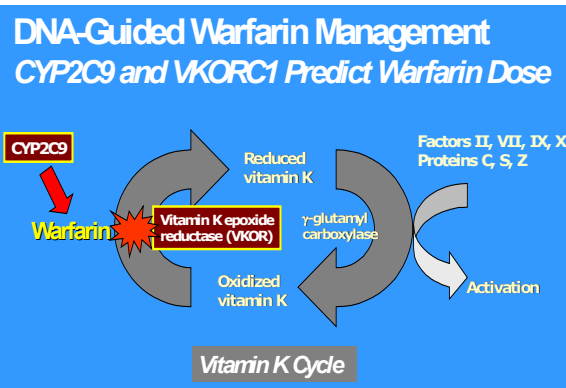


TECHNICAL INFORMATION



The *HILOmet* WARFARIN system performs high-resolution DNA Typing to individualize warfarin management. The System determines an individual's warfarin metabolic capacity and sensitivity by DNA Typing simultaneously the CYP2C9 and VKORC1 genes, at 12 variable sites. DNA Typing results and derived dosage guidelines are reported.

DNA Typing is performed at the Laboratory of Personalized Health (LPH), a division of Genomas Inc. (Hartford CT). LPH is a high-complexity clinical DNA testing center licensed by the Connecticut Department of Health (CL-0644) and certified by the Centers for Medicare and Medicaid Services (ID# 07D1036625) under CLIA (Clinical Laboratory Improvement Amendments). The *HILOmet* WARFARIN DNA Typing system is available through the Clinical Laboratory Partners (CLP) network throughout Connecticut.

DNA FOR WARFARIN PER FDA

The FDA has identified DNA Typing as a powerful tool to enhance drug safety for pharmaceuticals in the market now. DNA Typing is being added to supplement other precautionary measures to assure safe dosage and to avoid drug interactions.

The FDA Clinical Pharmacology Advisory Subcommittee in November 2005 recommended revising the warfarin label to include DNA Typing of both CYP2C9 and VKORC1 based on evidence that lower doses are needed for patients with certain gene variants. A label revision with both genes is expected in 2007. Healthcare will be revolutionized by the introduction of DNA-guided medicine into clinical practice.

ORDERING *HILOmet* WARFARIN

- Order forms are available from the website of the Laboratory of Personalized Health (LPH) at www.genomas.net/LPH
- The test is available through **Clinical Laboratory Partners (CLP)**. A listing of the CLP Patient Service Centers is on the LPH website or at www.clpct.com. CLP can be reached at 800-286-9800.

Further Questions?
Call the LPH @ 860-545-4589 or
e-mail to LPH@genomas.net or
visit www.genomas.net/LPH

LABORATORY OF PERSONALIZED HEALTH



HILOmet WARFARIN DNA Typing System for DNA-Guided Warfarin Management

LPH is a Division of Genomas, Inc.
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Tel (860) 545-4589 Fax (860) 545-4575
www.genomas.net/LPH

WARFARIN MANAGEMENT

Warfarin (Coumadin®) is a drug prescribed frequently for the treatment and prevention of thromboembolic complications. More than 21 million prescriptions were written in the U.S. in 2003 and 2 million doses are administered daily. Warfarin has a narrow therapeutic index with frequent complications despite dose adjustment for clinical variables such as age, gender, weight, nutritional factors and interactive medications. The warfarin label now carries a “Black Box” warning for “major or fatal bleeding” caused by the drug.

For the physician, warfarin side effects often represent a diagnostic conundrum. There is a broad range of warfarin maintenance doses within the population with individual patients requiring from 1 mg/day to 10 mg/day to obtain the same benefit. Despite early dose titration and subsequent periodic monitoring by Prothrombin Time (PT) and International Normalized Ratio (INR) hemorrhagic complications are frequent and can be fatal. Such complications range from occult bleeding and ecchymoses to overt bleeding and hemorrhage requiring blood transfusions. They lead to protracted management and great risk to patient safety.

For the patient, warfarin side effects represent an added burden on diseases they already have, and which are supposed to be treated, resulting in frustration and poor compliance.

DNA-GUIDED MEDICINE



The large majority of side effects are based on the patient’s own inherited metabolic traits. DNA Typing identifies these inherited factors from the patient’s DNA to predict individualized side effect risks. What is revolutionary for clinical practice is that by means of DNA Typing, the innate metabolic capacity and drug sensitivity of the patient relevant to a drug treatment can be predicted and diagnosed simply from a blood sample. With the *HILOmet* WARFARIN system, patients with greatly compromised metabolism of warfarin or with reduced sensitivity to the drug can be identified by DNA Typing to avoid clinical complications and side effects.

Today, most standard of care protocols for warfarin therapy consider height, weight, gender, co-medications and diet for dose adjustments. These factors account for at most ~20% of the variability in dosing. DNA alone accounts for ~50% of the dosing variability. DNA adds significant predictive power to warfarin therapeutic algorithms: the combined predictive power of the clinical factors and DNA is ~70%.

DNA-GUIDED WARFARIN DOSE

Warfarin is metabolized to inactive metabolites by the CYP2C9 isoenzyme of the Cytochrome P450 system. About 25% of the population is a carrier of one functionally deficient CYP2C9 DNA variant and 3% are carriers of two. Functionally deficient CYP2C9 variants lead to higher incidence of supra-therapeutic INR values (>4), delays in achieving a stable maintenance dose, and increased bleeding complications. CYP2C9 polymorphism accounts for ~25% of the overall variability in warfarin dosing needs.

Warfarin exerts its anticoagulant effect through its inhibition of Vitamin K Epoxide Reductase (VKOR). VKOR reduces Vitamin K, which is necessary for activation of Clotting Factors II, VII, IX and X. VKOR is coded by the Vitamin K Epoxide Reductase Complex, subunit 1 (VKORC1) gene. DNA variants of the VKORC1 gene decrease the sensitivity of VKOR to warfarin. About 75% of the population carries a DNA variant which reduces expression of the VKORC1 gene and accounts for an additional ~25% of clinical variance in warfarin dosage.

CYP2C9 and VKORC1 are independently segregating genes whose protein products act at two different sites of warfarin biochemistry. Their individual contributions when added yield at least ~50% prediction of warfarin variability by DNA Typing.