

DNA Test Helps Physicians Determine Proper Dosage of Warfarin

BY NICHOLAS T. POTTER, PhD

Warfarin (Coumadin®) is the most commonly prescribed oral anticoagulant in North America and Europe. In the United States, approximately 2 million people initiate warfarin treatment annually, primarily to prevent or reduce the risk of a thrombotic event.

Common clinical scenarios for treatment include patients with atrial fibrillation, surgical patients receiving a prosthetic heart valve replacement, orthopedic patients receiving hip or knee replacements, as well as individuals with a history of venous or arterial thrombosis or thrombo-embolism.

Despite widespread use, treatment management remains difficult as a result of the variable patient response to dosing, the drug's narrow therapeutic window and the risk for a serious bleeding event.

While treatment monitoring remains the international normalized ratio (INR), individual patient variability and responsiveness to treatment remains a challenge. Some of this variability is due to extrinsic factors such as patient age, height, weight, the effects of drug interaction and initial treatment indications.

However, genetic variation in at least two genes, *CYP2C9* and *VKORC1*, has also been noted to account for a significant proportion of the remaining variability. Collectively, the combination of extrinsic and genetic factors can account for upwards of 60 percent of a patient's variability in treatment responsiveness⁽¹⁾.

These two genes, *CYP2C9* (cytochrome P450 isoenzyme 2C9), and *VKORC1* (Vitamin K epoxide reductase complex 1) encode enzymes involved in warfarin metabolism and regulation.

CYP2C9 is the principle enzyme involved in the metabolism and clearance of the S-isomer (active form) of warfarin. Two common allelic variants, *CYP2C9*2* and *CYP2C9*3*, result in a reduction of enzymatic activity leading to an increase in warfarin sensitivity and the need for a lower initial and maintenance dose of the drug to achieve a stable INR.



VKORC1 is the molecular target of warfarin *in vivo* and is involved in the regeneration of vitamin K required for the activity of vitamin K-dependent clotting factors.

A polymorphism in the promoter region of the *VKORC1* gene results in a reduction in the production of *VKORC1* leading to decreased levels of vitamin K-dependent clotting factors. This reduction also leads to increased warfarin sensitivity and the need for a lower initial as well as maintenance doses of warfarin to achieve a stable INR.

The presence of either a *CYP2C9* or *VKORC1* variant is accountable for about 40 percent of an individual's variability in warfarin dose and is associated with a dose reduction that can range from 20 to 80 percent depending upon patient genotype^(2,3).

On August 16, 2007, these findings prompted the FDA to approve a labeling change for warfarin (Coumadin®) advising physicians that patients with genetic variations in these two genes may require a lower initial dose of the drug. This labeling change highlighted the opportunity for healthcare providers to consider incorporation of genetic information along with additional relevant clinical information to better estimate the initial warfarin dose (www.fda.gov).

Although it is anticipated that the FDA will approve additional DNA-based tests for warfarin sensitivity testing, there is currently only one FDA-approved test on the market. The Verigene® Warfarin Metabolism Nucleic Acid Test System (Nanosphere, Inc. Northbrook IL) is an *in vitro* diagnostic test for the detection and genotyping of the *2 and *3 alleles of the *CYP2C9* gene and a single polymorphism (1173C>T) in the *VKORC1* gene from a patient blood sample.

Using this test system, an individual

patient test result can be obtained in about three hours after blood collection. This genetic information, when combined with additional relevant clinical information, can then be incorporated into a warfarin dosing algorithm (such as the one available at www.warfarindosing.com) to get an estimate of patient-specific dosing requirements.

While the available clinical data suggest that a patient who has one or more of these genetic variations is at increased risk for an adverse clinical outcome, it needs to be emphasized that not all patients who carry these two variants will have a bleeding event nor will all patients without these genetic variants avoid a bleeding episode. As such, this DNA test does not replace the INR for monitoring of patients receiving warfarin therapy.

While the integration of a patient's specific genetic information into a physician's clinical decision-making algorithm has yet to be widely adopted, the potential promise of "personalized medicine" to improve the safety and effectiveness of drug therapy has considerable merit. Furthermore, in the case of warfarin therapy, it's estimated that the inclusion of personalized warfarin dosing decisions have the potential to avoid 85,000 serious bleeding events and 17,000 strokes annually, with an associated savings in healthcare cost of about \$1.1 billion annually⁽⁴⁾.

References

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Nicholas T. Potter, PhD, FACMG, is the chief scientific officer and director of molecular diagnostics at Molecular Pathology Laboratory Network, Inc., in Maryville, Tennessee. www.mplnet.com.