



SNP Testing for Warfarin Sensitivity

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Pharmacogenomics is the study of genetic variation as it relates to a patient's response to a given drug. Single nucleotide polymorphisms (SNPs) are examples of such genetic variation and can serve as a guide for the therapeutic dosing of pharmaceuticals. Among other drugs, SNP testing has been used to predict warfarin sensitivity and estimate appropriate starting doses. According to the US Food and Drug Administration (FDA), warfarin is among the top 10 drugs with serious adverse event reports. In this setting, the goal of pharmacogenetic testing is to improve the safety and effectiveness of anticoagulant therapy.

The pharmacokinetics of warfarin is crucial to understanding the basis for pharmacogenomic testing. Unbound warfarin is absorbed by the liver, where the S-enantiomer of warfarin inhibits vitamin K epoxide reductase (VKOR). This interferes with the vitamin K-dependent carboxylation of coagulation factors and other vitamin K-dependent proteins. The S-enantiomer is subsequently metabolized by CYP2C9 and excreted in the bile. SNPs in the cytochrome P450 complex, specifically CYP2C9*2 and/or CYP2C9*3, have been associated with decreased warfarin metabolism. Consequently, patients who are homozygous for a SNP in vitamin K epoxide reductase, VKORC1, exhibit increased warfarin sensitivity and can have increased toxicity with "normal" doses of warfarin.

In response to these findings, in August 2007, the FDA approved an update to warfarin labeling that highlighted the use of genetic testing to improve initial estimates of warfarin dosing. Since that time, additional research has both supported and refuted these findings, and professional societies have responded in kind. While both the American Association for Clinical Chemistry (AACC) and the College of American Pathologists (CAP) support the use of pharmacogenomic testing for warfarin metabolism, the Association for Molecular Pathology (AMP), the American Society of Hematology (ASH), and the American College of Medical Genetics (ACMG) recommend additional research on the subject. More recently, in August 2009, the Centers for Medicare and Medicaid Services (CMS) issued a memorandum stating that pharmacogenomic testing would be covered only in patients enrolled in clinical studies and that the available evidence does not support pharmacogenomic testing to predict warfarin responsiveness.

At the present time, pharmacogenomic testing for SNPs is largely limited to the direct-to-consumer setting. SNP testing can be used beyond the realm of pharmacogenomics to identify SNPs associated with genetically associated disorders, such as cystic fibrosis and sickle cell disease. SNP testing may eventually expand to include mainstream laboratories in the form of

vendor-supplied technology or reference laboratory testing. Regardless, the pathologist will play an essential role in the development and implementation of SNP testing. Pathologists' understanding of molecular techniques will be instrumental in overseeing SNP testing and evaluating the quality processes used to establish results. Pathologists will also serve as a guide for clinicians in the appropriate use and interpretation of SNP testing.

Clinical trials focused on SNP testing are ongoing, and the medical community's understanding of pharmacogenomics will undoubtedly expand and change as a result. Pharmacogenomic testing is an initial step towards personalized medicine, a type of medicine that requires both diagnostic innovation and careful exploration before its promises can be realized.

References and Suggested Reading

1. Gage RF, Lesko LJ. Pharmacogenetics of warfarin: regulatory, scientific, and clinical issues. *J Thromb Thrombolysis*. 2008;25:45-51.

2. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108967.htm

3.

www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?from2=viewdraftdecisionmemo.asp&id=224&

4.

www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtl_t_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtl_t%7BactionForm.contentReference%7D=committees%2Ftechnology%2Fsnps.html&_state=maximized&_pageLabel=cntvwr