Protocol

Genetic Testing for Warfarin Dose

(20448)

Medical Benefit		**Effective Date**: 04/01/18	**Next Review Date**: 01/19
Preauthorization	No	**Review Dates**: 01/11, 01/12, 01/13, 01/14, 01/15, 01/16, 01/17, 01/18	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With conditions requiring warfarin treatment	Interventions of interest are: • Genetic testing for *CYP2C9* and *VKORC1* variants to determine warfarin dose	Comparators of interest are: • Clinical management without genetic testing	Relevant outcomes include: • Test accuracy • Test validity • Other test performance measures • Morbid events • Medication use • Treatment-related morbidity

Description

Variants in the *CYP2C9* and *VKORC1* genes result in differences in warfarin metabolism. Using information about an individual's *CYP2C9* and *VKORC1* genotypes may help in personalizing warfarin dosing and could reduce the time to dose stabilization and selection of appropriate maintenance dose that might avoid consequences of too much or too little anticoagulation.

Summary of Evidence

For individuals with conditions requiring warfarin treatment who are being managed with genetic testing for *CYP2C9* and *VKORC1* variants to determine warfarin dose, the evidence includes multiple randomized controlled trial (RCTs), systematic reviews of the RCTs, and cohort studies. Relevant outcomes are test accuracy and validity, other test performance measures, morbid events, medication use, and treatment-related morbidity. The evidence on clinical validity from several retrospective and prospective cohort studies has shown that algorithms incorporating genetic variants and clinical factors explain greater variance in warfarin dosing over that predicted by clinical factors alone. However, the incremental gain using genetic testing depends on multiple factors, including ethnicity. Further, there is no consensus on a single algorithm that could be generalized to a diverse population. Multiple smaller randomized trials and meta-analyses of these trials have examined the clinical utility of genetic tests to guide warfarin dose and reported inconsistent results. Two large adequately powered RCTs attempted to address this inconsistency but reported contrasting results. Of these two trials, the larger U.S.-based RCT found no utility in adding genetic testing to a clinical dosing algorithm. The percentage of time in

the therapeutic international normalized ratio range was similar when genetic testing was and was not added. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

Genotyping to determine cytochrome p450 2C9 (*CYP2C9*) and vitamin K epoxide reductase subunit C1 (*VKORC1*) genetic variants is considered **investigational** for the purpose of managing the administration and dosing of warfarin, including use in guiding the initial warfarin dose to decrease time to stable international normalized ratio and reduce the risk of serious bleeding.

Policy Guidelines

Genetics Nomenclature Update

Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely Pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Medicare Advantage

For Medicare Advantage there may be potential for benefit under coverage with evidence development (CED) when the members are candidates for anticoagulation therapy with warfarin who:

1. Have not been previously tested for CYP2C9 or VKORC1 alleles; and
2. Have received fewer than five days of WARFARIN in the anticoagulation regimen for which the testing is ordered; and
3. Are enrolled in a prospective, randomized, controlled clinical study when that study meets CMS standards.

For Medicare Advantage the available evidence does not demonstrate that pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness improves health outcomes outside the context of CED, and is therefore **not medically necessary**.

Background

Warfarin is administered to prevent and treat thromboembolic events in high-risk patients; warfarin dosing is a challenging process, due to the narrow therapeutic window, variable response to dosing and serious bleeding events in 5% or more of patients (depending on definition). Patients are typically given a starting dose of two to five mg and monitored frequently with dose adjustments until a stable international normalized ratio (INR) value (a standardized indicator of clotting time) between two and three is achieved. During this adjustment period, a patient is at high risk of bleeding.

Stable or maintenance warfarin dose varies among patients by more than an order of magnitude. Factors influencing stable dose include body mass index, age, interacting drugs, and indication for therapy.

Warfarin, which is primarily metabolized in the liver by the CYP2C9 enzyme, exerts an anticoagulant effect by inhibiting the protein vitamin K epoxide reductase complex, subunit 1 (VKORC1). Three single-nucleotide variants (SNVs), two in the CYP2C9 gene and one in the VKORC1 gene play key roles in determining the effect of warfarin therapy on coagulation. CYP2C9*1 metabolizes warfarin normally, CYP2C9*2 reduces warfarin metabolism by 30%, and CYP2C9*3 reduces warfarin metabolism by 90%. Because warfarin given to patients with *2 or *3 variants will be metabolized less efficiently, the drug will remain in circulation longer, so lower warfarin doses will be needed to achieve anticoagulation. Recent genome-wide association studies have also identified that a SNV in the CYP4F2 gene has been reported to account for a small proportion of the variability in stable dose (the CYP4F2 gene encodes a protein involved in vitamin K oxidation).

Using the results of CYP2C9 and VKORC1 genetic testing to predict a warfarin starting dose that approximates a likely maintenance dose may benefit patients by decreasing the risk of serious bleeding events and the time to stable INR. Algorithms have incorporated not only genetic variation but also other significant patient characteristics and clinical factors to predict the best starting dose.

Regulatory Status

Several tests to help assess warfarin sensitivity, by determining the presence or absence of the relevant CYP2C9, VKORC1, and CYP4F2 variants, have been cleared by the U.S. Food and Drug Administration (FDA) for marketing (see Table 1). Similar tests also may be available as laboratory-developed services; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The tests are not identical in terms of the specific variants and number of variants detected. Generally, such tests are not intended as stand-alone tools to determine optimum drug dosage but should be used with clinical evaluation

and other tools, including the international normalized ratio, to predict the initial dose that best approximates the maintenance dose for patients.

Table 1. FDA-Cleared Warfarin Test[1]

Test (Laboratories)	Alleles Tested	Estimated Time to Completion, h
eSensor® Warfarin Sensitivity Test (GenMark Dx, Carlsbad, CA)[a]	CYPC9*2 and *3, VKORC1 1639G>A	3-4
Rapid Genotyping Assay (ParagonDx, Morrisville, NC)	CYPC9*2 and *3, VKORC1 1173 C>T	Not reported[b]
Verigene® Warfarin Metabolism Nucleic Acid Test (Nanosphere, Northbrook, IL)	CYPC9*2 and *3, VKORC1 1173 C>T	≤ 2
Infiniti® 2C9-VKORC1 Multiplex Assay for Warfarin (AutoGenomics, Vista, CA)[c]	CYP2C9*2 and *3, VKORC1 1639G>A	6-8
eQ-PCR™ LightCycler® Warfarin Genotyping Kit (TrimGen, Sparks Glencoe, MD)	CYP2C9*2 and *3, VKORC1 1639G>A	≤ 2

FDA: Food and Drug Administration.

[a] eSensor Warfarin Plus Test offers testing for CYP2C9 *2, *3, *5, *6, *11, *14, *15, and *16, VKORC1 1639G>A, and CYP4F2.

[b] Langley et al (2009) reported a turnaround time of 1.5 hours for the ParagonDx SmartCycler, which may be a precursor assay.[2]

[c] The expanded Infiniti CYP450 2C9 assay offers testing for CYP2C9 *2, *3, *4, *5, *6, and *11, VKORC1 1639G>A, and six additional VKORC variants.

In August 2007, the FDA approved updated labeling for Coumadin® to include information on testing for gene variants that may help "personalize" the starting dose for each patient and reduce the number of serious bleeding events. The label was updated again in January 2010. With each update, manufacturers of warfarin (generic for Coumadin®) were directed to add similar information to their products' labels. The 2010 update added information on personalizing initial dose by genotyping results for *CYP2C9* and *VKORC1*, providing a table of genotypes, and suggested initial dose ranges for each. However, suggested starting doses are also provided when genotyping information is unavailable, indicating that genetic testing is not required. Furthermore, the FDA did not include information on genetic variation in the label's black box warning on bleeding risk.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. Cavallari LH, Shin J, Perera MA. Role of pharmacogenomics in the management of traditional and novel oral anticoagulants. Pharmacotherapy. Dec 2011; 31(12):1192-1207. PMID 22122181

2. Langley MR, Booker JK, Evans JP, et al. Validation of clinical testing for warfarin sensitivity: comparison of CYP2C9-VKORC1 genotyping assays and warfarin-dosing algorithms. J Mol Diagn. May 2009; 11(3):216-225. PMID 19324988
3. King CR, Porche-Sorbet RM, Gage BF, et al. Performance of commercial platforms for rapid genotyping of polymorphisms affecting warfarin dose. Am J Clin Pathol. Jun 2008; 129(6):876-883. PMID 18480003
4. Daly AK. Optimal dosing of warfarin and other coumarin anticoagulants: the role of genetic polymorphisms. Arch Toxicol. Mar 2013; 87(3):407-420. PMID 23376975
5. Rosove MH, Grody WW. Should we be applying warfarin pharmacogenetics to clinical practice? No, not now. Ann Intern Med. Aug 18 2009; 151(4):270-273, W295. PMID 19687493
6. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Special Report: Genotyping for Cytochrome P450 Polymorphisms to Determine Drug-metabolizer Status. TEC Assessments. 2004; Volume 19: Tab 9.
7. Wadelius M, Sorlin K, Wallerman O, et al. Warfarin sensitivity related to CYP2C9, CYP3A5, ABCB1 (MDR1) and other factors. Pharmacogenomics J. 2004; 4(1):40-48. PMID 14676821
8. Gage BF, Eby C, Milligan PE, et al. Use of pharmacogenetics and clinical factors to predict the maintenance dose of warfarin. Thromb Haemost. Jan 2004; 91(1):87-94. PMID 14691573
9. Hillman MA, Wilke RA, Caldwell MD, et al. Relative impact of covariates in prescribing warfarin according to CYP2C9 genotype. Pharmacogenetics. Aug 2004; 14(8):539-547. PMID 15284536
10. Jonas DE, McLeod HL. Genetic and clinical factors relating to warfarin dosing. Trends Pharmacol Sci. Jul 2009; 30(7):375-386. PMID 19540002
11. Rieder MJ, Reiner AP, Gage BF, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med. Jun 2 2005; 352(22):2285-2293. PMID 15930419
12. Yuan HY, Chen JJ, Lee MT, et al. A novel functional VKORC1 promoter polymorphism is associated with inter-individual and inter-ethnic differences in warfarin sensitivity. Hum Mol Genet. Jul 1 2005; 14(13):1745-1751. PMID 15888487
13. Geisen C, Watzka M, Sittinger K, et al. VKORC1 haplotypes and their impact on the inter-individual and inter-ethnical variability of oral anticoagulation. Thromb Haemost. Oct 2005; 94(4):773-779. PMID 16270629
14. D'Andrea G, D'Ambrosio RL, Di Perna P, et al. A polymorphism in the VKORC1 gene is associated with an interindividual variability in the dose-anticoagulant effect of warfarin. Blood. Jan 15 2005; 105(2):645-649. PMID 15358623
15. Wadelius M, Chen LY, Downes K, et al. Common VKORC1 and GGCX polymorphisms associated with warfarin dose. Pharmacogenomics J. 2005; 5(4):262-270. PMID 15883587
16. Sconce EA, Khan TI, Wynne HA, et al. The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. Blood. Oct 1 2005; 106(7):2329-2333. PMID 15947090
17. Takeuchi F, McGinnis R, Bourgeois S, et al. A genome-wide association study confirms VKORC1, CYP2C9, and CYP4F2 as principal genetic determinants of warfarin dose. PLoS Genet. Mar 2009; 5(3):e1000433. PMID 19300499
18. Caldwell MD, Awad T, Johnson JA, et al. CYP4F2 genetic variant alters required warfarin dose. Blood. Apr 15 2008; 1 11(8):4106-4112. PMID 18250228
19. Borgiani P, Ciccacci C, Forte V, et al. CYP4F2 genetic variant (rs2108622) significantly contributes to warfarin dosing variability in the Italian population. Pharmacogenomics. Feb 2009; 10(2):261-266. PMID 19207028
20. McClain MR, Palomaki GE, Piper M, et al. A rapid-ACCE review of CYP2C9 and VKORC1 alleles testing to inform warfarin dosing in adults at elevated risk for thrombotic events to avoid serious bleeding. Genet Med. Feb 2008; 10(2):89-98. PMID 18281915
21. Zhu Y, Shennan M, Reynolds KK, et al. Estimation of warfarin maintenance dose based on VKORC1 (-1639 G>A) and CYP2C9 genotypes. Clin Chem. Jul 2007; 53(7):1199-1205. PMID 17510308
22. Schelleman H, Chen J, Chen Z, et al. Dosing algorithms to predict warfarin maintenance dose in Caucasians and African Americans. Clin Pharmacol Ther. Sep 2008; 84(3):332-339. PMID 18596683

23. Gage BF, Eby C, Johnson JA, et al. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. Clin Pharmacol Ther. Sep 2008; 84(3):326-331. PMID 18305455
24. Wu AH, Wang P, Smith A, et al. Dosing algorithm for warfarin using CYP2C9 and VKORC1 genotyping from a multi-ethnic population: comparison with other equations. Pharmacogenomics. Feb 2008; 9(2):169-178. PMID 18370846
25. Hatch E, Wynne H, Avery P, et al. Application of a pharmacogenetic-based warfarin dosing algorithm derived from British patients to predict dose in Swedish patients. J Thromb Haemost. Jun 2008; 6(6):1038-1040. PMID 18419746
26. Wadelius M, Chen LY, Eriksson N, et al. Association of warfarin dose with genes involved in its action and metabolism. Hum Genet. Mar 2007; 121(1):23-34. PMID 17048007
27. Lenzini P, Wadelius M, Kimmel S, et al. Integration of genetic, clinical, and INR data to refine warfarin dosing. Clin Pharmacol Ther. May 2010; 87(5):572-578. PMID 20375999
28. Wells PS, Majeed H, Kassem S, et al. A regression model to predict warfarin dose from clinical variables and polymorphisms in CYP2C9, CYP4F2, and VKORC1: Derivation in a sample with predominantly a history of venous thromboembolism. Thromb Res. Jun 2010; 125(6):e259-264. PMID 20421126
29. Sagreiya H, Berube C, Wen A, et al. Extending and evaluating a warfarin dosing algorithm that includes CYP4F2 and pooled rare variants of CYP2C9. Pharmacogenet Genomics. Jul 2010; 20(7):407-413. PMID 20442691
30. Liang R, Wang C, Zhao H, et al. Influence of CYP4F2 genotype on warfarin dose requirement-a systematic review and meta-analysis. Thromb Res. Jul 2012; 130(1):38-44. PMID 22192158
31. Wen MS, Lee M, Chen JJ, et al. Prospective study of warfarin dosage requirements based on CYP2C9 and VKORC1 genotypes. Clin Pharmacol Ther. Jul 2008; 84(1):83-89. PMID 18183038
32. Millican EA, Lenzini PA, Milligan PE, et al. Genetic-based dosing in orthopedic patients beginning warfarin therapy. Blood. Sep 1 2007; 110(5):1511-1515. PMID 17387222
33. Klein TE, Altman RB, Eriksson N, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med. Feb 19 2009; 360(8):753-764. PMID 19228618
34. Avery PJ, Jorgensen A, Hamberg AK, et al. A proposal for an individualized pharmacogenetics-based warfarin initiation dose regimen for patients commencing anticoagulation therapy. Clin Pharmacol Ther. Nov 2011; 90(5):701-706. PMID 22012312
35. Schwarz UI, Ritchie MD, Bradford Y, et al. Genetic determinants of response to warfarin during initial anticoagulation. N Engl J Med. Mar 6 2008; 358(10):999-1008. PMID 18322281
36. Wadelius M, Chen LY, Lindh JD, et al. The largest prospective warfarin-treated cohort supports genetic forecasting. Blood. Jan 22 2009; 113(4):784-792. PMID 18574025
37. Meckley LM, Wittkowsky AK, Rieder MJ, et al. An analysis of the relative effects of VKORC1 and CYP2C9 variants on anticoagulation related outcomes in warfarin-treated patients. Thromb Haemost. Aug 2008; 100(2):229-239. PMID 18690342
38. Limdi NA, Wiener H, Goldstein JA, et al. Influence of CYP2C9 and VKORC1 on warfarin response during initiation of therapy. Blood Cells Mol Dis. Jul-Aug 2009; 43(1):119-128. PMID 19297219
39. Pautas E, Moreau C, Gouin-Thibault I, et al. Genetic factors (VKORC1, CYP2C9, EPHX1, and CYP4F2) are predictor variables for warfarin response in very elderly, frail inpatients. Clin Pharmacol Ther. Jan 2010; 87(1):57-64. PMID 19794411
40. Ferder NS, Eby CS, Deych E, et al. Ability of VKORC1 and CYP2C9 to predict therapeutic warfarin dose during the initial weeks of therapy. J Thromb Haemost. Jan 2010; 8(1):95-100. PMID 19874474
41. Moreau C, Pautas E, Gouin-Thibault I, et al. Predicting the warfarin maintenance dose in elderly inpatients at treatment initiation: accuracy of dosing algorithms incorporating or not VKORC1/CYP2C9 genotypes. J Thromb Haemost. Apr 2011; 9(4):711-718. PMID 21255252
42. Gong IY, Tirona RG, Schwarz UI, et al. Prospective evaluation of a pharmacogenetics-guided warfarin loading and maintenance dose regimen for initiation of therapy. Blood. Sep 15 2011; 118(11):3163-3171. PMID 21725053

43. Horne BD, Lenzini PA, Wadelius M, et al. Pharmacogenetic warfarin dose refinements remain significantly influenced by genetic factors after one week of therapy. Thromb Haemost. Feb 2012; 107(2):232-240. PMID 22186998
44. Perlstein TS, Goldhaber SZ, Nelson K, et al. The Creating an Optimal Warfarin Nomogram (CROWN) Study. Thromb Haemost. Jan 2012; 107(1):59-68. PMID 22116191
45. Shaw PB, Donovan JL, Tran MT, et al. Accuracy assessment of pharmacogenetically predictive warfarin dosing algorithms in patients of an academic medical center anticoagulation clinic. J Thromb Thrombolysis. Aug 2010; 30(2):220-225. PMID 20204461
46. Lubitz SA, Scott SA, Rothlauf EB, et al. Comparative performance of gene-based warfarin dosing algorithms in a multiethnic population. J Thromb Haemost. May 2010; 8(5):1018-1026. PMID 20128861
47. Roper N, Storer B, Bona R, et al. Validation and comparison of pharmacogenetics-based warfarin dosing algorithms for application of pharmacogenetic testing. J Mol Diagn. May 2010; 12(3):283-291. PMID 20228265
48. Zambon CF, Pengo V, Padrini R, et al. VKORC1, CYP2C9 and CYP4F2 genetic-based algorithm for warfarin dosing: an Italian retrospective study. Pharmacogenomics. Jan 2011; 12(1):15-25. PMID 21174619
49. Hamberg AK, Wadelius M. Pharmacogenetics-based warfarin dosing in children. Pharmacogenomics. Feb 2014; 15(3):361-374. PMID 24533715
50. Hawcutt DB, Ghani AA, Sutton L, et al. Pharmacogenetics of warfarin in a paediatric population: time in therapeutic range, initial and stable dosing and adverse effects. Pharmacogenomics J. Dec 2014; 14(6):542-548. PMID 25001883
51. Vear SI, Ayers GD, Van Driest SL, et al. The impact of age and CYP2C9 and VKORC1 variants on stable warfarin dose in the paediatric population. Br J Haematol. Jun 2014; 165(6):832-835. PMID 24601977
52. Limdi NA, Wadelius M, Cavallari L, et al. Warfarin pharmacogenetics: a single VKORC1 polymorphism is predictive of dose across 3 racial groups. Blood. May 6, 2010; 115(18):3827-3834. PMID 20203262
53. Cavallari LH, Momary KM, Patel SR, et al. Pharmacogenomics of warfarin dose requirements in Hispanics. Blood Cells Mol Dis. Feb 15 2011; 46(2):147-150. PMID 21185752
54. Gan GG, Phipps ME, Lee MM, et al. Contribution of VKORC1 and CYP2C9 polymorphisms in the interethnic variability of warfarin dose in Malaysian populations. Ann Hematol. Jun 2011; 90(6):635-641. PMID 21110192
55. Perera MA, Gamazon E, Cavallari LH, et al. The missing association: sequencing-based discovery of novel SNPs in VKORC1 and CYP2C9 that affect warfarin dose in African Americans. Clin Pharmacol Ther. Mar 2011; 89(3):408-415. PMID 21270790
56. Perera MA, Cavallari LH, Limdi NA, et al. Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study. Lancet. Aug 31 2013; 382(9894):790-796. PMID 23755828
57. Ramirez AH, Shi Y, Schildcrout JS, et al. Predicting warfarin dosage in European-Americans and African-Americans using DNA samples linked to an electronic health record. Pharmacogenomics. Mar 2012; 13(4):407-418. PMID 22329724
58. Sangviroon A, Panomvana D, Tassaneeyakul W, et al. Pharmacokinetic and pharmacodynamic variation associated with VKORC1 and CYP2C9 polymorphisms in Thai patients taking warfarin. Drug Metab Pharmacokinet. 2010; 25(6):531-538. PMID 20930419
59. Shahin MH, Khalifa SI, Gong Y, et al. Genetic and nongenetic factors associated with warfarin dose requirements in Egyptian patients. Pharmacogenet Genomics. Mar 2011; 21(3):130-135. PMID 21228733
60. Bazan NS, Sabry NA, Rizk A, et al. Validation of pharmacogenetic algorithms and warfarin dosing table in Egyptian patients. Int J Clin Pharm. Dec 2012; 34(6):837-844. PMID 22851439
61. You JH, Wong RS, Waye MM, et al. Warfarin dosing algorithm using clinical, demographic and pharmacogenetic data from Chinese patients. J Thromb Thrombolysis. Jan 2011; 31(1):113-118. PMID 20585834
62. Ma C, Zhang Y, Xu Q, et al. Influence of warfarin dose-associated genotypes on the risk of hemorrhagic complications in Chinese patients on warfarin. Int J Hematol. Dec 2012; 96(6):719-728. PMID 23104259

63. Xu Q, Xu B, Zhang Y, et al. Estimation of the warfarin dose with a pharmacogenetic refinement algorithm in Chinese patients mainly under low-intensity warfarin anticoagulation. Thromb Haemost. Dec 2012; 108(6):1132-1140. PMID 23015069
64. Aomori T, Obayashi K, Fujita Y, et al. Influence of CYP2C9 and vitamin k oxide reductase complex (VKORC)1 polymorphisms on time to determine the warfarin maintenance dose. Pharmazie. Mar 2011; 66(3):222-225. PMID 21553655
65. Alzahrani AM, Ragia G, Hanieh H, et al. Genotyping of CYP2C9 and VKORC1 in the Arabic population of Al-Ahsa, Saudi Arabia. Biomed Res Int. 2013; 2013:315980. PMID 23586031
66. Ozer M, Demirci Y, Hizel C, et al. Impact of genetic factors (CYP2C9, VKORC1 and CYP4F2) on warfarin dose requirement in the Turkish population. Basic Clin Pharmacol Toxicol. Mar 2013; 112(3):209-214. PMID 23061746
67. Skov J, Bladbjerg EM, Leppin A, et al. The influence of VKORC1 and CYP2C9 gene sequence variants on the stability of maintenance phase warfarin treatment. Thromb Res. Feb 2013; 131(2):125-129. PMID 23159229
68. Valentin, II, Vazquez J, Rivera-Miranda G, et al. Prediction of warfarin dose reductions in Puerto Rican patients, based on combinatorial CYP2C9 and VKORC1 genotypes. Ann Pharmacother. Feb 2012; 46(2):208-218. PMID 22274142
69. Stergiopoulos K, Brown DL. Genotype-guided vs. clinical dosing of warfarin and its analogues: meta-analysis of randomized clinical trials. JAMA Intern Med. Aug 2014; 174(8):1330-1338. PMID 24935087
70. Franchini M, Mengoli C, Cruciani M, et al. Effects on bleeding complications of pharmacogenetic testing for initial dosing of vitamin K antagonists: a systematic review and meta-analysis. J Thromb Haemost. Sep 2014; 12(9):1480-1487. PMID 25040440
71. Goulding R, Dawes D, Price M, et al. Genotype-guided drug prescribing: a systematic review and meta-analysis of randomized control trials. Br J Clin Pharmacol. Oct 2015; 80(4):868-877. PMID 25060532
72. Liao Z, Feng S, Ling P, et al. Meta-analysis of randomized controlled trials reveals an improved clinical outcome of using genotype plus clinical algorithm for warfarin dosing. J Thromb Thrombolysis. Feb 2015; 39(2):228-234. PMID 24962733
73. Anderson JL, Horne BD, Stevens SM, et al. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. Circulation. Nov 27 2007; 116(22):2563-2570. PMID 17989110
74. Burmester JK, Berg RL, Yale SH, et al. A randomized controlled trial of genotype-based Coumadin initiation. Genet Med. Jun 2011; 13(6):509-518. PMID 21423021
75. Jonas DE, Evans JP, McLeod HL, et al. Impact of genotype-guided dosing on anticoagulation visits for adults starting warfarin: a randomized controlled trial. Pharmacogenomics. Oct 2013; 14(13):1593-1603. PMID 24088130
76. Kimmel SE, French B, Kasner SE, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. N Engl J Med. Dec 12 2013; 369(24):2283-2293. PMID 24251361
77. Pirmohamed M, Burnside G, Eriksson N, et al. A randomized trial of genotype-guided dosing of warfarin. N Engl J Med. Dec 12 2013; 369(24):2294-2303. PMID 24251363
78. Huang SW, Chen HS, Wang XQ, et al. Validation of VKORC1 and CYP2C9 genotypes on interindividual warfarin maintenance dose: a prospective study in Chinese patients. Pharmacogenet Genomics. Mar 2009; 19(3):226-234. PMID 19177029
79. Anderson JL, Horne BD, Stevens SM, et al. A randomized and clinical effectiveness trial comparing two pharmacogenetic algorithms and standard care for individualizing warfarin dosing (CoumaGen-II). Circulation. Apr 24 2012; 125(16):1997-2005. PMID 22431865
80. Mega JL, Walker JR, Ruff CT, et al. Genetics and the clinical response to warfarin and edoxaban: findings from the randomised, double-blind ENGAGE AF-TIMI 48 trial. Lancet. Jun 6 2015; 385(9984):2280-2287. PMID 25769357

81. Epstein RS, Moyer TP, Aubert RE, et al. Warfarin genotyping reduces hospitalization rates results from the MM-WES (Medco-Mayo Warfarin Effectiveness study). J Am Coll Cardiol. Jun 22 2010; 55(25):2804-2812. PMID 20381283
82. Flockhart DA, O'Kane D, Williams MS, et al. Pharmacogenetic testing of CYP2C9 and VKORC1 alleles for warfarin. Genet Med. Feb 2008; 10(2):139-150. PMID 18281922
83. Guyatt GH, Akl EA, Crowther M, et al. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. Feb 2012; 141(2 Suppl):7S-47S. PMID 22315257
84. Becquemont L, Alfirevic A, Amstutz U, et al. Practical recommendations for pharmacogenomics-based prescription: 2010 ESF-UB Conference on Pharmacogenetics and Pharmacogenomics. Pharmacogenomics. Jan 2011; 12(1):113-124. PMID 21174626
85. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Pharmacogenomic Testing for Warfarin Response (90.1). 2009; https://www.cms.gov/medicare-coverage-database/details/ncddetails.aspx?NCDId=333&ncdver=1&bc=AgAAQAAAAAAAAA%3d%3d&. Accessed May 31, 2017.