BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.48 Genotype-Guided Warfarin Dosing

Effective Policy Date: October 1, 2023

Original Policy Date: June 2012

Related Policies:

None

Genotype-Guided Warfarin Dosing

Description

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Using information about an individual's genotype may help in guiding warfarin dosing and could reduce the time to dose stabilization and selection of an appropriate maintenance dose that might avoid the consequences of too much or too little anticoagulation.

OBJECTIVE

The objective of this evidence review is to determine whether genotype-guided warfarin dosing improves the net health outcome (eg, to prevent or treat thromboembolic events [TEEs]) in individuals who require warfarin therapy.

POLICY STATEMENT

Genotyping to determine cytochrome P450 2C9 (*CYP2C9*), P450 4F2 (*CYP4F2*), 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 (INR) and to reduce the risk of serious bleeding.

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POLICY GUIDELINES

None

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA 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 (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 regarding 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 INR, to predict the initial dose that best approximates the maintenance dose for patients.

Table 1. FDA-Cleared Warfarin Tests

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

Adapted from Cavallari et al (2011).[49,]
CYP2C9: cytochrome P450 2C9 enzyme; FDA: Food and Drug Administration; VKORC1: vitamin K epoxide reductase complex, subunit 1.
[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.[23,]
[c] The expanded Infiniti *CYP450* 2C9 assay offers testing for *CYP2C9*2*, **3*, **4*, **5*, **6*, and **11*, *VKORC1* 1639G>A, and 6 other *VKORC* variants.

The FDA (2007) approved updated labeling for warfarin 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 2010. With each update, manufacturers of warfarin were directed to add similar information to their product labels. The 2010 update added information on guiding 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.

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RATIONALE

Summary of Evidence

For individuals with conditions requiring warfarin treatment who receive genotype-guided warfarin dosing, the evidence includes multiple randomized controlled trials (RCTs) and systematic reviews of RCTs. Relevant outcomes are morbid events, medication use, and treatment-related mortality and morbidity. Thirty RCTs and 6 recent systematic reviews were identified. Most RCTs were single-center studies including fewer than 250 patients. Systematic reviews found the percentage of time the international normalized ratio (INR) was in therapeutic range was higher in patients treated with genotype-guided warfarin therapy; however, the heterogeneity between studies was high for this outcome. No RCT reported statistically significant differences in major bleeding, and only 1 reported a significant reduction in thromboembolic events (TEEs) with genotype-guided dosing, but studies were not powered to show differences in these outcomes. Meta-analyses of RCTs found no difference between genotype-guided dosing and clinical dosing for mortality, and only 1 found reduction in TEEs, but genotype-guided dosing was associated with a lower risk of major bleeding. Very few trials enrolled sufficient numbers of subpopulations except White participants. In the Clarification of Optimal Anticoagulation through Genetics (COAG) study, Black individuals (constituting 27% of trial participants) fared better in the clinically-guided group than in the genotype-guided group. One trial of elderly Chinese patients with atrial fibrillation experienced improved time with INR in the therapeutic range and a reduced risk of ischemic stroke, but no difference in bleeding events. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Chest Physicians

In 2012, the ninth edition of the American College of Chest Physicians' evidence-based clinical practice guidelines on antithrombotic therapy and prevention of thrombosis stated: "For patients initiating VKA [vitamin K antagonist] therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of VKA (Grade 1B)."[85,] The updated 2021 guidelines make no mention of genotype-guided warfarin dosing.[86,]

Clinical Pharmacogenetics Implementation Consortium

In 2017, the Clinical Pharmacogenetics Implementation Consortium updated guidelines for pharmacogenetics-guided warfarin dosing.[87,] The guideline provides recommendations for genotype-guided warfarin dosing to achieve a target international normlized ratio (INR) of 2 to 3 for adult and pediatric patients specific to continental ancestry. The guideline also states that "Although there is substantial evidence associating CYP2C9 and VKORC1 variants with warfarin dosing, randomized clinical trials have demonstrated inconsistent results in terms of clinical outcomes."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare & Medicaid Services (2009) published a national coverage determination on pharmacogenomic testing for warfarin response.[88,] The Centers for Medicare & Medicaid Services stated that "the available evidence does not demonstrate that pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness improves health outcomes in Medicare beneficiaries outside the context of CED [coverage with evidence development], and is therefore not reasonable and necessary...."

However, the Centers also "believes that the available evidence supports that coverage with evidence development (CED) ... is appropriate for pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness by any method, and is therefore covered only when provided to Medicare beneficiaries who are candidates for anticoagulation therapy with warfarin who:

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1. Have not been previously tested for *CYP2C9* or *VKORC1* alleles; and
2. Have received fewer than 5 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 [described] standards."

REFERENCES

1. Pengo V, Denas G. Optimizing quality care for the oral vitamin K antagonists (VKAs). Hematology Am Soc Hematol Educ Program. Nov 30 2018; 2018(1): 332-338. PMID 30504329
2. Wadelius M, Chen LY, Downes K, et al. Common VKORC1 and GGCX polymorphisms associated with warfarin dose. Pharmacogenomics J. 2005; 5(4): 262-70. PMID 15883587
3. 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
4. Wadelius M, Chen LY, Lindh JD, et al. The largest prospective warfarin-treated cohort supports genetic forecasting. Blood. Jan 22 2009; 113(4): 784-92. PMID 18574025
5. 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
6. Hillman MA, Wilke RA, Caldwell MD, et al. Relative impact of covariates in prescribing warfarin according to CYP2C9 genotype. Pharmacogenetics. Aug 2004; 14(8): 539-47. PMID 15284536
7. Jonas DE, McLeod HL. Genetic and clinical factors relating to warfarin dosing. Trends Pharmacol Sci. Jul 2009; 30(7): 375-86. PMID 19540002
8. Rieder MJ, Reiner AP, Gage BF, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med. Jun 02 2005; 352(22): 2285-93. PMID 15930419
9. 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 01 2005; 14(13): 1745-51. PMID 15888487
10. 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): 773-9. PMID 16270629
11. 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): 645-9. PMID 15358623
12. 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 01 2005; 106(7): 2329-33. PMID 15947090
13. 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
14. Caldwell MD, Awad T, Johnson JA, et al. CYP4F2 genetic variant alters required warfarin dose. Blood. Apr 15 2008; 111(8): 4106-12. PMID 18250228
15. 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): 261-6. PMID 19207028
16. 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): 1199-205. PMID 17510308
17. 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): 332-9. PMID 18596683
18. 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): 326-31. PMID 18305455
19. 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): 169-78. PMID 18370846
20. 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): 1038-40. PMID 18419746
21. 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): 572-8. PMID 20375999
22. 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): e259-64. PMID 20421126
23. 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): 216-25. PMID 19324988
24. 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): 220-5. PMID 20204461
25. 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): 1018-26. PMID 20128861
26. 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): 283-91. PMID 20228265

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27. 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
28. Hamberg AK, Wadelius M. Pharmacogenetics-based warfarin dosing in children. Pharmacogenomics. Feb 2014; 15(3): 361-74. PMID 24533715
29. 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): 542-8. PMID 25001883
30. 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): 832-5. PMID 24601977
31. Cavallari LH, Momary KM, Patel SR, et al. Pharmacogenomics of warfarin dose requirements in Hispanics. Blood Cells Mol Dis. Feb 15 2011; 46(2): 147-50. PMID 21185752
32. Kaye JB, Schultz LE, Steiner HE, et al. Warfarin Pharmacogenomics in Diverse Populations. Pharmacotherapy. Sep 2017; 37(9): 1150-1163. PMID 28672100
33. 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): 408-15. PMID 21270790
34. 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): 790-6. PMID 23755828
35. 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): 407-18. PMID 22329724
36. 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): 208-18. PMID 22274142
37. 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): 531-8. PMID 20930419
38. 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): 130-5. PMID 21228733
39. 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): 837-44. PMID 22851439
40. 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): 113-8. PMID 20585834
41. 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): 719-28. PMID 23104259
42. 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): 1132-40. PMID 23015069
43. 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): 222-5. PMID 21553655
44. 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
45. zer 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): 209-14. PMID 23061746
46. Asiimwe IG, Zhang EJ, Osanlou R, et al. Genetic Factors Influencing Warfarin Dose in Black-African Patients: A Systematic Review and Meta-Analysis. Clin Pharmacol Ther. Jun 2020; 107(6): 1420-1433. PMID 31869433
47. Panchenko E, Kropacheva E, Dobrovolsky A, et al. CYP2C9 and VKORC1 genotyping for the quality of long-standing warfarin treatment in Russian patients. Pharmacogenomics J. Oct 2020; 20(5): 687-694. PMID 32024944
48. 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): 125-9. PMID 23159229
49. Cavallari LH, Shin J, Perera MA. Role of pharmacogenomics in the management of traditional and novel oral anticoagulants. Pharmacotherapy. Dec 2011; 31(12): 1192-207. PMID 22122181
50. Belley-Cote EP, Hanif H, D'Aragon F, et al. Genotype-guided versus standard vitamin K antagonist dosing algorithms in patients initiating anticoagulation. A systematic review and meta-analysis. Thromb Haemost. Oct 2015; 114(4): 768-77. PMID 26158747
51. Tse G, Gong M, Li G, et al. Genotype-guided warfarin dosing vs. conventional dosing strategies: a systematic review and meta-analysis of randomized controlled trials. Br J Clin Pharmacol. Sep 2018; 84(9): 1868-1882. PMID 29704269
52. Washington State Health Care Authority. Pharmacogenetic Testing for Patients Being Treated with Oral Anticoagulants:Final Evidence Report. 2018. Available at: https://www.hca.wa.gov/assets/program/pharmacogenetics-anticoagulants-final-rpt-20180418.pdf. Accessed May 4, 2023.
53. Yang T, Zhou Y, Chen C, et al. Genotype-guided dosing versus conventional dosing of warfarin: A meta-analysis of 15 randomized controlled trials. J Clin Pharm Ther. Apr 2019; 44(2): 197-208. PMID 30593674
54. Sridharan K, Sivaramakrishnan G. A network meta-analysis of CYP2C9, CYP2C9 with VKORC1 and CYP2C9 with VKORC1 and CYP4F2 genotype-based warfarin dosing strategies compared to traditional. J Clin Pharm Ther. Jun 2021; 46(3): 640-648. PMID 33346393
55. Wang X, Tang B, Zhou M, et al. Efficacy and safety of genotype-guided warfarin dosing versus non-genotype-guided warfarin dosing strategies: A systematic review and meta-analysis of 27 randomized controlled trials. Thromb Res. Feb 2022; 210: 42-52. PMID 34999431
56. Hillman MA, Wilke RA, Yale SH, et al. A prospective, randomized pilot trial of model-based warfarin dose initiation using CYP2C9 genotype and clinical data. Clin Med Res. Aug 2005; 3(3): 137-45. PMID 16160068
57. 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): 2563-70. PMID 17989110

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58. Caraco Y, Blotnick S, Muszkat M. CYP2C9 genotype-guided warfarin prescribing enhances the efficacy and safety of anticoagulation: a prospective randomized controlled study. Clin Pharmacol Ther. Mar 2008; 83(3): 460-70. PMID 17851566
59. 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): 226-34. PMID 19177029
60. Burmester JK, Berg RL, Yale SH, et al. A randomized controlled trial of genotype-based Coumadin initiation. Genet Med. Jun 2011; 13(6): 509-18. PMID 21423021
61. McMillin GA, Melis R, Wilson A, et al. Gene-based warfarin dosing compared with standard of care practices in an orthopedic surgery population: a prospective, parallel cohort study. Ther Drug Monit. Jun 2010; 32(3): 338-45. PMID 20386359
62. Korneva E, Ratchina S, Miljagin V, Kozhuhova L, Romanov A, Eidelshtein M. Evaluation of pharmacogenetic-based warfarin therapy in patients with atrial fibrillation in Smolensk region of Russion: results. Basic Clin Pharmacol Toxicol. 109(2011):27-28. https://doi.org/10.1111/j.1742-7843.2011.00731.x.
63. Borgman MP, Pendleton RC, McMillin GA, et al. Prospective pilot trial of PerMIT versus standard anticoagulation service management of patients initiating oral anticoagulation. Thromb Haemost. Sep 2012; 108(3): 561-9. PMID 22836303
64. Wang M, Lang X, Cui S, et al. Clinical application of pharmacogenetic-based warfarin-dosing algorithm in patients of Han nationality after rheumatic valve replacement: a randomized and controlled trial. Int J Med Sci. 2012; 9(6): 472-9. PMID 22927772
65. Radhakrishnan AV, D.; Tayur, S.; et al. Genotype Guided Therapeutic Dosing of Warfarin in Geriatric Patients. J Am Coll Cardiol. 2012;59:E1696. PMID
66. 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): 1593-603. PMID 24088130
67. 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): 2283-93. PMID 24251361
68. 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): 2294-303. PMID 24251363
69. Verhoef TI, Ragia G, de Boer A, et al. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. N Engl J Med. Dec 12 2013; 369(24): 2304-12. PMID 24251360
70. Li J, Liu S, Yang JH, et al. [A randomized controlled study of the VKORC1 and CYP2C9 genotypes in guiding warfarin therapy for pulmonary thromboembolism]. Zhonghua Jie He He Hu Xi Za Zhi. Dec 2013; 36(12): 950-3. PMID 24503429
71. Pengo V, Zambon CF, Fogar P, et al. A Randomized Trial of Pharmacogenetic Warfarin Dosing in Nave Patients with Non-Valvular Atrial Fibrillation. PLoS One. 2015; 10(12): e0145318. PMID 26710337
72. Šupe S, Poljaković Z, Bo<9e>ina T, et al. Clinical Application of Genotype-guided Dosing of Warfarin in Patients with Acute Stroke. Arch Med Res. May 2015; 46(4): 265-73. PMID 25989350
73. Duan L, Zhang N, Liu C. A randomized controlled study of the VKORC1 and CYP2C9 genotypes in guiding warfarin initial dosing algorithm for pulmonary thromboembolism. Chest 2016;149: A519.
74. Jin H, Jiang F, Wei J, Yao Y, Yuan H, Yu M, et al. CYP2C9 and VKORC1 genotype-guided individualized warfarin therapy in Chinese patients with acute pulmonary thromboembolism: a randomized controlled clinical study. Int J Clin Exp Med 2017;10(3): 5595-602.
75. Wen MS, Chang KC, Lee TH, et al. Pharmacogenetic dosing of warfarin in the Han-Chinese population: a randomized trial. Pharmacogenomics. Feb 2017; 18(3): 245-253. PMID 28112575
76. Jiang NX, Ge JW, Xian YQ, et al. Clinical application of a new warfarin-dosing regimen based on the CYP2C9 and VKORC1 genotypes in atrial fibrillation patients. Biomed Rep. Apr 2016; 4(4): 453-458. PMID 27073631
77. Makar-Au<9a>perger K, Kr<9e>elj K, Lovrić Benčić M, et al. Warfarin Dosing According to the Genotype-guided Algorithm is Most Beneficial in Patients With Atrial Fibrillation: A Randomized Parallel Group Trial. Ther Drug Monit. Jun 2018; 40(3): 362-368. PMID 29494423
78. Xu Z, Zhang SY, Huang M, et al. Genotype-Guided Warfarin Dosing in Patients With Mechanical Valves: A Randomized Controlled Trial. Ann Thorac Surg. Dec 2018; 106(6): 1774-1781. PMID 30205115
79. Syn NL, Wong AL, Lee SC, et al. Genotype-guided versus traditional clinical dosing of warfarin in patients of Asian ancestry: a randomized controlled trial. BMC Med. Jul 10 2018; 16(1): 104. PMID 29986700
80. Hao Y, Yang J, Zheng X, et al. Chinese Patients With Heart Valve Replacement Do Not Benefit From Warfarin Pharmacogenetic Testing on Anticoagulation Outcomes. Ther Drug Monit. Dec 2019; 41(6): 748-754. PMID 31259883
81. Guo C, Kuang Y, Zhou H, et al. Genotype-Guided Dosing of Warfarin in Chinese Adults: A Multicenter Randomized Clinical Trial. Circ Genom Precis Med. Aug 2020; 13(4): e002602. PMID 32510984
82. Lee KE, Yee J, Lee GY, et al. Genotype-guided warfarin dosing may benefit patients with mechanical aortic valve replacements: randomized controlled study. Sci Rep. Apr 24 2020; 10(1): 6988. PMID 32332930
83. Zhu Y, Xu C, Liu J. Randomized controlled trial of genotype-guided warfarin anticoagulation in Chinese elderly patients with nonvalvular atrial fibrillation. J Clin Pharm Ther. Dec 2020; 45(6): 1466-1473. PMID 32710457
84. Gage BF, Bass AR, Lin H, et al. Effect of Genotype-Guided Warfarin Dosing on Clinical Events and Anticoagulation Control Among Patients Undergoing Hip or Knee Arthroplasty: The GIFT Randomized Clinical Trial. JAMA. Sep 26 2017; 318(12): 1115-1124. PMID 28973620
85. 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
86. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. Chest. Dec 2021; 160(6): e545-e608. PMID 34352278
87. Johnson JA, Caudle KE, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. Clin Pharmacol Ther. Sep 2017; 102(3): 397-404. PMID 28198005

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88. 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/view/ncd.aspx?NCDId=333. Accessed May 4, 2023.

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
June 2012	New policy	
March 2013	Replace policy	Policy updated with literature review; no changes to policy statement. References 18, 29, 40, 43, 52, 57, 62 added.
March 2014	Replace policy	Policy updated with literature review through November 14, 2013; no changes to policy statement. References 17, 53, 57, 59-60, 62-64, 71-73 and 75 added; references renumbered.
June 2015	Replace policy	Policy updated with literature review through October 30, 2014; references 49-51, 69-72, and 78 added; policy statement unchanged.
September 2018	Replace policy	Policy updated with literature review through April 9, 2018; references 5, 31, 51, 52-54, 56-57, 63-66, and 69 were added. Policy revised with updated genetics nomenclature. Investigational policy statement expanded to include genotyping for CYP4F2. Title changed to reflect focus on genotype-guided dosing as an intervention.
September 2019	Replace policy	Policy updated with literature review through April 18, 2019; references added. Policy statement unchanged.
September 2020	Replace policy	Policy updated with literature review through April 16, 2020; references added. Policy statement unchanged.
September 2021	Replace policy	Policy updated with literature review through April 30, 2021; references added. Policy statement unchanged.
September 2022	Replace policy	Policy updated with literature review through April 20, 2022; references added. Minor editorial refinements to policy statement; intent unchanged.
September 2023	Replace policy	Policy updated with literature review through May 4, 2023; reference added. Policy statement unchanged.

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