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Heritable thrombophilia testing in British Columbia: A report on practice patterns and prevalence

Results from a survey and data from records for factor V Leiden mutation testing indicate that provincial HT testing guidelines may be needed.

ABSTRACT:

***Background*: Given the lack of agreement in the literature regarding the clinical utility of testing for heritable thrombophilia, we conducted a study to determine if variability in testing is found among specialists in British Columbia and to assess testing practice at Vancouver General Hospital, a tertiary care centre.**

***Methods*: A questionnaire about heritable thrombophilia testing was sent to 12 specialists in BC and the anonymized responses were analyzed. In addition, electronic records for factor V Leiden mutation testing performed over a 4-year period were analyzed to determine testing volume and assess patterns of ordering according to patient and clinician characteristics.**

***Results*: Eleven of 12 specialists completed the survey. The responses indicated that while the specialists felt very confident in their ability to interpret test results, most ordered these tests knowing that the results are unlikely to contribute to patient care. When asked whether testing was appropriate in 15 clinical scenarios, the agreement beyond chance (kappa) was only 38.7%. The data from Vancouver General Hospital revealed that factor V Leiden testing was performed on nearly 2000 patients annually during the study period, with over half of the tests ordered by family physicians and general internists. Most tests were performed on outpatients, and more women than men were tested, particularly women between ages 10 and 40.**

***Conclusions*: Surveyed specialists agreed that heritable thrombophilia testing is usually unhelpful in patient care and disagreed regarding the appropriate indications for testing. Much testing in BC occurs in female outpatients of reproductive age.**

Background

The term "thrombophilia" derives from the Greek words *thrombos* and *philia*, and translates as "clot loving." Patients with thrombophilia have a higher risk of incident and recurrent venous thromboembolism (VTE) and may have a heritable or an acquired thrombophilia. Over the past 2 decades, there has been great interest in predicting an individual's genetic predisposition to clotting disorders, particularly when evaluating patients with a strong family history of VTE and those without a known acquired risk factor for thrombosis.

Interest in clotting disorders has led to widespread testing for the five most common kinds of heritable thrombophilia (HT) (**Table**).[1] These can be classified according to their associated risk factors for VTE: the low-risk factor V Leiden (FVL) muta-

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tion and the prothrombin gene mutation (PGM), and the high-risk deficiencies of protein C, protein S, and antithrombin. Although these forms of HT increase the relative risk of incident VTE, studies have shown them to have a rather modest effect on increasing the risk of recurrent VTE.[2,3]

Unfortunately, the limitations of HT testing are numerous. A set of negative results does not exclude the presence of other heritable thrombophilic factors, nor does it mean that a patient is at low risk of thromboembolic disease. Recent studies have shown that clinical features are strong predictors of recurrent thrombosis, with confirmation of FVL and prothrombin mutations being noncontributory, and confirmation of protein C, protein S, and antithrombin deficiencies remaining of uncertain value.[4-7] More importantly, studies have yet to show any benefit for HT testing in terms of important outcomes for the patient or cost-effectiveness.[7,8] In addition to being expensive (the five-test panel costs $292.09 per patient in BC, based on the 2012 Medical Service Plan laboratory fee schedule), the assays are not well standardized and need to be performed by laboratory technologists with specialized training. Another problem is that functional assays for deficiencies of antithrombin and proteins C and S are subject to interferences, including those caused by anticoagulants and acute thrombosis, and repeat testing is required to confirm deficiencies. Interpretation of the results thus requires an in-depth understanding of the technical limitations of testing and the clinical circumstances in which the testing was performed. Finally, HT test results are unlikely to influence management in most cases and can heighten anxiety in patients.

Given these limitations, we undertook a formal assessment of HT test ordering by physicians in BC. We began by surveying academic hematologists and other specialists to determine their level of agreement on the clinical utility of HT testing, and then reviewed HT tests performed at Vancouver General Hospital (VGH), a tertiary care and academic referral centre, to assess the volume of provincial HT tests performed and the patterns of testing according to patient and clinician characteristics.

Table. Most common heritable thrombophilias in the general population and in patients with incident and recurrent venous thromboembolic disease (VTE).[1]

Heritable thrombophilia	Prevalence in general population	Incident VTE prevalence	Relative risk (95% CI)	Recurrent VTE prevalence	Relative risk (95% CI)
Factor V Leiden G1691A	3%–7%	12%–20%	4.3 (1.9–9.7)	40%–50%	1.3 (1.0-3.3)
Prothrombin G20210A	1%–3%	3%–8%	1.9 (0.9–4.1)	15%–20%	1.4 (0.9-2.0)
Protein S deficiency	0.01%–1%	1%–3%	32.4 (16.7–62.9)	5%–10%	2.5
Protein C deficiency	0.02%–0.05%	2%–5%	11.3 (5.7–22.3)	5%–10%	2.5
Antithrombin deficiency	0.02%–0.04%	1%–2%	17.5 (9.1–33.8)	2%–5%	2.5

Methods

In May 2009, 12 BC specialists with expertise in thrombosis (eight academic hematologists, two community hematologists, one internist in obstetrical medicine, and one general internist) received a questionnaire by e-mail that asked their opinions on the utility of HT testing and how they determined when to test. The survey consisted of two background data questions, six general questions about the utility of HT testing, and questions describing specific clinical scenarios and asking whether HT testing was appropriate. Of the 15 clinical scenarios described, seven involved pregnancy and/or hormonal contraception, two involved screening before high-risk events or procedures, and six related to the circumstances of a patient's thrombosis, such as age, site, and presence/absence of provoking factor (see box). The results were anonymized and the overall agreement beyond chance (kappa) was calculated for the 15 clinical scenarios.

To determine what happens in practice regarding HT testing, VGH Hematology Laboratory electronic records were used to establish how many tests for FVL were performed from 1 April 2005 to 30 March 2009. FVL was chosen to represent HT testing patterns because it is the most prevalent heritable thrombophilia and roughly 80% of the testing for this mutation in BC was performed at VGH during the study period (based on unpublished BC Medical Service Plan data from 2008), whereas tests for deficiencies of antithrombin and proteins C and S are performed at numerous regional and private labs in BC. The testing data were sorted according to patient gender, age, and inpatient/outpatient status, as well as according to the specialty of the ordering physician.

Results

Survey responses

Eleven of the 12 specialists surveyed (92%) completed the survey. Most respondents (82%; 9 of 11) stated they see at least 50 patients a year with thrombosis and 64% (7 of 11) stated they order HT testing between 10 and 49 times a year. With regard to the interpretation of HT test results, most of the respondents (73%; 8 of 11) felt "very confident" of their ability to interpret the results and the remaining 3 felt confident but admitted to having "some uncertainty." Interestingly, 82% of respondents (9 of 11) felt that the results of testing influenced patient management less than 10% of the time. Furthermore, 73% of respondents (8 of 11) admitted to ordering HT testing "at least some of the time" when they did not believe the results would affect patient management.

When specialists were asked whether HT testing was appropriate in 15 specific clinical scenarios, there was good agreement (9 or 10 of 11 respondents) for only 27% of the scenarios (4 of 15), partial agreement (8 of 11 respondents) for 40% of the scenarios (6 of 15), and poor agreement (6 or 7 of 11 respondents) for 33% of the scenarios (5 of 15). No single scenario was judged appropriate for testing by all of the respondents. In aggregate, the calculated kappa measure of agreement beyond chance was 0.387, with the level of disagreement being rather evenly distributed across the scenarios.

Clinical scenarios from survey sent to 12 BC specialists with expertise in thrombosis

Which of the following are appropriate indications for thrombophilia screening?

- Before prescribing hormonal contraception to a woman with family history of thrombophilia.
- When evaluating a woman with recurrent pregnancy loss.
- Prenatal screening of a woman with family history of documented thrombophilia.
- Before prescribing hormonal contraception to a woman with family history of thrombosis.
- Prenatal screening of a woman with family history of thrombosis.
- Before high-risk situations events or procedures for patients with family history of documented thrombophilia.
- When evaluating a woman with obstetrical vascular complications.
- Before high-risk events or procedures for patients with family history of thrombosis.

Which of the following are appropriate indications for thrombophilia testing?

- Unprovoked thrombosis in patient < 50 years.
- Unusual site of thrombosis.
- Unprovoked recurrent episode of thrombosis, regardless of age.
- Thrombotic event in context of a soft risk factor.
- Thrombotic event in setting of hormonal-related event.
- Unprovoked first event of thrombosis, regardless of age.
- Provoked thrombosis in patient < 50 years.

Provincial FVL test data

As shown in **Figure 1**, VGH received 7928 orders for FVL testing during the 4-year study period, most of which were for outpatients (68.3%; 5418 of 7928 tests). Overall, FVL was requested more frequently for female patients (65.3%; 5182 of 7928 tests). This excess testing in women was more pronounced in the outpatient setting (70.6%; 3824 of 5418 tests) than in the inpatient setting (54.1%; 1358 of 2510 tests).

Figure 2 shows that women tested for FVL (median age 38 years) tended to be younger than men (median age 49 years), in outpatients as well as inpatients. The proportion of patients tested who were between the ages of 10 and 40 years was much higher in women (52.4%; 2713 of 5182 tests) than in men (23.5%; 644 of 2746 tests).

Figure 3 shows that clinicians ordering the most FVL tests at VGH were general practitioners (36.8%; 2914 of 7928 orders), followed by general internists (16.3%; 1296 of 7928 orders), obstetricians (13.7%; 1088 of 7928 orders), hematologists (9.5%; 752 of 7928 orders), and neurologists (6.9%; 550 of 7928 orders).

Of the 7928 test orders issued, FVL testing was not performed in 308 instances (3.9%). The majority of cancelled tests were for orders on previously tested patients (89.3%; 275 of 308 instances). Most of the remaining tests were canceled due to problems with the submitted specimen.

Of the patients tested, positive FVL results were seen in 16.3% of outpatient men (249 of 1531), 9.7% of inpatient men (106 of 1092), 10.3% of outpatient women (383 of 3694), and 9.2% of inpatient women (120 of 1303).

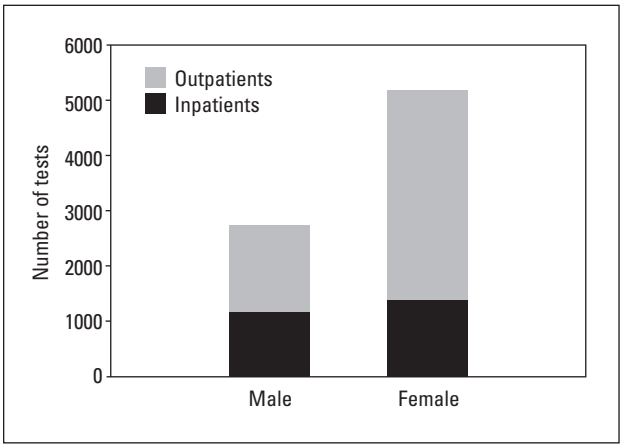

Figure 1. Factor V Leiden test order volume at Vancouver General Hospital according to gender and inpatient/outpatient status, 1 April 2005 to 30 March 2009.

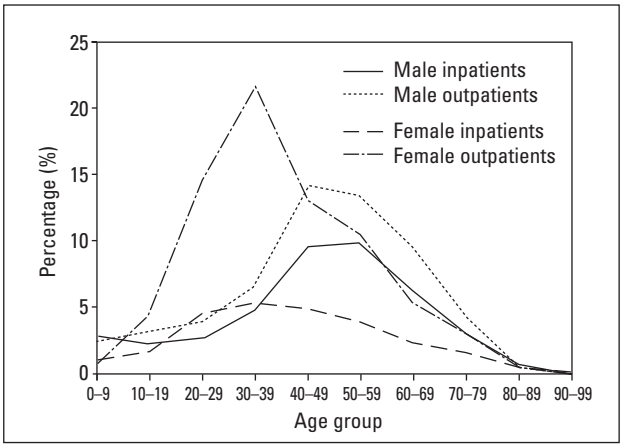

Figure 2. Gender, outpatient/inpatient status, and age of patients tested for heritable thrombophilia at Vancouver General Hospital, 1 April 2005 to 30 March 2009.

Conclusions

Our study is the first to document the volume and practice patterns of HT test ordering in any Canadian province. Responses to the clinical scenario questions in the survey revealed that significant variability exists when specialists, including academic hematologists, are asked to consider indications for HT testing, with a kappa value of only 35.7% agreement beyond chance. Another noteworthy survey finding is the coexistence of a high level of clinician confidence in HT test interpretation and the surprisingly high level of ordering frequency despite clinician acknowledgment that the results are unlikely to influence management in the majority of cases. This practice is clearly questionable and raises concerns regarding the value and utility of laboratory testing and its impact on patient outcomes.

The FVL testing data from VGH highlight several important issues in HT testing.

First, the volume of HT testing in the province is significant. Almost 2000 FVL tests per year were performed at VGH during the study period, at an annual cost of over half a million dollars (based on 2012 MSP rates). This seems to be a rather expensive exercise for uncertain clinical utility. Furthermore, considering that the expected number of annual incident VTE cases in BC is roughly 4400 (based on an overall incidence rate of 1 in 1000 and BC's 2011 population estimate of 4.4 million), either half of the patients with a new VTE are being tested for HT or, more likely, a significant amount of testing is occurring in patients without a history of VTE.[9,10] Given that HT testing is generally not indicated for patients without VTE and for those with a known risk factor for thrombosis (provoked VTE), the volume of testing appears excessive and inappropriate.

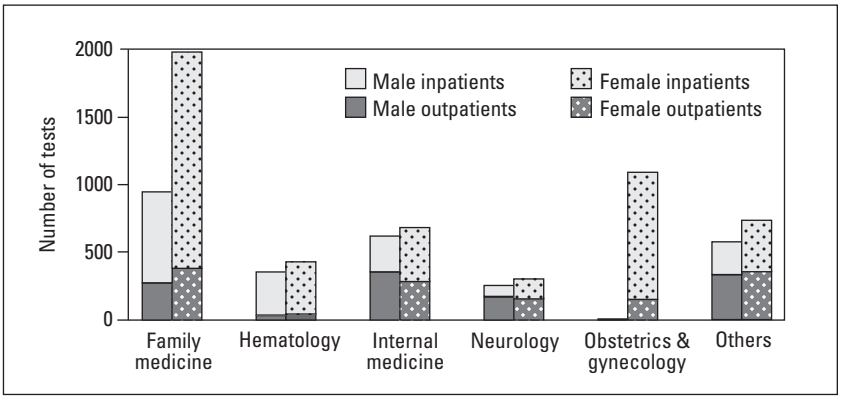

Figure 3. Specialty of clinicians testing for heritable thrombophilia, as well as gender and outpatient/inpatient status of patients tested at Vancouver General Hospital, 1 April 2005 to 30 March 2009.

Second, 32% of FVL tests were performed in patients admitted to hospital. This is an inappropriate setting for HT testing because levels of antithrombin, protein C, and protein S can be affected by the acute medical or surgical problems responsible for the patient's admission and make the results unreliable. Although the results of genetic testing for FVL and PGM would not be affected, they are also

unlikely to influence management decisions. With these considerations, inpatient HT testing should be strongly discouraged.

Third, the data show that HT tests ordered by general practitioners account for over one-third of all FVL tests ordered in BC. Consequently, future HT testing educational initiatives will need to target general practitioners. Possible strategies to eliminate inappropriate testing include establishing provincial HT testing guidelines, identifying inappropriate orders, limiting HT test ordering to specialists, or changing the reimbursement arrangements for HT testing.

Last, a disproportionate amount of outpatient testing occurs in younger women. This likely reflects clinician concerns about women who are pregnant and women considering hormonal contraception. HT testing in these two patient populations remains controversial because of the emotional issues, the lack of studies demonstrating positive impact on patient outcomes, and the questionable cost-effectiveness of testing.[8,11] The British Committee for Standards in Haematology summarizes these issues in detail.[12] Based on our findings on testing patterns, effective educational initiatives or guidelines are needed to address testing in these patient populations.

Our study has several limitations. Because most of the specialists surveyed were academic hematologists from the Vancouver region, the results obtained cannot be generalized to other specialists who commonly order HT tests (see **Figure 3**), nor can the results be assumed to represent specialists in other regions in Canada. In addition, the small sample size of 11 respondents limits our ability to draw strong conclusions. Nonetheless, given there are only 27 adult hematologists in the province of BC (excluding leukemia and lymphoma specialists), 11 respondents is a very reasonable representation of this specialty group. Finally, the testing patterns found by analyzing FVL test data may not be the same as testing patterns for other forms of HT. Although the tests for the five common heritable thrombophilias are generally ordered together, it is conceivable that FVL may be ordered in isolation in certain circumstances (e.g., for members of a family known to carry FVL).

This study demonstrates that although BC specialists agree that HT test results are of limited clinical utility in their practice, the way these specialists actually use these tests is extremely variable. Most HT tests in BC are ordered for outpatients, with a disproportionately high number of the orders being for young women. To encourage appropriate ordering of HT tests, educational initiatives will need to target general practitioners and specifically address clinical scenarios involving pregnancy and hormonal contraceptive therapy.

Competing interests

None declared.

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References

1. Heit J. Thrombophilia: Common questions on laboratory assessment and management. Hematology Am Soc Hematol Educ Program 2007;127-135.
2. Segal JB, Brotman DJ, Necochea AJ, et al. Predictive value of factor V Leiden and prothrombin G20210A in adults with venous thromboembolism and in family members of those with a mutation: A systematic review. JAMA 2009;301: 2472-2485.
3. van den Belt AGM, Sanson BJ, Simioni P, et al. Recurrence of venous thromboembolism in patients with familial thrombophilia. Arch Intern Med 1997;157: 2227-2232.
4. Rodger MA, Kahn SR, Wells PS, et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. CMAJ 2008;179:417-426.
5. Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med 1999;340: 901-907.
6. Lindmarker P, Schulman S, Sten-Linder M, et al. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. Thromb Haemost 1999;81:684-689.
7. Baglin T. Thrombophilia testing: What do we think the tests mean and what should we do with the results? J Clin Pathol 2000;53:167-170.
8. Wu O, Greer IA. Is screening for thrombophilia cost-effective? Curr Opin Hematol 2007;14:500-503.
9. White RH. The epidemiology of venous thromboembolism. Circulation 2003;107 (suppl1):14-18.
10. Population and dwelling counts, for Canada, provinces and territories, 2011 and 2006 censuses. Accessed 8 June 2012. https://www12.statcan.gc.ca/census-recensement/2011/dp-pd/hlt-fst/pd-pl/Table-Tableau.cfm?LANG=Eng&T=101&S=50&O=A.
11. Middeldorp S. Evidence-based approach to thrombophilia testing. J Thromb Thrombolysis 2011;31:275-281.
12. Baglin T, Gray E, Greaves M. et al. Clinical guidelines for testing for heritable thrombophilia. Br J Haematol 2010; 149:209-220. BCMJ