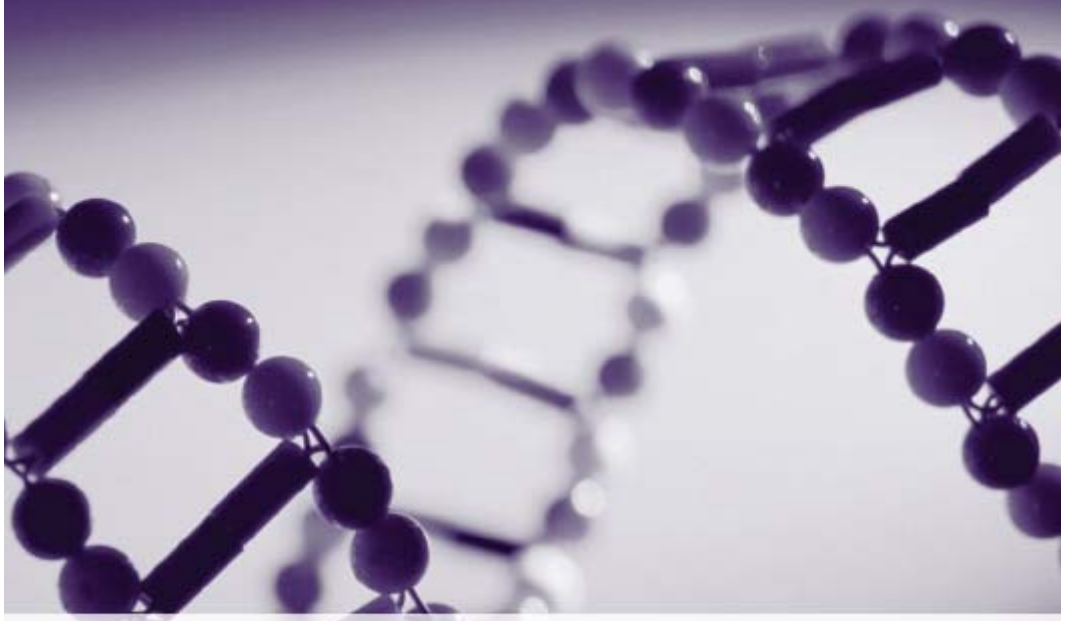
Personalized health care report 2008: Warfarin and genetic testing

Twenty-one percent of patients who receive anticoagulant therapy experience either major or minor bleeding events. Knowing a patient's genotype may aid in initial warfarin dosing.



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Knowing a patient's genotype may aid in initial warfarin dosing

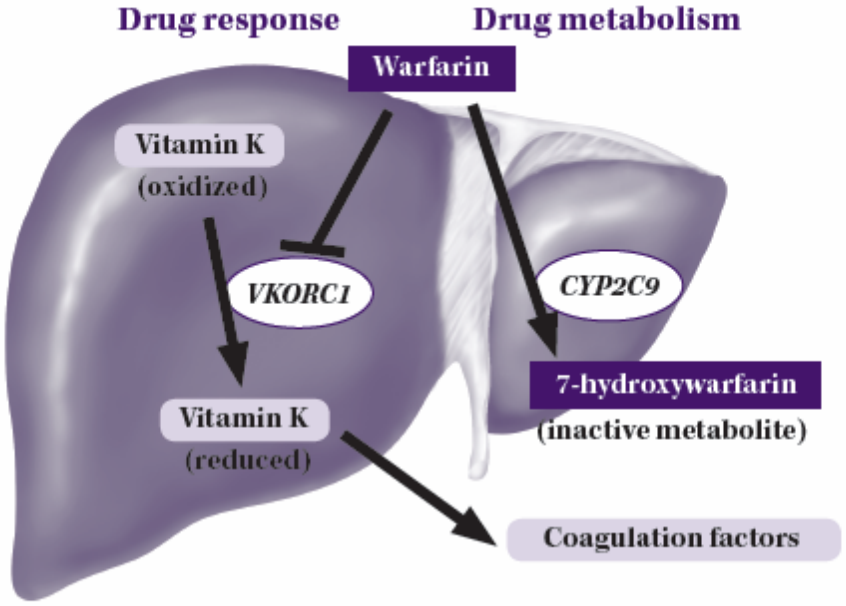
Physicians face a challenge in initiating warfarin therapy. Its narrow therapeutic range and wide variability in patient response can lead to inadequate response or increased risk of bleeding. Studies have estimated that half of patients who could benefit from anticoagulant therapy are not receiving it, in part because of concern that patients could experience some form of bleeding complication.[1,2] Patient response to warfarin is partly dependent on the DNA sequence of the genes expressing cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase complex 1 (VKORC1). The use of genetic tests may reduce the time required to achieve a stable dose. The warfarin drug label now recommends that health care providers consider genetic risk factors when selecting an initial dose of warfarin. This brochure summarizes the genetic influence on warfarin metabolism and response, and the genetic tests now available that reveal a patient's *CYP2C9* and *VKORC1* genotype.

Comparison of drug metabolism and drug response in *CYP2C9* and *VKORC1* gene variants

Drug metabolism	Drug response
CYP2C9	***VKORC1***
Gene variations explain approximately 15% of patient variability in warfarin dose response.[3]	Gene variations explain up to 25% of patient variability in warfarin dose response.[4]
Prevalence of gene variations differs depending on racial background: Approximately 20% of Caucasians, 5% of African-Americans and 2% of Asians carry at least one variant copy of *CYP2C9*.[5]	Prevalence of gene variations differs depending on racial background: Approximately 37% of Caucasians, 14% of African-Americans and 89% of Asians carry at least one variant copy of *VKORC1*.[4,6]
Patients with *CYP2C9* gene variations require more time to achieve stable international normalized ratio (INR) and are at increased risk of bleeding.[7]	Patients with certain *VKORC1* gene variations have an increased risk for anticoagulant overdose.[8]
Patients with *CYP2C9* gene variations may require lower doses of warfarin to achieve and maintain therapeutic INR.[9]	Patients with certain *VKORC1* gene variations may require lower doses of warfarin to achieve and maintain therapeutic INR.[7]

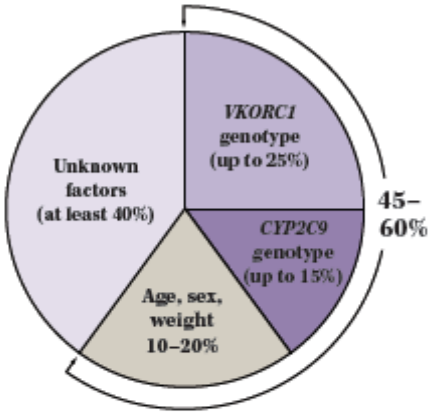
Warfarin metabolism and response

Warfarin is metabolized by the hepatic cytochrome P450 enzyme expressed by the *CYP2C9* gene. Warfarin's anticoagulant effect is mediated by the enzyme VKORC1, which is the target enzyme inhibited by warfarin. Variation in the *CYP2C9* gene causes some patients to have slow metabolism of warfarin and a longer half-life of the drug, resulting in higher than usual blood concentrations of warfarin and greater anticoagulant effect. Certain variations in the *VKORC1* gene result in reduced activity of the enzyme and subsequently reduced function of vitamin K–dependent coagulation factors. Slow metabolism of warfarin caused by *CYP2C9* gene variations and reduced coagulation caused by *VKORC1* gene variations can lead to an increased risk of bleeding during warfarin therapy.



Impact on dosing

Several factors can contribute to variation in a patient's response to warfarin. A patient's *CYP2C9* and *VKORC1* genotype, plus age, sex and weight, together account for 45 to 60 percent of the variation in warfarin response. A large part of the variation is still unknown, but may be at least partially attributed to interactions with other drugs and with food.



How would a genetic test be used in the determination of warfarin dose?

Method without genetic testing
Determine initial dose based on clinical features (body surface area, sex, weight, age).

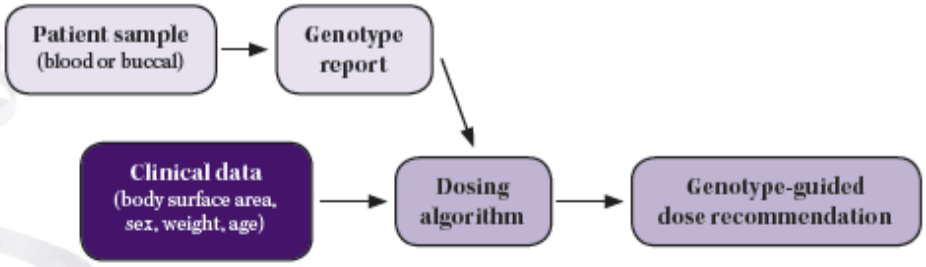
Method utilizing genetic testing
Determine initial dose based on clinical features and *CYP2C9* and *VKORC1* genotypes.

Changes to the warfarin product label

The warfarin product label now includes evidence of reduced warfarin clearance in patients carrying *CYP2C9* gene variations and a caution that genetic variations in the CYP2C9 and VKORC1 enzymes may influence the response of the patient to warfarin. According to the labeling, lower initial doses should be considered for patients with genetic variations in *CYP2C9* and *VKORC1*. An explicit recommendation to perform genetic testing before prescribing warfarin is not included in the label, and the dosage recommendations have not been changed. Genetic testing should not delay the initiation of warfarin therapy when it is needed. The change in the label is intended to inform physicians that a significant proportion of their patients may have genetic variations that place them at risk for an adverse response to usual doses of warfarin. More changes in the label are expected as additional information on the role of genetics in patient response to warfarin becomes available.

Genetic testing

Genotyping tests aim to improve the safety of warfarin dosing. Genetic variations of *CYP2C9* and *VKORC1* can be identified by genotyping tests. These tests may be useful in determining safer warfarin dose by identifying patients with high risks of bleeding complications.[10] There is an FDA-approved *CYP2C9* and *VKORC1* genotyping test, and several other laboratories offer the genotyping tests. In most cases, the test is performed on a blood or buccal sample collected from the patient. Determination of optimal warfarin dose is often based on a dosing algorithm that relies on clinical features such as age, sex and weight, along with genotype. Visit *www.warfarindosing.org* to view one such algorithm. For information on the correct test to order, availability, and interpretation of results, consult with your hospital laboratory, reference laboratory, or a clinical geneticist.[3]



The cost of *CYP2C9* and *VKORC1* genotyping is currently approximately $500. As the testing technology advances, the cost of performing the test may eventually decrease. Insurance and Medicare coverage decisions are made on a local, case-by-case basis.

Note: Determination of genotype is a tool that may aid in selecting the correct dose of warfarin. **Careful monitoring of INR is still required for optimal dose adjustment.** It is not appropriate to wait for test results when immediate anticoagulant therapy is required.

Drug interactions with warfarin: The influence of genetics may be altered dramatically, and the value of genetic tests could be negated, by drug or food interactions with warfarin. More than 300 drugs have been reported to interact with warfarin, requiring its dose to be adjusted. The use of a reliable source, such as the Medical Letter Adverse Drug Interactions Program, is strongly recommended for adjusting warfarin dosage when an interacting drug is also prescribed.

Summary

- Patient response to warfarin is influenced by genetic factors.
- Genetic testing is available and may aid in correct initial warfarin dosing.
- Careful monitoring of INR is required for optimal dose adjustment.
- Drug interactions with warfarin may negate the influence of genetic variations and must be considered.

References

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Additional information

For more information about genomics and pharmacogenomics:

- American Medical Association (*www.ama-assn.org/go/genetics*)
- American Academy of Family Physicians 2005 Annual Clinical Focus (*www.aafp.org/online/en/home/clinical/acf/genomics.html*)
- National Coalition for Health Professional Education in Genetics (*www.nchpeg.org*)
- U.S. Centers for Disease Control and Prevention (*www.cdc.gov/genomics*)
- U.S. Food and Drug Administration (*www.fda.gov/cder/genomics*)

For more information about genetic testing for warfarin dosing, warfarin labeling changes and drug interactions:

- American Medical Association (*www.ama-assn.org/go/genetics*)
- Warfarin dosing (*www.warfarindosing.org*)
- U.S. Food and Drug Administration (*http://www.fda.gov/bbs/topics/NEWS/2007/NEW01684.html*)
- Indiana University School of Medicine, Division of Clinical Pharmacology (*www.drug-interactions.com*)

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- U.S. Centers for Disease Control and Prevention, National Office of Public Health Genomics
- U.S. Food and Drug Administration

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