Pharmacogenetics
GENETICS GUIDING THERAPY

Warfarin DoseAdvise™ Genetic Test

Warfarin (eg. Coumadin®) is a difficult drug to manage due to its narrow therapeutic index and wide interindividual variability in anticoagulant response and maintenance dose. The most frequent complication of warfarin therapy is bleeding, which is fatal in 1% of patients per year and serious in 2-7% per year.

Common genetic variations in two genes, CYP2C9 and VKORC1, have been discovered to significantly decrease warfarin maintenance dose requirements. CYP2C9 and VKORC1 genotype together account for approximately 35-40% of the variability in dose requirement. Previously, only patient clinical factors (such as age, race, body surface area, vitamin K intake, co-prescribed drugs, and co-existing diseases), contributing to 12-20% of dose variability, could be used for estimating dose. The combination of genotype with these clinical factors accounts for 55-60% of the variability in dose requirement, making greatly improved estimates of optimal dose possible.

In November of 2005, the Clinical Pharmacology Subcommittee, an FDA advisory committee, agreed that sufficient evidence exists to support use of lower doses of warfarin for patients with genetic variation in CYP2C9 and VKORC1 that lead to reduced activities. A label change for warfarin is underway to reflect this recommendation.

Benefits of Pharmacogenetic Testing

Pharmacogenetic testing provides information about individual genetic variation affecting drug response and helps clinicians tailor pharmacotherapy for each patient. The Warfarin DoseAdvise™ Genetic Test detects the common variants in the CYP2C9 and VKORC1 genes and identifies patients who require a lower maintenance dose of warfarin and are at an increased risk for bleeding events. Using pharmacogenetics-based dosing has the potential to increase the safety and efficacy of warfarin therapy.

Indications for Warfarin DoseAdvise™ Genetic Testing:

- Patients requiring initiation of warfarin therapy
- Patients receiving warfarin therapy who have a history of unstable dosing

The Warfarin DoseAdvise™ Genetic Test Identifies Individuals Who:

- Require a lower maintenance dose of warfarin
- Are at an increased risk for supratherapeutic INR values and bleeding events
- Require a longer time to achieve stable warfarin dosing (patients with one or more CYP2C9 variants)
- Are at increased risk for certain drug interactions (patients with one or more CYP2C9 variants)

Our Warfarin DoseAdvise™ Genetic Test Service Provides:

- Detection of CYP2C9*2, CYP2C9*3, and VKORC1 (-1639G>A) variants using PCR and fluorescent signal amplification by Invader assay
- Detailed reports with genetic interpretation, recommendations and education
- Genetic consultation for physicians, patients and families by board-certified genetic counselors

Specimen Requirements:

- 5 ml blood in EDTA (lavender top) tube OR cheek cell sample
- Send at room temperature. Specimens are stable for several days.

Turnaround Time:

- 1 business day

kimball genetics

101 University Blvd., Suite 350, Denver, Colorado 80206 • Tel: 800-320-1807 • 303-320-1807 • Fax: 303-388-9220

Warfarin Pharmacogenetics

Gene Variations that Increase Warfarin Sensitivity

CYP2C9: Cytochrome P450 isoenyme 2C9 is the principle enzyme involved in the metabolism and clearance of S-warfarin (the main active form of the drug). Two common variant alleles in the CYP2C9 gene, CYP2C9*2 and CYP2C9*3, decrease the activity of this enzyme to 12% and 5% respectively. This reduces the rate at which warfarin is cleared, leading to a lower maintenance dose requirement. Patients with one or more of these variants usually take longer to achieve stable INR due to a prolonged half-life of the drug. In addition, patients with the CYP2C9*2 or *3 variant have an increased risk for certain drug interactions. Numerous drugs are metabolized by CYP2C9 and, if co-prescribed with warfarin, may reduce warfarin metabolism through competition. Other drugs inhibit or induce CYP2C9 activity. These effects may be further complicated by presence of CYP2C9 variants. CYP2C9*2 and CYP2C9*3 variants are found in approximately 20-30% of Caucasians and in 5% or less of Asians and African Americans.

VKORC1: Vitamin K epoxide reductase (VKOR) is the target for warfarin action and is involved in making vitamin K available in a form that activates vitamin K-dependent clotting factors. Warfarin inhibits VKOR activity, resulting in anticoagulation through reduction of the levels of these activated clotting factors. The associated gene, VKORC1, has a promoter variant (-1639G>A) that reduces the amount of VKOR and leads to decreased levels of vitamin K-dependent clotting factors. This results in increased sensitivity to warfarin and a lower maintenance dose requirement. Among Caucasians, approximately 50% of individuals are heterozygous and 14% are homozygous for the VKORC1 variant. Frequencies are very high in Asians (approximately 18% are heterozygous and 80% are homozygous) and low in African Americans (15-20% are heterozygous and <1% are homozygous).

Warfarin Dose Reductions Based on Genotype

CYP2C9 Variants	CYP2C9 Genotype†	% Dose Reduction††	
		Range††	Mean†††
Negative for *2 and *3	*1/*1	0	n/a
Heterozygous for *2	*1/*2	14-30	17
Homozygous for *2	*2/*2	28-47	n/a
Heterozygous for *3	*1/*3	28-70	37
Homozygous for *3	*3/*3	72-87	n/a
Heterozygous for both *2 and *3	*2/*3	58-81	n/a
VKORC Variant (-1639G>A)	**VKORC1 Genotype**	**% Dose Reduction††**	
Negative for variant	GG	0	
Heterozygous for variant	AG	20-28	
Homozygous for variant	AA	40-50	

† *1 represents the normal allele, lacking CYP2C9 *2 and *3 variants and assumed to be lacking rare variants.

†† The dose reduction required for some patients may fall out of these ranges due to the presence of other genetic and clinical factors.

††† Mean percent dose reductions are from a meta-analysis of 8 publications (Sanderson et al. 2005). n/a: Not available.

Pharmacogenetics-Based Warfarin Therapy

Many studies have confirmed the strong association of CYP2C9 and VKORC1 genotype with warfarin maintenance dose. The table above shows examples of published percent dose reductions for each genotype. The table is for informational purposes only. Kimball Genetics does not make dosing recommendations. Dosing algorithms have been developed to help clinicians use genetic and other patient information to assist in predicting maintenance doses. www.WarfarinDosing.org is an interactive website using several such algorithms. In addition to aiding dose selection for warfarin initiation, it can also assist in dose refinement using the INR value after the third and/or fourth dose (Millican et al. 2007). Prospective, pharmacogenetics-based dosing for warfarin therapy has been conducted in a few studies and shown to be feasible, with improved time to stable dosing (Voora et al. 2005) and fewer bleeding events in a small pilot study (Hillman et al. 2005).

References

1. **Gage BF** (2006). Pharmacogenetics-based coumarin therapy. *Hematology.* American Society of Hematology Education Program Book (1) 467-473. http://asheducationbook.hematologylibrary.org/cgi/reprint/bloodbook;2006/1/467.
2. **Hillman MA** et al. (2005). A prospective, randomized pilot trial of model-based warfarin dose initiation using CYP2C9 genotype and clinical data. *Clin Med & Res* 3(3):137-145.
3. **Millican E** et al. (2007). Genetic-based dosing in orthopaedic patients beginning warfarin therapy. *Blood* Prepublished online March 26, 2007; doi: 10.1182/blood-2007-01-069609.
4. **Reider MJ** et al. (2005). Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. *N Engl J Med* 353(22):2285-93.
5. **Reynolds KK** et al. (2007). Individualizing warfarin therapy. *Personalized Med* 4(1):11-31.
6. **Sanderson S** et al. (2005). CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: a HuGEnet systematic review and meta-analysis. *Genet Med* 7(2):97-104.
7. **Sconce EA** et al. (2005). The impact of CYP2C9 and VKORC1 genetic polymorphisms and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. *Blood* 106(7):2329-33.
8. **Voora D** et al. (2005). Prospective dosing of warfarin based on cytochrome P-450 2C9 genotype. *Thromb Haemost* 93:700-705.
9. **Yuan H-Y** et al. (2005). A novel functional VKORC1 promoter polymorphism is associated with inter-individual and inter-ethnic differences in warfarin sensitivity. *Hum Mol Genet* 14(13):1745-51.