

**Test:** Warfarin Sensitivity Genotyping

**Date:** November 3, 2008

**Test Overview:**

The FDA recently approved a change in warfarin drug labeling, stating that lower initiation doses should be considered for patients with certain genetic variations in Cytochrome P450, family 2, subfamily C, polypeptide 9 (CYP2C9) and Vitamin K epoxide reductase complex, subunit 1 (VKORC1) enzymes. This test simultaneously detects and genotypes two polymorphisms of the CYP2C9 gene, CYP2C9\*2 (3608C>T) and CYP2C9\*3 (42614A>C), and a single-point polymorphism of the VKORC1 (1173C>T). VKORC1 -1639G>A, shares a strong linkage disequilibrium with VKORC1 1173C>T. Individuals who are heterozygous or homozygous variant for any of these alleles are generally more sensitive to standard doses of warfarin than similar individuals who lack the variant alleles, thus they are at increased risk for bleeding.

**Clinical Significance:**

Warfarin sodium can cause major or fatal bleeding. Regular monitoring of INR should be performed on all treated patients. Identification of risk factors for bleeding and certain genetic variations in CYP2C9 and VKORC1 in a patient may increase the need for more frequent INR monitoring and the use of lower warfarin doses.

The variant alleles CYP2C9\*2 and CYP2C9\*3 result in decreased *in vitro* CYP2C9 metabolism of S-warfarin. The frequencies of these alleles in Caucasians are approximately 11% and 7% for CYP2C9\*2 and CYP2C9\*3, respectively (1). Patients with one or more of these variant CYP2C9 alleles have decreased S-warfarin clearance. Patients carrying at least one copy of the CYP2C9\*2 allele required a mean daily warfarin dose that was 17% less than the mean daily dose for patients homozygous for the CYP2C9\*1 allele. For patients carrying at least one copy of the CYP2C9\*3 allele, the mean daily warfarin dose was 37% less than the mean daily dose for patients homozygous for the CYP2C9\*1 allele (2).

Warfarin reduces the regeneration of vitamin K from vitamin K epoxide in the vitamin K cycle, through inhibition of vitamin K epoxide reductase (VKOR), a multiprotein enzyme complex. Certain single nucleotide polymorphisms in the VKORC1 gene (especially the -1639G>A allele) have been associated with lower dose requirements for warfarin. In one study, about 30% of the variance in warfarin dose could be attributed to variations in the VKORC1 gene alone; about 40% of the variance in warfarin dose could be attributed to variations in VKORC1 and CYP2C9 genes combined (3). About 55% of the variability in warfarin dose could be explained by the combination of VKORC1 and CYP2C9 genotypes, age, height, body weight, interacting drugs, and indication for warfarin therapy in Caucasian patients(3). Similar observations have been reported in Asian patients (4,5).

**References:**

This information was taken from <http://www.fda.gov/cder/foi/label/2007/009218s105lblv2.pdf>

1. Yasar U et al. *Biochem Biophys Res Comm.* 1999; 254:628-631.
2. Sanderson S et al. *Genet Med.* 2005;7:97-104.
3. Wadelius M et al. *Pharmacogenomics J.* 2005;5:262-270.
4. Veenstra DL et al. *Pharmacogenet Genomics.* 2005;15-687-691.
5. Takahashi H et al. *Pharmacogenet Genomics.* 2006;16:101-110.

**Method:**

DNA Hybridization to solid array.

**Availability:**

Monday -Saturday; Results in 48 hours.

**Specimen:**

Whole blood

**Collect:**

One 5.0 mL EDTA (Lavender) tube.

**Volume:** 5.0 mL (minimum: 3.0 mL)

**Transport:**

Refrigerate

**Reference Range:**

With report

**CPT Codes:**

83891; 83896 x11; 83908 x3; 83912

**Additional Information:**

Client list fee: \$395