 5 to 7 months after VTE	Several authors declared consultant fees, travel assistance, or honoraria from Industry

DVT = deep vein thrombosis; LMW = low–molecular-weight; PE = pulmonary embolism; VT or VTE = venous thromboembolism.

APPENDIX 6: PATIENT CHARACTERISTICS

Table 9: Patient Characteristics				
First Author, Year	**Study Arms**	**Number Enrolled**	**Gender (Male/Female)**	**Age (Mean Years)**
Coppens et al., 2008[23]	Patients with a 2nd VTE	197 (106 had idiopathic VTE)	120(60%) / 77(40%)	50 ± 13 SD
	Control: Patients with 1st VTE only	324 (130 had idiopathic VTE)	179(55%) / 145(45%)	49 ± 13 SD
Kruse et al., 2006[24]	Patients with idiopathic PE	49	32(65%) / 17(35%)	56 ± 16 SD
	Control: Patients with a) non-idiopathic PE; b) patients with PE excluded; and c) patients not suspected of having PE	Total: 436 a)152; b) 91; and c) 193	a) 55(36%) / 97(64%); b) 30(33%) / 61(67%); and c) 77(40%) / 116(60%)	a) 53 ± 17 SD; b) 46 ± 10 SD; and c) 50 ± 10 SD
Mansilha et al., 2006[25]	Patients < 40 years old, with1st DVT	99	31(31%) / 68 (69%)	27 (range 16 to 40)
	Healthy controls	100	NR	NR
Obeidat et al., 2009[26]	Patients with acute PE	92	34(37%) / 58(63%)	49.5 ± 16.7 SD
	Healthy controls	99	38(38%) / 61(62%)	31.0 ± 10.1 SD
Rodger et al., 2008[27]	Patients with recurrent VTE following OAC	91	63(69%) / 28(31%)	54 ± 15 SD
	Patients with no recurrent VTE following OAC treatment	555	269(48%) / 286(52%)	52 ± 18 SD

DVT = deep vein thrombosis; NR = not reported; OAC = oral anticoagulation; PE = pulmonary embolism; SD = standard deviation; VTE = venous thromboembolism.

APPENDIX 7: SUMMARY OF CRITICAL APPRAISAL OF INCLUDED STUDIES

Table 10: Critical Appraisal of Clinical Studies (Downs and Black Checklist)[21]

First Author, Year	Strengths	Limitations
Coppens et al., 2008[23]	• The hypothesis/aim/objective of the study is clearly described. • The main outcomes to be measured, patient characteristics, interventions of interest, and main findings of the study are clearly described. • The study provides estimates of the random variability in the data for the main outcomes. • The included subjects 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. • Statistical tests used to assess the main outcomes were appropriate. • The main outcomes measures used were accurate (valid and reliable). • The cases and controls were recruited from the same population and 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 was < 5%.	• 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. • Other important adverse events that may be a consequence of the intervention were not reported. • Actual probability values were not reported. • It is not apparent that an attempt was made to blind those measuring the main outcomes of the intervention.
Kruse et al., 2006[24]	• The hypothesis/aim/objective of the study is clearly described. • The main outcomes to be measured 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. • 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 staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive. • An attempt was made to blind those measuring the main outcomes of the intervention.	• 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. • The subjects comprised a high proportion of African-Americans, so may not be representative of the entire population from which they were recruited.

Table 10: Critical Appraisal of Clinical Studies (Downs and Black Checklist)[21]		
First Author, Year	**Strengths**	**Limitations**
	• 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 outcomes 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. • There was adequate adjustment for confounding in the analyses from which the main findings were drawn. • The study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance was < 5%.	
Mansilha et al., 2006[25]	• 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 distribution 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. • The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive. • 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 outcomes 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	• 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 the 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.

Table 10: Critical Appraisal of Clinical Studies (Downs and Black Checklist)[21]		
First Author, Year	**Strengths**	**Limitations**
	probability value for a difference being due to chance was < 5%.	
Obeidat et al., 2009[26]	• The hypothesis/aim/objective of the study is clearly described. • The main outcomes to be measured 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. • Statistical tests used to assess the main outcomes were appropriate. • The main outcomes 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 was < 5%.	• The distributions of principal confounders in each group of subjects to be compared is clearly described; however, they are not presented in a clear enough manner for use of some data. • The study provides estimates of the random variability in some data, but not for FVL or PG. • It is not reported if an attempt was made to blind those measuring the main outcomes of the intervention.
Rodger et al., 2008[27]	• The hypothesis/aim/objective of the study is clearly described. • The main outcomes to be measured are clearly described. • The characteristics of the patients included in the study are clearly described. • The interventions of interest are clearly described. • The distributions of principal confounders in each group of subjects to be compared are 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. • The characteristics of patients lost to follow-up are described.	• Adverse events reported were limited to the main outcomes. • The subjects participating in the study were not completely representative of the entire population from which they were recruited, as patients with known high-risk thrombophilia were excluded; and most patients were Caucasian.

Table 10: Critical Appraisal of Clinical Studies (Downs and Black Checklist)[21]		
First Author, Year	**Strengths**	**Limitations**
	• Actual probability values are reported (except where *P* is less than 0.001). • The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive. • An attempt was made to blind those measuring the main outcomes of the intervention. • The time period between the intervention and outcome was the same for cases and controls. • Statistical tests used to assess the main outcomes were appropriate. • The main outcomes 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. • There was adequate adjustment for confounding in the analyses from which the main findings were drawn. • Losses of patients to follow-up were taken into account.	• It is unclear if the study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance was < 5%.

APPENDIX 8: SUMMARY OF CRITICAL APPRAISAL OF INCLUDED GUIDELINES

Table 11: Critical Appraisal of Evidence-Based Guidelines (AGREE II)[22]

Guideline Producer, Publication Year	Strengths	Limitations
Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group,[28] 2011	• The scope and purpose of the guidelines are clear. • The recommendations are specific and unambiguous. • The methods for searching for and selecting the evidence are clear. • The methods used for formulating the recommendations are clearly described. • The health benefits, side effects, and risks were stated in the recommendations. • The target users of the guideline are clearly defined. • The 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,[9] 2010	• The scope and purpose of the guidelines are clear. • The recommendations are specific and unambiguous. • The methods for searching for and selecting the evidence are clear. • The methods used for formulating the recommendations are clearly described. • The health benefits, side effects, and risks were stated in the recommendations. • The target users of the guideline are clearly defined. • The level of evidence was 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),[5] 2012	• The scope and purpose of the guidelines are clear. • The recommendations are specific and unambiguous. • The methods for searching	• Unclear whether patients' views and preferences were sought

Table 11: Critical Appraisal of Evidence-Based Guidelines (AGREE II)[22]		
Guideline Producer, Publication Year	**Strengths**	**Limitations**
	for and selecting the evidence are clear. • The methods used for formulating the recommendations are clearly described. • The health benefits, side effects, and risks were stated in the recommendations. • The target users of the guideline are clearly defined. • The guideline was piloted among target users. • The procedure for updating the guidelines were provided. • The potential cost implications of applying the recommendation was considered. • The level of evidence was graded.	

APPENDIX 9: SUMMARY OF EXCLUDED ECONOMIC STUDIES

First Author, Year	Country	Reason for Exclusion	Summary
Compagni et al., (2013)[34]	Italy	Not in the relevant patient population	Two decision models were undertaken to screen for FVL and PG mutation in women who requested oral contraception.
Smith et al. (2013)[39]	US	Conference abstract — not enough information	The authors developed a clinical decision tool and 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 PG mutation. 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 US$13,700 to US$3,600. The authors note that patient outcome should be assessed in future studies.
Mahajerin et al. (2012)[40]	US	Conference abstract — not enough information	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 PG mutation. The costs associated with thrombophilia testing were sourced from hospital charge and US Medicaid rates. It is not stated, but the assumption is that patients underwent panel testing for various mutations. The authors identified no benefits to testing and, because of the low prevalence of positive tests, concluded that Medicaid could save up to US$365 per patient by eliminating routine thrombophilia testing in hospitalized children with VTE.
Donadini and Agino (2011)[37]	Review	Not an economic evaluation — review of literature	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. Whereas costs associated with the risk of bleeding were discussed in the abstract, there was no explicit discussion of the costs of testing or treatment.
O'Brien and Smith (2009)[43]	US	Hypothetical cohort, not informed by relevant clinical data	Markov model was developed to evaluate the cost-utility of 3 strategies: • no testing and 3 months AC • no testing and 6 months AC • 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

First Author, Year	Country	Reason for Exclusion	Summary
			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 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.[63] paper to provide proxy values. The results indicated a cost per QALY of between US$4,500 and US$7,000 for all strategies, with no test, and 3 months' AC dominating the other strategies.
Paci and Ibaretta (2009)[38]	Review	Not an economic evaluation — review of literature	This paper provided a synthesis of past and emerging literature on cost-effectiveness studies that evaluate PGx tests – including FVL and PG mutation — 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.
Simpson et al. (2009)[42]	UK	Hypothetical cohort, not informed by relevant clinical data	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 the 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.
Smith et al. (2008)[35]	NR	Not in the relevant patient population	This economic evaluation focused on female relatives of FVL carriers being screened prior to oral contraceptive use.
Wu et al. (2006)[36]	Review	Not in the relevant patient population	The authors undertook a systematic review and cost-effectiveness analysis of universal and selective VTE in women receiving oral contraceptives, HRT, at onset of pregnancy, or in patients undergoing major orthopedic surgery. Thus, these were not patients with idiopathic VTE.
Auerbach et al. (2004)[41]	US	Hypothetical cohort, not	Presented a Markov model assessing strategies of not testing followed by 6 to 36

First Author, Year	Country	Reason for Exclusion	Summary
		informed by relevant clinical data	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. The relative risk of subsequent events alters based on test result, age, year in the model. The risk of events based on health treatment and health states were included. Mortality based on age and event was included. Utility values based on health state was included. Costs were included. A lifetime time horizon was used, 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 represented a marginal cost-effectiveness (US$11,000/QALY).
Eckman et al. (2002)[44]	US	Not in the relevant patient population	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 (APCR, 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.
Marchetti et al. (2001)[45]	Italy	Not in the relevant patient population	Presented a Markov model using a hypothetical cohort of Italian patients with an initial DVT to compare standard AC prophylaxis to screening for FVL and PG mutation, 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

First Author, Year	Country	Reason for Exclusion	Summary
			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).

AC = anticoagulation therapy; APCR = activated protein C resistance; CE = cost-effectiveness; DVT = deep vein thrombosis; FVL = factor V Leiden; HRT = hormone replacement therapy; NR = not reported; PCR = polymerase chain reaction; PE = pulmonary embolism; PG = prothrombin gene; PGx = pharmacogenomics; QALY = quality-adjusted life-years.