Pharmacogenetic Testing Prior to Initiation of Warfarin Therapy

Introduction
Variability in an individual’s response to a given drug may be due to a number of different genetic factors. Genetic variants may influence drug response by altering (1) drug metabolizing enzymes, (2) drug target(s) or receptor(s), and/or (3) drug transport protein(s) or a combination thereof.1 Pharmacogenetics is the investigation of the genetic basis of drug response. Unlike traditional therapeutic drug monitoring, a significant advantage of pharmacogenetic testing is that investigation can be undertaken prior to initiation of drug therapy to enable more effective initial dose stratification or identify specific situations in which a specific therapy will not be effective.1 Warfarin is an ideal drug target for the application of pharmacogenetic testing due to its narrow therapeutic index, large interindividual variation in dose requirements and high frequency of identified genetic variants that have an impact on both its effect and metabolism.2,3

Daily maintenance doses of warfarin in study subjects range widely, from 1.25 mg to 34 mg.4 Given this significant variation in required dose and warfarin’s narrow therapeutic index, the anticoagulant effect of warfarin must be regularly monitored. This is accomplished using a mathematical conversion of the prothrombin time (PT).2 The PT is converted to the International Normalized Ratio (INR) based on the mean PT of the population and responsiveness of the test reagent (INR = [patient PT/mean PT])0.2.5 The recommended therapeutic range for patients on warfarin therapy is an INR value between 2.0 and 3.0.2 Below this range, patients are at risk of thrombosis while supratherapeutic INR values increase the potential for bleeding.6,7 There is a sharp increase in bleeding risk when the INR is above the therapeutic range such that the risk of hemorrhage doubles with each one point rise in INR.5

Bleeding Complications
Bleeding is the most clinically significant complication associated with warfarin therapy.4,6 Risk for bleeding is highest during warfarin initiation as required dose is not easily predicted in the individual patient.4,6 Commonly occurring genetic variants in warfarin’s target enzyme (or the enzyme system largely responsible for its metabolism) account for much of the observed variation in warfarin’s anticoagulant effect.7 Individuals who carry these common genetic variants require lower maintenance doses of warfarin.4,7 The application of pharmacogenetic testing prior to the start of warfarin therapy to identify these genetic variants, therefore, can identify a population that is hypersensitive to warfarin therapy, avoiding the potential for serious and life-threatening bleeding complications.3,4,7

Warfarin’s anticoagulant effect is mediated through its ability to block hepatic synthesis of functional vitamin K-dependent clotting factors, specifically factors II, VII, IX, and X.2 Warfarin inhibits the intrahepatic vitamin K cycle and thus impairs vitamin K-dependent gamma-carboxylation.2 Recently, the gene encoding the vitamin K epoxide cycle has been identified (VKORC1).8 Alterations in the VKORC1 gene can affect the ability of warfarin to impair the activity of the vitamin K-dependent factors and, therefore, alter response to therapy.9 VKORC1 variants (polymorphisms) are thought to account for as much as 25% of the interindividual variation in required warfarin dose while about 10% of this variation is due to CYP2C9 variants.4,9 The VKORC1 genetic variant that is a marker for warfarin hypersensitivity is designated (-)1639 G>A.7,10 Carriers of this variant require significantly lower maintenance doses of warfarin than noncarriers.7 The frequency of (-)1639 G>A varies with ethnicity; it is more common in Chinese,10 less common in Caucasians, and even less common among those of African American ancestry.11

Warfarin Metabolism
Warfarin is metabolized in the liver through the cytochrome P450 (CYP) system.2 The CYP drug metabolizing enzyme 2C9 is responsible for the metabolism of the biologically active isomer of warfarin (S-warfarin), as well as other agents including certain antiepileptics (phenytoin), antidiabetic drugs (glipizide, tolbutamide), nonsteroidal anti-inflammatory agents and antihypertensive agents (losartan).1,3,12,13 Genetic variants in the CYP2C9 system can impair the degree to which warfarin is metabolized, thereby altering drug response.13 Common genetic variants (polymorphisms) of CYP2C9, designated CYP2C9*2 and CYP2C9*3, have been shown to decrease the in vivo clearance of warfarin therapy.14 In CYP2C9*2 homozygotes, metabolism of warfarin is reduced by 40% and in those who are homozygous for CYP2C9*3, warfarin metabolism is reduced by almost 90%.12,14 During initiation of warfarin therapy, individuals with the CYP2C9*2 and/or CYP2C9*3 genotype are more likely than noncarriers to have INR values greater than 4 and suffer a twofold to threefold elevated bleeding rate.14 Carriers of these variants, furthermore, require more frequent dose adjustments during warfarin initiation and take longer to reach a stable maintenance dose.15 The CYP2C9*2 and CYP2C9*3 polymorphisms are common, occurring in up to 30% of Caucasian populations, while both of these variants are less common in African and Asian populations.12 It has been estimated that 18% of Caucasians have both VKORC1 and one of the CYP2C9 variants16 and these individuals therefore require significantly lower doses of warfarin to achieve a therapeutic response and prevent overdose.4,10,16
Predicting warfarin dose at therapy initiation is enhanced by genotyping for CYP2C9*2 or *3 and (-)1639 G>A and consideration of other factors. For each CYP2C9*2 variant, required warfarin dose is reduced by 19% and reduction in dose is 29% with CYP2C9*3 alleles. In determination of optimum warfarin dose, other factors such as patient age, intercurrent illness(es), nutrition, drug-drug interactions and body surface area should be taken into account. Certain drugs such as amiodorone, isoniazid, and phenylbutazone have been shown to decrease warfarin clearance and, therefore, reduce the required dose while rifampin and barbiturates have been shown to enhance warfarin metabolism, increasing the required amount of drug.

Pharmacogenetic testing for warfarin detects the presence of CYP2C9*2, *3, and VKORC1 (-)1639 G>A variants. CYP2C9 DNA analysis is performed by allele-specific PCR followed by electrophoresis to detect the *2 and *3 alleles. VKORC1 DNA analysis is performed by PCR followed by restriction enzyme digestion to detect (-)1639 G>A. Individuals with one or more of these variant alleles are hypersensitive to warfarin therapy and have an increased risk for bleeding if warfarin therapy is initiated at standard doses. The dose of warfarin can be individually determined based on CYP2C9 and VKORC1 genotype, patient age, body surface area, and concurrent drug therapies.

References


For the most current information regarding test options, including specimen requirements and CPT codes, please consult the online Test Menu at www.LabCorp.com.