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A risk–benefit analysis of factor V Leiden testing to improve pregnancy outcomes: a case study of the capabilities of decision modeling in genomics

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Purpose: We sought to assess the benefits, risks, and personal utility of factor V Leiden mutation testing to improve pregnancy outcomes and to assess the utility of decision-analytic modeling for complex outcomes in genomics.

Methods: We developed a model to evaluate factor V Leiden testing among women with a history of recurrent pregnancy loss, including heparin therapy during pregnancy in mutation-positive women. Outcomes included venous thromboembolism, major bleeds, pregnancy loss, maternal mortality, and quality-adjusted life-years.

Results: Factor V Leiden testing in a hypothetical cohort of 10,000 women led to 7 fewer venous thromboembolic events, 90 fewer pregnancy losses, and an increase of 17 major bleeding events. Small improvements in quality-adjusted life-years were largely attributable to reduced mortality but also to improvements in health-related quality of life. However, sensitivity analyses indicate large variance in results due to data uncertainty. Furthermore, the complexity of outcomes limited our ability to fully capture the repercussions of testing in the quality-adjusted life-year measure.

Conclusion: Factor V Leiden testing involves tradeoffs between clinical and personal utility, and additional effectiveness data are needed for heparin use to prevent pregnancy loss. Decision-analytic methods offer somewhat limited value in assessing these tradeoffs, suggesting that evaluation of complex outcomes will require novel approaches to appropriately capture patient-centered outcomes.

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Key Words: clinical utility; decision analysis; factor V Leiden; genetic testing; pregnancy

Decision-analytic methods are often used in health-care decision making to quantify the anticipated clinical risks and benefits of implementing a proposed intervention. These methods provide a framework for transparently assembling data and estimating the effects of an intervention on health outcomes.[1] Although these methods have been used to assess a multitude of interventions, it is unclear whether they are capable of adequately capturing clinical and personal utility of genomic testing.

Specifically, genomic testing in complex indications may be challenging to represent within the context of a traditional decision-analytic framework that uses quality-adjusted life-years (QALYs) as a summary measure of benefit.[2] Genomic tests impart knowledge to both the patient and provider. To the extent that this information guides treatment decisions, the impact on health outcomes is relatively straightforward to capture using decision-analytic methods.[3] However, complexity arises due to the inherent value the information obtained from a genomic test may have to the patient. This information has potential to be the source of anxiety or to relieve anxiety, may have implications for reproductive decisions, and has implications for others, as spouses of carriers are affected by the decisions informed with this knowledge and relatives of a mutation-positive patient learn that they have a higher likelihood to be carriers.[4–8] The growing availability and use of genomic tests merit closer examination of the role of decision modeling in assessing the clinical and personal utility of testing.

The objective of this study was to explore the capability and flexibility of decision-analytic methods to examine a complex case study involving genomic testing: the use of factor V Leiden (FVL) testing to improve pregnancy outcomes. A genomic test for the FVL mutation has been commercially available since 2003, but recent consensus recommendations differ on the indications that require screening among pregnant women, and the strength of evidence underlying these recommendations is weak.[9,10] The FVL mutation affects an estimated 5% of European Americans, and estimates range from 0.5 to 2.5% among Americans of other ancestries.[11] Heterozygous carriers of the FVL mutation have a three- to eightfold increased risk of experiencing venous thromboembolisms (VTEs) and homozygous carriers are estimated to have a further elevated risk wherein the estimates range from a nine- to 80-fold increased risk as compared with noncarriers.[12] Furthermore, studies have indicated a potential association between the FVL mutation and risk of recurrent pregnancy loss (RPL) and other adverse pregnancy outcomes.[13] However, the uncertainty in study findings and strong influence of patient values and preferences for medical treatment during pregnancy have not allowed decision makers to impart strong recommendations on the clinical scenarios that warrant FVL testing and treatment.[9]

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The findings from this study will provide further insight into the application of decision-analytic methods to assess the utility of genomic testing, specifically illuminating the complexities in the measurement of and tradeoffs in personal vs. clinical outcomes.

MATERIALS AND METHODS

Decision-analytic frameworks involve the synthesis of a "chain of evidence," enabling the estimation of net benefits afforded by an intervention for which no direct evidence exists. Each node of a decision tree reflects the possibility of multiple, mutually exclusive potential outcomes, and each end-to-end path represents the series of outcomes that a particular patient may experience. Health benefit is often measured using QALYs—a measure that adjusts length of life by health-related quality of life. Health-related quality of life is measured on an interval scale of zero to one, where a value of zero represents death and a value of one represents perfect health.

Here, we developed a decision-tree framework to quantify the risks and benefits of FVL testing among women with a history of RPL but without any prior VTE events or family history of VTE. The framework was developed from a patient-centered perspective, and the overall benefits and risks were informed by studies of patient preferences, as feasible. We conducted reviews of the scientific literature to inform the probabilities and utilities for each outcome of interest.

Model structure

The model was structured with two arms—FVL testing and no testing—as described below. A depiction of the decision tree model is provided in **Figure 1**. We constructed the model using Microsoft Excel.

For the intervention, we evaluated the effects of testing all women in the population described for the FVL mutation. We assumed that all women who tested positive as carriers of the mutation would receive thromboprophylaxis with low-molecular-weight heparin (LMWH) if and when they experienced a subsequent pregnancy. LMWH is considered safe for use during pregnancy because it is unable to cross the placental barrier.[9] We assumed that women who tested negative for the mutation would not be administered any treatment.

For comparison, we evaluated outcomes in the same population, assuming women were not tested for the FVL mutation. We assumed that thromboprophylaxis was not administered to any woman in the comparator arm. This assumption is plausible, as current guidelines do not recommend thromboprophylaxis

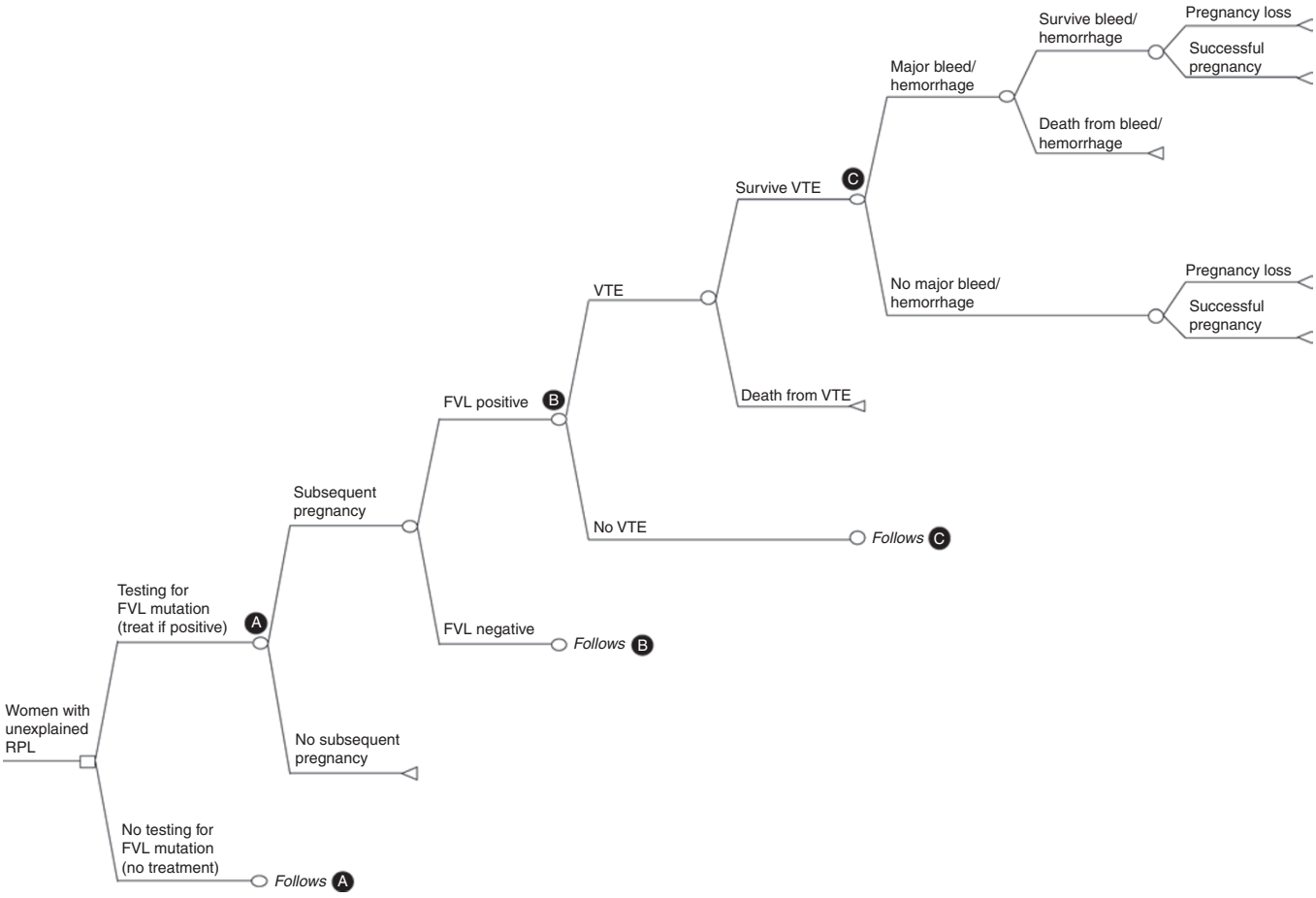

Figure 1 Decision tree diagram comparing universal testing and no testing for the FVL mutation among women with a history of recurrent pregnancy loss but no history of VTE. FVL, factor V Leiden; RPL, recurrent pregnancy loss; VTE, venous thromboembolism.

for women with a history of RPL, no prior VTE events or familial history of VTE, and no identified inherited thrombophilia.

Patient population

The population modeled is reflective of the US patient population. We assessed a hypothetical cohort of women with a history of RPL, and RPL was defined as two or more pregnancy losses. Furthermore, the population was limited to women with no personal or family history of VTE, as women with a history of VTE are likely to receive treatment with anticoagulants during pregnancy regardless of FVL carrier status. The average age at first birth was assumed to be 25.2 years, reflecting the average maternal age in the United States, and life expectancy was assumed to be 56.3 years, consistent with females 25 years of age.[14,15]

Outcomes

The outcomes considered in this analysis included pregnancy loss, VTE, major bleed/hemorrhage, death due to VTE or major bleed/hemorrhage, and QALYs. Pregnancy loss was included because it is the foremost concern for women in this population, and desire to avoid subsequent loss is most often the impetus for testing and treatment. VTE was included in the analysis because it is a primary outcome resulting from thrombophilia and, in this case, the FVL mutation. Major bleeding or hemorrhage is the primary adverse event resulting from treatment with LMWH and was thus included as a measure of risk resulting from treatment. Finally, death was included as potential complication of VTE or major bleeding/hemorrhage.

Outcome assessment was limited to the hypothetical population of women, and beyond pregnancy loss, morbidity and mortality affecting only the fetus were not considered. The intervention (gestational anticoagulation treatment with LMWH among women testing positive for the FVL mutation) was assessed for the duration of pregnancy through 6 weeks postpartum—approximated as 1 year. Outcomes were also assessed for this same time period, although lifetime mortality effects were captured.

Assumptions

In this study, homozygous carriers of the FVL mutation were not explicitly considered. Although homozygous carriers are believed to be at a much greater risk of VTE, they represent a small proportion of all carriers of the FVL mutation, and therefore the majority of the risk conferred by the FVL mutation is captured in heterozygous carriers. Furthermore, guidelines for treatment of homozygous carriers are less uncertain due to the well-established risk estimates in these patients.[9] The analysis was also limited to the US Caucasian population; although the prevalence of the FVL mutation is known to vary by race, prevalence in other populations is less well characterized. In addition, the presence of other forms of inherited thrombophilia was not considered in this analysis. The FVL mutation is the most common inherited form of thrombophilia and was thus believed to be sufficient for the purposes of this study.

A fourth simplification in this study was the decision not to differentiate between early and late pregnancy loss both in the definition of RPL and in measurement of outcomes. Although there is some suggestion in current literature that FVL carriers have a higher risk of late pregnancy loss, this differential risk has not been confirmed.[13] Furthermore, we elected not to separately model the postpartum period of pregnancy; although women are known to be at a higher risk of VTE during this period, we focused our analysis on the potential to improve pregnancy outcomes and reduce VTE events during pregnancy—the time period when treatment benefit is less evident. In both cases, a conservative approach was taken.

The final assumption made in this study was that sensitivity and specificity of the FVL test are captured in the risk estimates reported in previous epidemiologic studies. Because the estimates of risk are calculated based on those who test positive or negative, the clinical impact and inefficiencies resulting from imperfect sensitivity and specificity of FVL testing are inherent in these risk estimates.

Data inputs

We conducted literature reviews within PubMed to identify probabilities and utilities for each event. Where available, data were extracted from clinical trials and meta-analyses. All searches were limited to English-language literature based on human subjects. In conducting the literature reviews, the most common reasons for exclusion were as follows: population included women with a history of VTE, population included women with other hereditary or acquired thrombophilia, population was not restricted to women with a history of RPL, and inclusion criteria for RPL differed significantly from those used in this study. Where data were not available, we estimated parameters with input from clinical experts and tested these assumptions in one-way sensitivity analyses. Key parameters were also tested in the sensitivity analysis. Probability and utility values used as inputs in the model are summarized in **Table 1**.

Data inputs: key clinical data

We obtained an estimate of prevalence of the FVL mutation among women with a history of RPL by conducting a literature review using the following search terms: "recurrent pregnancy loss", "factor V Leiden", "thrombo*", "risk", and "association". We leveraged the studies published by Kovalevsky et al.[16] and Bradley et al.[17] to inform the estimate. These studies are meta-analyses of 16 and 33 studies, respectively, and specifically examined the prevalence of the FVL mutation among women with RPL. Notably, both studies have their limitations, including predominant use of case–control studies, moderate heterogeneity, and potential for publication bias in the results.

We identified studies evaluating the association between carriers of the FVL mutation and risk of VTE during pregnancy using the following search terms: "factor V Leiden", "thrombo*", and "pregnancy". We elected to leverage the study by Biron-Andreani et al.[18] because the authors conducted a meta-analysis that included many of the individual studies identified in our

Table 1 Model inputs

Parameter	Base case	Low estimate	High estimate	Reference(s)
Prevalence of FVL mutation				
US Caucasian population	0.0527	0.0442	0.0622	11
OR: Women with RPL vs. population	2.0	1.5	2.7	16,17
VTE in women with RPL				
Risk in FVL– women	0.001792	0.00165	0.00185	30,31
OR: FVL+/FVL–	8.2	5.9	11.3	18
Risk of death from VTE	0.000011	—	—	31
Utility: VTE[a]	0.80	0.75	0.85	32,33
Major bleed/hemorrhage due to LMWH				
Risk in untreated women	0	—	—	Assumption
Risk in women treated with LMWH	0.0198	0.0150	0.0257	34
Risk of death from major bleed	0.09	0.03	0.19	35
Utility: major bleed[b]	0.8	0.75	0.85	32,36,37
Pregnancy loss in women with RPL				
Risk in FVL– women	0.11	0.05	0.18	38
OR: FVL+/FVL–	1.93	1.21	3.09	17
Short-term utility: pregnancy loss[c]	0.80	0.75	0.85	25
Utility: successful pregnancy[c]	1.0	0.90	1.0	26
LMWH effectiveness (treated:untreated)				
RR: VTE	0.40	0.70	0.20	19,20
RR: pregnancy loss	0.50	1.00	0.25	20,22
Other				
Probability: subsequent pregnancy	0.80	0.50	1.00	Assumption
Long-term utility: RPL/infertility	0.82	0.77	0.87	27,28
Utility: pregnancy	0.92	0.90	0.94	39
Long-term utility: average lifetime	0.85	0.75	0.95	Assumption
Utility: death	0.00	—	—	Definition

FVL, factor V Leiden; LMWH, low-molecular-weight heparin; OR, odds ratio; RPL, recurrent pregnancy loss; RR, relative risk; VTE, venous thromboembolism.
[a]Applied for a duration of 1 week. [b]Applied for 2 weeks. [c]Applied postpregnancy loss for 32 weeks.

search. Furthermore, the authors evaluated the risk of a first VTE separately from the risk of a recurrent VTE—an important distinction in the timing of testing and treatment in this population.

We identified studies evaluating the risk for a subsequent pregnancy loss in our population using the search terms: "factor V Leiden", "thrombo*", and "risk of pregnancy loss". We elected to use the estimates reported in the study conducted by Bradley et al.[17] The meta-analysis leveraged results from four cohort studies, and the summary odds ratio was found to have low heterogeneity.

We estimated the effectiveness of LMWH in preventing VTE and future pregnancy loss by searching with the following terms: "low-molecular-weight heparin", "pregnancy", "thrombo*", and "factor V Leiden". We did not identify any placebo-controlled studies specifically in women with the FVL mutation and without a history of VTE that estimated the effectiveness of LMWH as prophylaxis for future VTEs. We therefore estimated the parameter on the basis of a review article by Dobesh et al.[19] and a cohort study by Tormene et al.,[20] which provided similar estimates. In addition, we found limited trial-based evidence of LMWH effectiveness in preventing future pregnancy loss; as Bradley et al.[17] conclude, trials studying this relationship have been underpowered for women with inherited thrombophilia and thus are inconclusive as to the treatment effect within this population.[21] We leveraged the cohort studies conducted by Carp et al.[22] and Tormene et al.[20] for estimates of LMWH effectiveness in preventing future pregnancy loss. Although these studies considered broader populations—inclusive of other hereditary thrombophilia and women with a history of VTE—we felt the estimates of LMWH effectiveness were closest to those that would be expected in our population. To address the uncertainty in treatment effect raised in these studies and in the aforementioned clinical trials, we evaluated the possibility that LMWH is ineffective in reducing subsequent pregnancy loss in the sensitivity analysis.

Data inputs: utility data

We searched the PubMed database and the Tufts Cost-Effectiveness Analysis Registry to identify appropriate utility estimates for the various outcomes. We were unable to find utility estimates specific to our population, and, in some cases, specifically for women during pregnancy. Of note, the estimates of utility of a successful pregnancy after multiple failed pregnancy attempts and the inability to conceive reported in previous studies are largely based on expert opinion, and studies apply the impact of such outcomes for varying durations.[23–26] In light of this, we selected utility estimates most widely used and accounted for this inaccuracy by conducting sensitivity analyses around these estimates.

Analysis

Health impacts, measured by QALYs, were calculated by multiplying the utility for each event experienced by the duration of the event (as listed in Table 1). These values were summed to obtain total estimated QALYs for each path of the decision tree in a 1-year timeframe. Mortality effects were captured over a lifetime, based on an average maternal age at first birth of 25.2 years, total life expectancy of 81.5 years at the age of 25.2 years (or 56.3 remaining years of life), and an assumed average utility of 0.85 in future years. Lifetime QALYs were discounted at a rate of 3% to reflect time preference.

We conducted one-way sensitivity analyses to assess the impact of parameter uncertainty. To do so, we varied inputs one by one—using either 95% confidence intervals reported in the literature or a manually selected interval believed to reflect the amount of uncertainty in the estimates. We also conducted scenario analyses to understand the potential range in results when multiple parameters were varied simultaneously.

RESULTS

The predicted numbers of events for the intervention and comparator arms are presented in Table 2. The base-case scenario suggests that 7 VTE events and 89 pregnancy losses would be prevented in every 10,000 women tested for the FVL mutation and subsequently treated if positive. This benefit is balanced by an increase of 17 major bleed/hemorrhage events due to LMWH treatment.

The predicted QALYs in each arm, per 10,000 women, are also presented in Table 2. These results are presented for 1 year of pregnancy and the lifetime perspective. Testing for FVL and subsequent treatment would result in a gain of 3 QALYs per 10,000 women during the year of pregnancy, as compared with a strategy of no testing. From a lifetime perspective, the results indicate that testing and treatment would result in 40 QALYs gained per 10,000 women tested.

Table 2 Results: base case—predicted outcomes in each arm, per 10,000 women

	Predicted outcomes (per 10,000 women)		Difference in outcomes with FVL testing
	FVL testing	No testing	
VTEs	18	25	7
Major bleeds/ hemorrhages	17	0	−17
Pregnancy losses	877	966	89
QALYs: 1 year	9,080	9,077	3
QALYs: lifetime	235,104	235,064	40

FVL, factor V Leiden; QALY, quality-adjusted life-year; VTE, venous thromboembolism.

The results are evidence that benefits of FVL testing and subsequent treatment are largely attributable to the effectiveness of LMWH in preventing pregnancy loss and the subsequent utility improvements for women who are able to conceive. Reduction in VTE events, increase in major bleeds, and the associated impacts on health-related quality of life appear to have a small effect on overall QALYs.

Sensitivity analysis

The one-way sensitivity analyses indicated notable variability in the findings due to parameter uncertainty. Results of the analyses for 1-year and lifetime QALYs are depicted in Figures 2 and 3. The analyses indicate sensitivity of results to various parameters, but in particular to the association between the FVL mutation and RPL, effectiveness of LMWH in preventing pregnancy loss, and utilities associated with pregnancy loss and successful pregnancy. For instance, the reduction in 7 VTE events ranged from 4 to 10, and 89 pregnancy losses ranged from 0 to 134 per 10,000 women due to variability in estimates of LMWH effectiveness. The impact of testing and treatment on the risk of VTE events had minimal impact on the results, likely due to the low risk of VTE, small risk of death due to VTE, and minimal reduction in utility due to occurrence of a VTE event.

Scenario analyses

We evaluated multiple scenarios to understand how the results are affected when key inputs are varied simultaneously. Because the effectiveness levels of LMWH in preventing

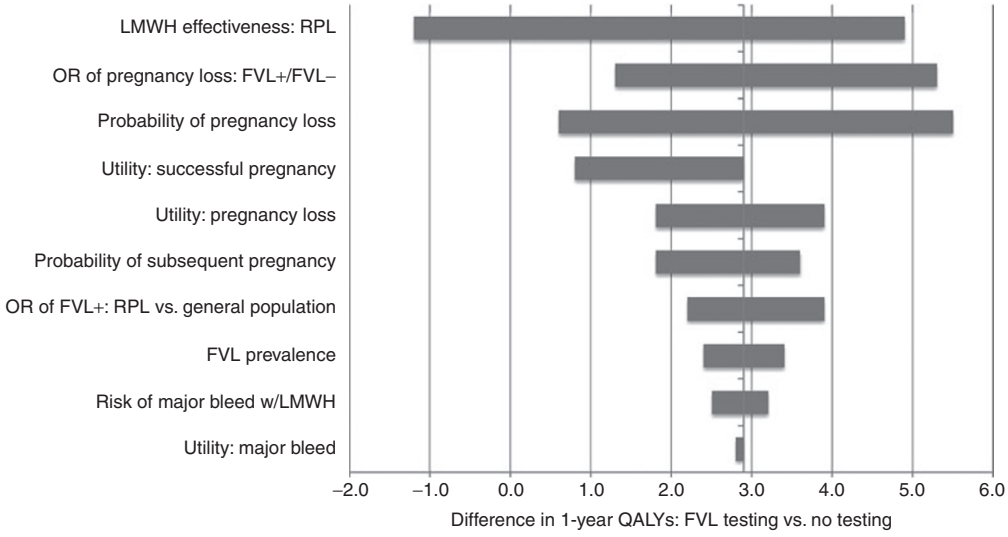

Figure 2 One-way sensitivity analysis evaluating the impact of parameter uncertainty on the difference in QALYs between FVL-testing and no-testing strategies during the 1-year timeframe in which women attempt a subsequent pregnancy. FVL, factor V Leiden; LMWH, low molecular weight heparin; OR, odds ratio; QALYs, quality-adjusted life-years; RPL, recurrent pregnancy loss.

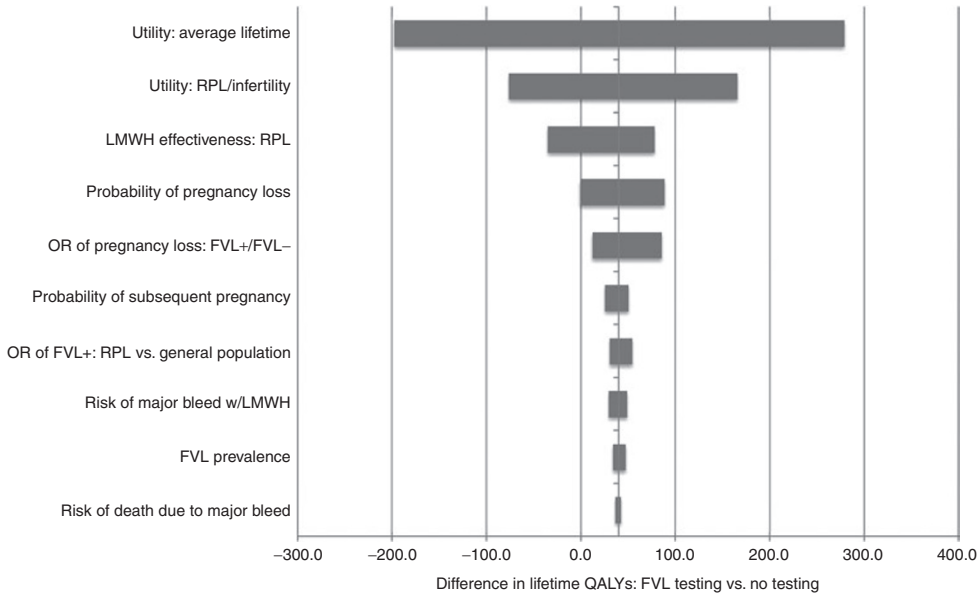

Figure 3 One-way sensitivity analysis evaluating the impact of parameter uncertainty on the difference in QALYs between FVL-testing and no-testing strategies over the lifetime of the women in each cohort. FVL, factor V Leiden; LMWH, low molecular weight heparin; OR, odds ratio; QALYs, quality-adjusted life-years; RPL, recurrent pregnancy loss.

subsequent pregnancy loss and disutility of pregnancy loss are largely uncertain parameters that have considerable impact on results, we selected these to assess the impact on lifetime QALYs.

The scenario analyses further demonstrate that effectiveness of LMWH in preventing subsequent pregnancy loss has a substantial impact on the difference in lifetime QALYs between the intervention and control arms. Using our base-case utility values, we see a loss of 36 lifetime QALYs among 10,000 women who are tested and subsequently treated if they are carriers of the FVL mutation when LMWH is ineffective in preventing subsequent pregnancy loss; alternatively, if we assume that the LMWH reduces subsequent pregnancy losses by 90%, we estimate a gain in 101 lifetime QALYs. Albeit to a lesser degree, short-term and long-term disutility of pregnancy loss also have a non-negligible impact on lifetime QALYs—ranging from an increase of 39 to 46 QALYs—when we assume that LMWH is 50% effective.

Detailed results of these scenario analyses are presented in the **Supplementary Table S1** online.

DISCUSSION

Summary

We evaluated the clinical utility of testing women with a history of RPL for the FVL mutation and administering gestational anticoagulation therapy to women who test positive for the mutation. The results of our analysis indicate that the benefits of reducing the incidence of VTEs in these women is counterbalanced by the increase in major bleeds and hemorrhages resulting from anticoagulation therapy. Furthermore, robust conclusions regarding the benefits related to the prevention of subsequent pregnancy losses cannot be drawn because of a lack of strong evidence of the treatment effect on pregnancy loss.

Implications

Much of the controversy as to whether FVL testing should be done is due to the fact that the effects of treatment on pregnancy-related outcomes are not well understood, and the potential exists for more harm than good to result from treatment. Previous studies, although often not powered to study the efficacy of LMWH specifically in women with RPL and inherited thrombophilia, have led to inconclusive and sometimes contradictory findings.[17,20–22] This study further underscores the need for a firmer understanding of the effect of anticoagulation therapy on all pertinent outcomes; the scenario analysis suggests a potential loss in QALYs if LMWH is ineffective in preventing future pregnancy loss. Notably, two ongoing clinical trials seek to directly quantify the effectiveness in our intended population and will help to answer these questions; however, trial completion and publication of results are not expected before 2014.[27,28]

Quantifying the risk–benefit tradeoffs of FVL testing is challenging using a decision-analytic framework also because of the difficulties in outcomes assessment, potential heterogeneity in utility measurement, and broad impacts of testing. It is necessary to understand how a woman values each possible outcome to understand the tradeoff and to make testing and treatment decisions for that particular individual. Understanding the impact of genetic information on others is also imperative to develop a more comprehensive model for FVL testing in this scenario and for the evaluation of other genomic tests. For example, in the case of FVL testing, there is an impact on the carrier's partner's utility if the couple is unable to ever successfully have children or gives up on childbearing due to multiple failed pregnancy attempts, and if the couple ultimately has a successful pregnancy after multiple failed attempts. Complexities also exist when genomic test information affects reproductive decision making, whether explicitly related to

childbearing, as is the case with the current model for FVL testing, or when mutations are known to be indicative of elevated risk for serious or untreatable diseases that may then be passed down to future generations. Relatives of carriers are also affected by genetic knowledge because the information may suggest a higher likelihood that they too are carriers of the mutation in question. Therefore, the development of approaches to understand the psychosocial effects of testing on patients and their families is necessary to better capture the positive and negative effects of testing for the FVL mutation in this population in totality. Grosse et al.[29] argue that cost–benefit analyses may be better suited than cost-effectiveness analyses in the evaluation of utility of genomic tests and advocate the use of discrete-choice experiments to assess patient preferences. We agree that the use of such methods may be necessary; measurement of these impacts will provide a better understanding of the implications of testing, and, in conjunction with a framework such as that developed here, may inform decision making at the individual level and inform future policy recommendations for testing in this population.

Limitations

In applying decision-analytic methods to quantify the utility of FVL testing, we encountered challenges in fully capturing the implications of testing. One limitation of the approach is the difficulty in fully quantifying the health-related quality of life impacts on the mother in the event of a subsequent pregnancy loss or a successful pregnancy. The utility associated with bearing a child (and conversely, repeated failure in pregnancy attempts) is an area of research that requires further work. Our scenario analyses suggest a potential range of 39–46 additional lifetime QALYs among 10,000 women when women are tested and treated if positive. However, the values and duration of utility impacts tested are largely speculative, and it is unclear to what degree utility values may vary across individuals. The lack of research in this area has implications for many treatment decisions in the area of reproductive medicine: until we can more appropriately assess the value to patients of bearing a child, it is difficult to truly capture the risks and benefits of an intervention as perceived by the patient.

The utility that women may derive from knowing whether they are carriers of the FVL mutation is another parameter that is challenging to quantify and limits our ability to capture the impacts of testing comprehensively. Where knowledge of one's carrier status results in clarity as to the cause of a health condition and informs the selection of more effective treatments, this knowledge may relieve an individual's anxiety and result in utility improvements. However, in situations such as that of the FVL mutation, less is known about the disease pathway and the efficacy of potential interventions, therefore knowledge of one's carrier status has the potential to either alleviate or be the source of additional anxiety.

Furthermore, our findings may be conservative in that we limited the evaluation of outcomes to women with RPL. Testing for the FVL mutation, knowledge of one's mutational status, and impact on health outcomes are relevant not only to the woman tested, but also to the fetus, woman's partner, and family members. The broader impacts of testing and treatment ought to be formally considered once methods of measurement have been developed and employed to quantify these impacts.

In summary, we sought to understand the benefits and risks of FVL testing in a high-risk population of women with a history of RPL but no prior VTEs. However, lack of strong evidence of the effectiveness of anticoagulation therapy on pregnancy outcomes and limited research related to patient preferences render us unable to make strong conclusions with respect to widespread FVL testing in this population. Further research and novel methods enabling robust assessment of the implications of genetic testing are necessary to render a complete analysis of the clinical utility of FVL testing, at the population and individual levels.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/gim

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DISCLOSURE

The authors declare no conflict of interest.

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