

Warfarin Sensitivity DetectR™ **Helps achieve safe and stable warfarin dosing**

Overview

Warfarin, an anti-coagulant widely used for the prevention of thromboembolic events, is associated with about 29,000 emergency department visits per year for bleeding complications.¹ Warfarin is difficult to manage because of its narrow therapeutic index and wide interindividual variability in dose response. Thus, for an individual patient, there is little difference between a warfarin dose that is too high and can bring about hemorrhage and one that is too low and can lead to thrombotic episodes. In addition, correct doses vary widely between individuals – by as much as 150 fold.² Stable dosing can take months to achieve, with patients at risk for excessive bleeding or ineffective clot control during that time.³

Variations in at least six genes affect the interindividual variability in warfarin requirements, but the strongest predictors of the correct dose are the genes that code for vitamin K epoxide reductase complex 1 (VKORC1) and cytochrome P450 (CYP) 2C9.⁴ Of the interindividual variability, 56% can be accounted for by variation in these two genes together with age, gender, and body weight.⁵

Indeed, in 2005 the Clinical Pharmacology Subcommittee of the FDA agreed that sufficient evidence exists to recommend lower warfarin doses for patients with genetic variations in CYP2C9 and VKORC1,⁶ and in August 2007, FDA announced a labeling change for warfarin. Part of the added text states

“...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.”⁷

Specialty is pleased to announce a new test, the **Warfarin Sensitivity DetectR™**, which detects the CYP2C9*2 and CYP2C9*3 variants in the P450 (CYP) 2C9 gene and the –1639G→A variant in the VKORC1 gene.

Clinical Value

- Helps estimate optimal dosage of warfarin for each patient
- Helps achieve stable dosing earlier than when VKORC1 and CYP2C9 are not considered

Interpretation of Results

Test results give the patient’s genotype with respect to the CYP2C9*2, CYP2C9*3, and –1639G→A loci, and *Specialty* provides a table for the interpolation of daily maintenance warfarin doses, using genotype, with respect to these two genes, together with height and age.

The metabolism of warfarin is also influenced by ethnicity, diet, digestive and hepatic function, and other medications. The Warfarin Sensitivity DetectR™ targets only the two common CYP2C9 and one common VKORC1 variants. No other genetic variants or environmental factors that may impact warfarin sensitivity are measured by this test. All these factors can be important.

Ordering Information and Specimen Requirements

Test Code	Test Name	Specimen Type, Requirements
5055	Warfarin Sensitivity DetectR™	5 (3) mL whole blood EDTA; ambient or refrigerated stability 1 week.

Specify “Send Warfarin Sensitivity DetectR™ to Specialty Laboratories”.
For immediate attention and sample pick-up, call 800-421-4449.

Method

Multiplex PCR, Luminex detection

Warfarin Pharmacogenetics

Warfarin exerts its anticoagulant effect by inhibiting vitamin K epoxide reductase complex 1 (VKORC1), the enzyme that catalyzes the rate-limiting step in the regeneration of vitamin K. Genetic variation in the gene that encodes VKORC1 can lead to deficient VKORC1 activity and also to warfarin resistance, and thus to variation in warfarin dose requirements. One VKORC2 allele, -1639G→A, is especially useful in predicting warfarin requirements.^{8,5}

S-warfarin, is primarily broken down by cytochrome P450 (CYP) 2C9. Two common variant alleles, CYP2C9*2 and CYP2C9*3, encode defective versions of CYP2C9, which catabolize warfarin at reduced rates, leading to lower warfarin requirements and the possibility of overdosing when usual amounts of warfarin are administered.

References

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