

Genetics

Warfarin Sensitivity Test



Molecular Pathology Laboratory Network, Inc. (MPLN) offers the FDA-cleared Warfarin Sensitivity Test (Verigene® by Nanosphere, Inc.) to assist clinicians with the determination of optimal drug dosage.

The Warfarin Sensitivity Test detects and genotypes the *2 and *3 alleles of the CYP2C9 gene and a single polymorphism (1173C>T) in the VKORC1 gene.

FDA Recommendations for Warfarin Therapy

In August 2007, the FDA approved a labeling change for warfarin (Coumadin®), advising physicians that patients with genetic variations in the CYP2C9 and VKORC1 genes may require a lower initial dose of the drug².

This labeling change encourages healthcare providers to consider incorporating genetic information with relevant clinical information to better estimate the initial warfarin dose.

Warfarin is prescribed to millions of patients and therapy is associated with a high frequency of adverse events. The major risk is bleeding, which can be frequent and severe.

Test Code

WARF

Specimen Requirement

5.0 mL whole blood in EDTA

Storage and Handling

Store at 4°C

Ship ambient

Specimen Stability

18°-25° C for 24 hours; 4° C for up to 4 days

CPT Codes

- 83891
- 83896 x 11
- 83908 x3
- 83912

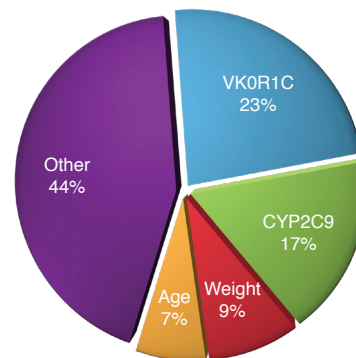
Turnaround Time

2-3 days

Related Test Options

- PT-INR
- ThomboFLEX™ profile
- Factor II Prothrombin
- Factor V Leiden

For more information about warfarin, contact your local account representative or contact a client service specialist at 800.932.2943.



~40% of the variability in warfarin dose can be attributable to genetic variation in the CYP2C9 and VKORC1 genes.

Inclusion of a patient's genetic information can aid in the prediction of initial and maintenance doses of the drug. Patient-specific dosing requirements can be obtained by combining this genetic information with additional relevant clinical information in a warfarin dosing algorithm such as:

Warfarin dosing algorithm: www.warfarindosing.com

It is important to note that not all patients who carry gene variations in their CYP2C9 and VKORC1 genes will have a bleeding event, nor will all patients without these genetic variants avoid a bleeding episode. As such, the Warfarin Sensitivity Test does not replace the PT INR for monitoring patients receiving warfarin therapy.



Pharmacogenetics

Warfarin is metabolized in the liver by an enzyme called cytochrome P4502C9 (CYP2C9 or 2C9). As the drug is metabolized, it is inactivated and eliminated from the body. Unmetabolized drug remains active and exhibits its blood-thinning effects.

Inhibition of CYP2C9 enzyme function and thus metabolism of warfarin can be caused by underlying genetic variation. There are two common mutations in the CYP2C9 gene that give rise to less functional forms of the enzyme. These mutations are referred to as: CYP2C9*2 and CYP2C9*3. Having one or more of these mutations will impair an individual's ability to metabolize warfarin and thus will require a lower dose to reach a stable PT-INR of 2.0-3.0.

The molecular target of warfarin is the Vitamin K Epoxide Reductase Complex, subunit 1 (VKORC1). In the body, the VKORC1 enzyme uses Vitamin K and other cofactors to activate clotting factors in the blood.

The amount of VKORC1 can vary due to underlying genetic variation and numerous mutations have been observed in the VKORC1 gene. Unlike CYP2C9, no VKORC1 mutations have been identified that produces a clearly dysfunctional protein. But rather, a series of mutations have been identified that alter the amount of VKORC1 protein that is produced. The presence of one or more of these VKORC1 mutations gives rise to two groups of patients. A high-dose group also referred to in the literature as haplotype B or haplotype BB and a low-dose group also referred to in the literature as haplotype A or haplotype AA.

Combined with other clinical data, knowledge of an individual's CYP2C9 genotype (as it relates to CYP2C9*2 and CYP2C9*3) and their VKORC1 haplotype can explain a significant portion of the variability in Warfarin dose required to achieve a stable coagulation state (INR).

About MPLN

Pursuing excellence in laboratory medicine since 1989, Molecular Pathology Laboratory Network, Inc. (MPLN) offers integrated approaches to meet health management challenges of physicians and their patients. To provide a comprehensive diagnostic and prognostic picture of each patient, our pathologists and laboratory directors are available for personalized diagnostic consultations.

Headquartered in Maryville, Tennessee, MPLN is a fully licensed laboratory, certified by the Clinical Laboratory Improvement Amendment, accredited by the College of American Pathologists, and licensed in the states of Tennessee, New York, Florida and Maryland.

References

1. Wadelius M et al (2005). Common VKORC1 and GGCX polymorphisms associated with warfarin dose. *Pharmacogenetics J.* 5:262-270.
2. www.fda.gov
3. 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* 7:97-104.
4. McClain MR et al (2007). A rapid ACCE review of CYP2C9 and VKORC1 allele testing to inform warfarin dosing in adults at elevated risk for thrombotic events to avoid serious bleeding. www.acmg.net
5. McWilliams A et al (2006). Health care savings from personalizing medicine using genetic testing: The case of warfarin. <http://www.aei.brookings.org/publications/abstract.php?pid=1127>
6. Voora D, McLeod HL, Eby C, Gage BF. The pharmacogenetics of coumarin therapy. *Pharmacogenomics* 2005;6:503-13.
7. Takahashi H, Wilkinson GR, Nutescu EA, Morita T, Ritchie MD, Scordo MG, et al. Different contributions of polymorphisms in VKORC1 and CYP2C9 to intra- and inter-population differences in maintenance dose of warfarin in Japanese, Caucasians and African-Americans. *Pharmacogenet Genomics* 2006;16:101-10.

Trademarks

Coumadin is a trademark of Bristol Myers Squibb.

Verigene® is a trademark of Nanosphere, Inc., Northbrook, IL.

ThromboFLEX is a trademark of MPLN.