

Summary

- ✓ **Dosing algorithms tailored to individual genetic, demographic, and clinical factors may minimize the risk for bleeding during the initiation of warfarin therapy.**
- ✓ **Pharmacogenomic testing should be used in addition to (rather than replacing) routine International Normalized Ratio (INR) monitoring.**
- ✓ **Prospective studies are needed to determine whether pharmacogenomic testing improves patient outcomes, identify which subgroups of patients may benefit, and clarify the risks and costs associated with the use of these tests. Several randomized controlled trials are currently evaluating the impact of pharmacogenomics on dosing accuracy, time to achieve and maintain target INR, incidence of bleeding or thromboembolic events, and monitoring requirements.**
- ✓ **In August 2007, the FDA updated the product label for warfarin to include genetic variations in *CYP2C9* and *VKORC1* as one of the factors to consider for more precise initial dosing. Guidelines for pharmacogenomics-based warfarin dosing are under development.**

Background

Warfarin (Coumadin) is an oral anticoagulant indicated for patients with a history of atrial fibrillation, myocardial infarction, deep vein thrombosis, or pulmonary embolism, and for patients with certain types of artificial heart valves.¹ Warfarin acts by interfering with the synthesis of vitamin K-dependent clotting factors in the liver.² Bleeding is the most common adverse effect associated with warfarin.³ While

the risk for bleeding events is highest in the first 90 days of therapy, it persists throughout the course of warfarin therapy.⁴ Pharmacogenomics-based warfarin dosing has the potential to reduce the risk for bleeding, increase dosing accuracy, shorten the time to dose stabilization, and help identify individuals who may require more frequent monitoring with long-term therapy.



Illustration by Alison E. Burke.

Reprinted with permission: JAMA 2006;Sept 27, Vol 296(12):1453-1454. Copyright © (2006), American Medical Association. All rights reserved.

The Technology

At least 30 genes have been associated with the metabolism and action of warfarin.² Single nucleotide polymorphisms in *CYP2C9* (the gene encoding cytochrome P450 2C9) and *VKORC1* (the gene encoding vitamin K epoxide reductase complex subunit 1) are strongly associated with warfarin dose requirements.

CYP2C9 encodes the enzyme that metabolizes S-warfarin, the enantiomer responsible for 60% to 70% of the anticoagulation response.⁵ Many different polymorphisms in *CYP2C9* have been described.⁶ The most studied *CYP2C9* alleles include *1 (wild-type), and the partially functional *CYP2C9**2(430C>T) and *CYP2C9**3(1075A>C) variants. Studies have shown that *CYP2C9**2 and *CYP2C9**3 variants

have 12% and 5% respectively of the enzyme activity of *CYP2C9*1*.² Individuals who carry the *CYP2C9*2* allele or the *CYP2C9*3* allele, or both alleles, metabolize warfarin more slowly, increasing the risk for bleeding with standard warfarin dosing.⁵

Vitamin K epoxide reductase (VKOR) is involved in making vitamin K-dependent clotting factors and is the target enzyme for warfarin.⁵ Anticoagulation is achieved by the inhibition of VKOR activity resulting in a reduction of clotting factors. There is evidence that specific haplotypes can help determine dosing.⁷ Single-nucleotide polymorphisms found in haplotype A (–1639G>A, 1173C>T, 1542G>C, 2255T>C, 3730G>A) versus wild-type alleles in haplotype B can be used to determine whether patients require low (genotype AA), intermediate (genotype AB), or high (genotype BB) doses of warfarin.⁷

Current pharmacogenomic tests detect *CYP2C9*2*(430C>T), *CYP2C9*3*(1075A>C), and *VKORC1* (–1639G>A) variants.⁸⁻¹⁰ The tests use polymerase chain reaction (PCR) amplification of selected DNA fragments. Test results are intended to help health care professionals individualize warfarin dosing. Whether other variants should be added to the warfarin testing panel is not yet known.

Regulatory Status

In Canada, all pharmacogenomic tests intended for diagnostic purposes and patient management are categorized as Class III medical devices, which require approval for marketing from Health Canada.¹¹ No tests are currently licensed in Canada for pharmacogenomic testing for warfarin dosing (Sebastien Landry, Health Canada, Ottawa: personal communication, 2007 Jul 10). However, some of the tests marketed in the US are available to Canadians through direct order.

The US Food and Drug Administration (FDA) has prepared guidance documents for the use of pharmacogenomic tests,^{12,13} but FDA approval of pharmacogenomic assays is not required for clinical use. Tests that are commercially

available in the US include Genelex [Warfarin (Coumadin) Target Dose Safety Test],⁸ Clinical Data, Inc. (PGxPredict:WARFARIN™),⁹ and Kimball Genetics, Inc. (Warfarin DoseAdvise™).¹⁰ These tests must meet US Clinical Laboratory Improvement Amendments (CLIA) standards, but CLIA does not examine the clinical validity or utility of the tests. Clinical laboratories may also develop and validate tests in-house that must also meet CLIA requirements. Several manufacturers including AutoGenomics, Third Wave Technologies, Luminex, and Nanogen are developing genetic assays for FDA approval. In September 2007, the FDA approved the Nanosphere Verigene Warfarin Metabolism Nucleic Acid Test.¹⁴

Patient Group

In North America, warfarin is the anticoagulant of choice for therapy that lasts longer than three months.¹⁵ One source estimates that there are currently more than 200,000 Canadians in publicly funded drug programs receiving long-term therapy with warfarin.¹⁶

Current Practice

The International Normalized Ratio (INR) is a standardization of the prothrombin time, a measure of the anticoagulant effect of warfarin. For most patients, a target INR of 2.5 (range 2.0 to 3.0) is indicated.¹ Traditional dosing algorithms rely on trial and error for adjustments after an initial dose of 5 mg or 10 mg in Caucasians and 3.5 mg in Asians.⁵ Current guidelines recommend starting INR monitoring after the initial two or three doses.¹⁵ Optimal anticoagulation with warfarin requires close monitoring because of a narrow therapeutic window, wide variability in patient response, and many drug and dietary interactions.¹⁷ Follow-up is especially important in older patients and those at high risk for bleeding.¹⁵ As a result, INR measurements every one to two days are initially required to establish the target level of anticoagulation. Steady state (a constant concentration of drug in the blood) usually occurs between three to five days after initiation of warfarin therapy. Once the anticoagulation

effect and warfarin dose have been stabilized for at least one to two weeks, the INR is usually monitored every two to four weeks throughout the course of warfarin therapy.¹⁵

The Evidence

Although studies have shown that genetic polymorphisms in *CYP2C9* and *VKORC1* affect warfarin dosing, no randomized controlled trials have linked the use of pharmacogenomic testing to improvements in clinical outcomes. Most of the studies performed to date have been of retrospective or cross-sectional design. Consequently, individuals who stop warfarin early because of adverse effects or those who have difficulty attaining a therapeutic maintenance dose may have been excluded.⁴ Furthermore, many studies were underpowered to investigate the risk of bleeding.

Several retrospective studies evaluating the effect of the *CYP2C9* genotype on warfarin dose and risk for bleeding have been conducted. A recent meta-analysis of nine studies including 2,775 patients (99% Caucasian) reported that the mean difference in daily dose for the *CYP2C9**2/*2 genotype was 0.85 mg (95% CI: 0.6 to 1.11; relative reduction 17%), 1.47 mg (95% CI: 1.24 to 1.71; relative reduction 27%) for the *CYP2C9**2/*3 genotype, and 1.92 mg (95% CI: 1.37 to 2.47; relative reduction 37%) for the *CYP2C9**3/*3 genotype, when compared to the mean daily dose for the *CYP2C9**1/*1 genotype.¹⁸ Results from three studies (n=1,757) showed that the relative bleeding risk for the *CYP2C9**2/*2 genotype was 1.91 (95% CI: 1.16 to 3.17), 2.26 (95% CI: 1.36 to 3.75) for the *CYP2C9**2/*3 genotype, and 1.77 (95% CI: 1.07 to 2.91) for the *CYP2C9**3/*3 genotype.¹⁸

The risk for bleeding achieved statistical significance in the meta-analysis, but the evidence from individual trials is conflicting.¹⁹⁻²² This may be due to differences in treatments, monitoring regimens, or patient selection criteria resulting in an underestimation of bleeding risk. One study found that variant *CYP2C9* alleles were independent predictors of bleeding during the initiation phase of anticoagulation (hazard

ratio=3.94, 95% CI: 1.29 to 12.06), but could not determine if increased bleeding risk continued once anticoagulation therapy was stabilized.¹⁹ Another study reported that time to reach steady state was six to eight days for those with a *CYP2C9**2/*2 genotype and 12 to 15 days for those with a *CYP2C9**3/*3 genotype.²³ This delay in achieving steady state may have long-term implications regarding INR monitoring, especially when warfarin doses are being modified. There is evidence that those with at least one variant allele require a significantly longer time (median difference 95 days) to achieve a stable dose.¹⁹

The *CYP2C9**2 and *3 alleles appear to be prevalent in Caucasian populations at frequencies of 10% to 15% and 5% to 10% respectively.^{17,24} In African-American populations, approximately 2% to 4% carry the *CYP2C9**2 allele, while 1% to 2% carry the *CYP2C9**3 allele.²⁴ In the Asian population, the *CYP2C9**2 allele is absent, and the frequency of the *CYP2C9**3 allele is 1% to 4%.²² Less common *CYP2C9* alleles *4 (identified in the Japanese) and *5 and *6 (found in African-Americans) have not been shown to significantly affect warfarin dose.²⁵ This suggests that genotyping for *CYP2C9* alone may not be useful in ethnic populations other than Caucasians.^{26,27} Moreover, *CYP2C9* genotype has been estimated to independently explain only 20% of the observed inter-individual variability in warfarin response, when other clinical factors, such as age, body weight, gender, and concomitant medications, have been taken into account.²⁸

Single-nucleotide polymorphisms in *VKORC1* have also been correlated with differences in warfarin dose requirements.^{7,29-34} The 1173C>T and -1639G>A polymorphisms are those most commonly associated with lower warfarin dose.²⁸ However, their influence on bleeding risk during the initiation of therapy has not been evaluated. One retrospective study examined 186 European-American patients on long-term warfarin therapy.⁷ The 10 most common polymorphisms were used to construct five major haplotypes that were then divided into groups of low warfarin

dose (haplotype A) or high warfarin dose (haplotype B). Daily warfarin maintenance dose requirements differed significantly ($p < 0.001$) among the three haplotype combinations A/A, A/B, and B/B (2.7 ± 0.2 mg/day, 4.9 ± 0.2 mg/day, and 6.2 ± 0.3 mg/day respectively). This observation remained statistically significant when controlling for *CYP2C9* genotype.

When the genotype of 368 European-American subjects was studied, polymorphisms in *CYP2C9* and *VKORC1* accounted for 6% to 10% and 21% to 25% respectively of the variation in warfarin dose. Evaluation of three secondary populations of Asian-Americans, European-Americans, and African-Americans revealed that haplotypes A and B accounted for 99%, 96%, and 62% of haplotypes respectively. Furthermore, the low-dose haplotype A group was more frequently found in Asian-Americans (89%) compared with European-American (37%) and African-American (14%) populations. Therefore, genetic variations in *VKORC1* may partly explain the ethnic differences observed in clinical practice and contribute more substantially to variations in response than *CYP2C9*.

Other studies have shown that *VKORC1* and *CYP2C9* genotypes, in conjunction with other demographic and clinical factors, account for 50% to 60% of the variability in warfarin dosing requirements.^{30,32,33,35-38} A few dosing algorithms that incorporate genetic, clinical, and demographic factors have been developed, but large prospective trials are needed to determine their validity in various populations.³⁹⁻⁴² Results from prospective pilot studies^{41,43,44} indicate that pharmacogenomics-based warfarin dosing is feasible in a clinical setting; however, these studies were underpowered to detect differences in clinical outcomes.

Adverse Effects

Warfarin is commonly associated with emergency-room visits due to bleeding complications. One study estimates that there were approximately 29,000 visits per year between 1999 and 2003 in the US.⁴⁵ Furthermore, between 1993 and 2006, a total of

9,766 cases of warfarin-related bleeding events were entered into an adverse-event reporting system, 10% of which resulted in death.⁴⁵ There is evidence that patients on warfarin are outside the target INR range one third of the time.⁴⁶ A recent meta-analysis showed that 44% (95% CI: 39% to 49%) of bleeding events occurred when INRs were above the target therapeutic range, and 48% (95% CI: 41% to 55%) of thromboembolic events occurred when INRs were below this range.⁴⁴ Studies are needed to establish the risk of adverse effects associated with possible inaccuracies in pharmacogenomic testing (i.e. false-positives increasing the risk of stroke or false-negatives increasing the risk of bleeding).⁴⁷

Administration and Cost

Genotyping for *CYP2C9* or *VKORC1* variants can be accomplished using cheek swabs or blood samples. In the US, the typical turnaround time for test results averages 24 to 48 hours.⁸⁻¹⁰ Rapid one-hour tests have also been developed to allow for same-visit dosing adjustments.⁴⁸

Pharmacogenomic testing will not replace routine INR monitoring and will add to the costs associated with warfarin therapy. Prices for some of the commercial tests available in the US range from US\$400⁹ to US\$550.⁸ A recent US policy paper suggests that the additional cost may be offset by reducing the expenses associated with adverse events including bleeding and strokes.⁴⁹ Two economic evaluations reported a marginal cost of approximately US\$6,000 to prevent one bleeding event with testing for *CYP2C9* polymorphisms.^{50,51} Further evaluations incorporating the impact of pharmacogenomic testing with reliable estimates of warfarin-related adverse events are needed to confirm economic benefit over standard practice.⁵²

Concurrent Developments

Several new anticoagulants are currently under development.⁵³ Both rivaroxaban (a factor Xa inhibitor) and dabigatran etexilate (a thrombin receptor antagonist) are in phase 3 trials for post-surgical thromboprophylaxis in knee or hip replacement patients, for prevention and treatment

of venous thromboembolism, and for stroke prevention in atrial fibrillation.⁵³

The availability of portable point-of-care testing devices allows for INR testing outside the laboratory (e.g., in a clinic or patient's home).¹⁶ Results are immediately available, facilitating self-management of dosage by the patient or quick adjustments by the physician. Results from a meta-analysis indicate that patients using point-of-care devices are at lower risk for death and thromboembolic events, and have better INR control than patients who rely on conventional laboratory testing.¹⁶ However, no significant difference in the rate of bleeding events was observed.

Rate of Technology Diffusion

In August 2007, the FDA approved the addition of pharmacogenomic information to the warfarin product label.⁵⁴ Although genetic variations in *CYP2C9* and *VKORC1* have been added to the list of considerations for warfarin prescribing, specific dosing recommendations have not changed.⁵⁵ Health care professionals are not required to conduct genetic testing before initiating warfarin therapy nor should genetic testing delay the start of therapy. The FDA has also added genetic information on the product label for 6-mercaptopurine, azathioprine, irinotecan, and atomoxetine.⁵⁵

Several randomized controlled trials are evaluating the impact of genetic testing on initial dosing, time to reach and maintain the target INR, rates of bleeding or thromboembolic events, and INR monitoring requirements in comparison to standard care.⁵⁶⁻⁵⁹ Other studies are focusing on developing new nomograms and algorithms that incorporate both genetic and clinical information for more precise warfarin dosing.^{60,61}

A recent report by the American College of Medical Genetics provides an extensive review of the evidence for genetic testing in warfarin therapy and identifies areas where important gaps in knowledge exist.⁵² Currently, there are no evidence-based guidelines for interpreting and

using genetic testing in warfarin therapy. The National Academy of Clinical Biochemistry has assembled a committee of experts from academia, industry, and government who are in the process of formulating practice guidelines intended for use by scientists, pharmacists, clinical practitioners, and regulatory agencies.⁶² The FDA's Critical Path Initiative has also funded a research project to help develop personalized dosing algorithms for patients starting warfarin therapy.⁵⁴

Implementation Issues

Challenges associated with pharmacogenomics include standardization and quality control of genetic tests, storage of genetic information, and ethical issues, including confidentiality and possible genetic discrimination.⁶³ Training in accurate interpretation and provision of test results (e.g., counselling for patients) will be needed if genetic testing is established in routine therapy.

There is evidence that variability in other genes believed to be involved in the action and metabolism of warfarin, including *PROC* (protein C), *APOE* (apolipoprotein E), *GGCX* (gamma-glutamyl carboxylase), *CALU* (calumenin), and *EPHX1* (microsomal epoxide hydrolase), may also affect warfarin response.^{33,38,64-66} When all the alleles that influence warfarin response have been identified in patients regardless of ethnic background, a comprehensive dosing algorithm that is applicable to the entire population can be developed.

The precise role of pharmacogenomics is not completely clear, and further evidence on its clinical and economic utility will help define its place in individualized warfarin therapy.

References

1. Valentine K.A., et al. Clinical use of warfarin. In: *UpToDate* [database online]. Waltham(MD): UpToDate; 2007.
2. Wadelius M, et al. *Pharmacogenomics J* 2007;7(2):99-111.
3. Waniewski J, et al. *J Clin Immunol* 1994;14(2):90-7.

4. Gardiner SJ, et al. *Pharmacol Rev* 2006;58(3):521-90.
5. Yin T, et al. *Thromb Res* 2007;120(1):1-10.
6. Human Cytochrome P450 (CYP) Allele Nomenclature Committee. *CYP2C9* allele nomenclature. In: *Cytochrome P450 Allele nomenclature* [web site]. Stockholm: The Committee; 2006. Available: <http://www.cypalleles.ki.se/cyp2c9.htm>
7. Rieder MJ, et al. *N Engl J Med* 2005;352(22):2285-93.
8. Genelex. Pharmacogenetics: personalizing medicine today! In: *Health and DNA* [web site]. Seattle (WA): Genelex; 2007. Available: <http://www.healthanddna.com/professional/pharmacogenetics.html#2c9>
9. Clinical Data. PGxPredict™: warfarin test. In: *PGxPredict* [web site]. Newton (MA): Clinical Data; 2007. Available: <http://www.pgxhealth.com/geneticstests/warfarin/>
10. Kimball Genetics. Kimball Genetics: hemochromatosis DNA testing. In: *Kimball Genetics* [web site]. Denver (CO): Kimball Genetics; 2007. Available: <http://www.kimballgenetics.com/>
11. Health Canada. Submission of pharmacogenomic information [guidance document]. In: *Drugs and Health Products* [web site]. Ottawa: Health Canada; 2007. 07-103797-737. Available: http://hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/pharmaco/pharmaco_guid_id_2007-02_e.html
12. Harper C. Drug metabolizing enzyme genotyping system — class II special controls guidance document: guidance for industry and FDA staff. In: *IVD Guidance Documents* [web site]. Rockville (MD): Center for Devices and Radiological Health; 2005. Available: <http://www.fda.gov/cdrh/oivd/guidance/1551.pdf>
13. Food & Drug Administration (US). Guidance for industry: pharmacogenomic data submissions. In: *Guidance Documents* [web page]. Rockville (MD): Center for Drug Evaluation and Research (CDER); 2005. Available: <http://www.fda.gov/cder/guidance/6400fnl.pdf>
14. Food & Drug Administration (US). FDA clears genetic lab test for warfarin sensitivity [news release September 17, 2007]. In: *FDA News* [web page]. Washington (DC): FDA; 2007. Available: <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01701.html>
15. Ansell J, et al. *Chest* 2004;126(3 Suppl):204S-33S.
16. Brown A, et al. Point-of-care monitoring devices for long-term oral anticoagulation therapy: clinical and cost effectiveness. [Technology Report issue 72]. Ottawa: CADTH; 2007. Available: http://www.cadth.ca/media/pdf/H0299_anticoagulation-therapy_tr_e.pdf
17. Clark N. *J Clin Ligand Assay* 2005;28(3):136-40.
18. Sanderson S, et al. *Genet Med* 2005;7(2):97-104.
19. Higashi MK, et al. *JAMA* 2002;287(13):1690-8.
20. Aithal GP, et al. *Lancet* 1999;353(9154):717-9.
21. Ogg MS, et al. *Lancet* 1999;354(9184):1124.
22. Joffe HV, et al. *Thromb Haemost* 2004;91(6):1123-8.
23. Linder MW, et al. *J Thromb Thrombolysis* 2002;14(3):227-32.
24. Lesko LJ. *Clin Pharmacol Ther* 2007;81(6):807-16.
25. Moridani M, et al. *Clin Biochem* 2006;39(6):606-12.
26. Kealey C, et al. *Pharmacogenomics* 2007;8(3):217-25.
27. Wiwanitkit V. *Clin Applied Thrombosis/Hemostasis* 2006;12(2):219-22.
28. Dumas TE, et al. *Current Clin Pharmacol* 2007;2(1):11-21.
29. D'Andrea G, et al. *Blood* 2005;105(2):645-9.
30. Lee SC, et al. *Clin Pharmacol Ther* 2006;79(3):197-205.
31. Li T, et al. *J Med Genet* 2006;43(9):740-4.
32. Veenstra DL, et al. *Pharmacogenet Genomics* 2005;15(10):687-91.
33. Wadelius M, et al. *Pharmacogenomics J* 2005;5(4):262-70.
34. Mushiroda T, et al. *J Hum Genet* 2006;51(3):249-53.
35. Sconce EA, et al. *Blood* 2005;106(7):2329-33.
36. Takahashi H, et al. *Pharmacogenet Genomics* 2006;16(2):101-10.
37. Aquilante CL, et al. *Clin Pharmacol Ther* 2006;79(4):291-302.
38. Vecsler M, et al. *Thromb Haemost* 2006;95(2):205-11.
39. Gage BF, et al. *Thromb Haemost* 2004;91(1):87-94.

40. Sconce EA, et al. *Eur J Haematol* 2006;77(6):457-62.
41. Voora D, et al. *Thromb Haemost* 2005;93(4):700-5.
42. Tham LS, et al. *Clin Pharmacol Ther* 2006;80(4):346-55.
43. Zhu Y, et al. *Clin Chem* 2007;53(7):1199-205.
44. Hillman MA, et al. *Clin Med Res* 2005;3(3):137-45.
45. Wysowski DK, et al. *Arch Intern Med* 2007;167(13):1414-9.
46. Jones M, et al. *Heart* 2005;91(4):472-7.
47. Constable S, et al. *Expert Rev Mol Diagn* 2006;6(2):193-205.
48. Kuznar W. Rapid genotype testing: state-of-the-art warfarin dose selection. In: *Internal Medicine World Report (IMWR)* [web site]. Princeton (NJ): IMWR; 2007. Available: http://www.imwr.com/issues/articles/2007-05_10.asp
49. McWilliam A, et al. Health care savings from personalizing medicine using genetic testing: the case of warfarin [working paper]. In: Washington (DC): AEI-Brookings Joint Center; 2006. 06-23. Available: <http://www.aei-brookings.org/admin/authorpdfs/page.php?id=1337&PHPSESSID=3fa429b4f09842b9d2cffe0fd1b4a68>
50. Higashi MK, et al. *Am J Manag Care* 2003;9(7):493-500.
51. You JHS, et al. *Thromb Haemost* 2004;92(3):590-7.
52. McClain MR, et al. *A rapid ACCE1 review of CYP2C9 and VKORC1 allele testing to inform warfarin dosing in adults at elevated risk for thrombotic events to avoid serious bleeding* [web site]. Bethesda (MD): American College of Medical Genetics; 2007. Available: <http://www.acmg.net/AM/Template.cfm?Section=Home3&Template=/CM/ContentDisplay.cfm&ContentID=2263>
53. Weitz JI, et al. *Expert Opin Invest Drugs* 2007;16(3):271-82.
54. Federal Food & Drug Administration (US). FDA approves updated warfarin (coumadin) prescribing information: new genetic information may help providers improve initial dosing estimates of the anticoagulant for individual patients [press release]. In: *FDA News* [web site]. Washington (DC): FDA; 2007. Available: <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01684.html>
55. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Questions and answers on new labeling for warfarin (marketed as Coumadin). In: *Drug Information* [web site]. Washington (DC): CDER; 2007. Available: <http://www.fda.gov/cder/drug/infopage/warfarin/qa.htm>
56. ClinicalTrials.gov. The association of warfarin dosage and plasma enantiomer concentration with the gene polymorphisms of CYP and VKOR. In: *ClinicalTrials.gov* [database online]. Bethesda (MD): NLM; 2005. NCT00247702. Available: <http://www.clinicaltrials.gov/ct/show/NCT00247702?order=1>
57. ClinicalTrials.gov. Prospective evaluation comparing initiation of warfarin strategies (PRECISE): pharmacogenetic-guided versus usual care. In: *ClinicalTrials.gov* [database online]. Bethesda (MD): NLM; 2006. NCT00377143. Available: <http://www.clinicaltrials.gov/ct/show/NCT00377143?order=1>
58. ClinicalTrials.gov. A pharmacogenetic study of warfarin dosing: the COUMA-GEN Study. In: *ClinicalTrials.gov* [database online]. Bethesda (MD): NLM; 2006. NCT00334464. Available: <http://www.clinicaltrials.gov/ct/show/NCT00334464?order=1>
59. ClinicalTrials.gov. Genetic determinants of warfarin anticoagulation effect. In: *ClinicalTrials.gov* [database online]. Bethesda (MD): NLM; 2007. NCT00162435. Available: <http://www.clinicaltrials.gov/ct/show/NCT00162435?order=1>
60. ClinicalTrials.gov. Study to develop a reliable nomogram that incorporates clinical and genetic information. In: *ClinicalTrials* [database online]. Bethesda (MD): NLM; 2007. NCT00401414. Available: <http://www.clinicaltrials.gov/ct/show/NCT00401414?order=1>
61. Pirmohamed M. Variability in response to warfarin: a prospective analysis of pharmacogenetic and environmental factors. In: *Pharmacogenetics Research Programme* [web site]. London [UK]: Department of Health; 2007. Available: <http://www.genres.org.uk/prp/projects/liverpool2.htm>
62. Valdes R, et al. Guidelines and recommendations for laboratory analysis and application of pharmacogenetics to clinical practice [draft, version 60806]. In: *Online Guidelines* [database online]. Washington (DC): American Association for Clinical Chemistry (AACC); 2006. Available: <http://www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/DraftGuidelines/Pharmacogenetics/>

63. Phillips KA, et al. *Am J Manag Care* 2004;10(7 I):425-32.
64. Herman D, et al. *Thromb Haemost* 2006;95(5):782-7.
65. Kimura R, et al. *Thromb Res* 2007;120(2):181-6.
66. Loebstein R, et al. *Clin Pharmacol Ther* 2005;77(5):365-72.

Glossary

Allele: Alternative form of a gene at a specific location on the chromosome.

Genotype: Genetic composition (alleles) of an individual in total or at a specific location on the chromosome.

Haplotype: Set of polymorphisms that are inherited together.

Pharmacogenomics: Process of genetic testing to study the effect of genetic variations on drug response in order to maximize efficacy and minimize adverse effects.

Polymorphism: Nucleotide variations within a gene.

Wild-type: Most common allele for a certain gene in a population.

NCBI databank reference single-nucleotide polymorphism numbers are *CYP2C9**2 (rs1799853), *CYP2C9**3 (rs1057910), *VKORC1* -1639G>A (rs9923231), -1173C>T (rs9934438), 1542G>C (rs8050894), 2255T>C (rs2359612), 3730G>A (rs7294).

Cite as: Ndegwa, S. *Pharmacogenomics and warfarin therapy* [Issues in emerging health technologies issue 104]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007.

CADTH takes sole responsibility for the final form and content of this bulletin. The statements and conclusions in this bulletin are those of CADTH and not those of its advisory committee members or reviewers.

CADTH thanks the external reviewers who kindly provided comments on an earlier draft of this bulletin.

Reviewers: **Pollen K.F. Yeung, BScPharm PhD**, Dalhousie University, **Ronald E. Reid, BSP PhD**, University of British Columbia.

Production of this report is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon. The Canadian Agency for Drugs and Technologies in Health takes sole responsibility for the final form and content of this report. The views expressed herein do not necessarily represent the views of Health Canada or any provincial or territorial government.

ISSN 1488-6324 (online)
ISSN 1488-6316 (print)
PUBLICATIONS MAIL AGREEMENT NO. 40026386
RETURN UNDELIVERABLE CANADIAN ADDRESSES TO
CANADIAN AGENCY FOR DRUGS AND TECHNOLOGIES IN HEALTH
600-865 CARLING AVENUE
OTTAWA ON K1S 5S8