Pharmacogenomic Testing and Warfarin Management

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Warfarin has been used for the prevention of thrombosis for more than 50 years and is the most frequently prescribed vitamin K antagonist in North America (Gage & Eby, 2003). Its mode of action is to prevent vitamin K from converting to vitamin KH2, thereby inhibiting clotting factors (Johnson & Cavallari, 2015). Warfarin metabolism is affected by variations in the cytochrome P450 2C9 (CYP2C9) and the vitamin K epoxide reductase complex 1 (VKORC1) genotypes. CYP2C9 affects the drug's pharmacokinetics, or metabolism, whereas VKORC1, the target protein of warfarin, affects the drug's pharmacodynamics, or its impact on cell proteins.

CYP2C9 variations can influence the dosage requirements of warfarin (Johnson & Cavallari, 2015). Most variations are caused by single nucleotide polymorphisms (SNPs) that lead to lower dosage requirements, with the exception of the CYP2C9*6 allele, which is a single nucleotide deletion. Individuals who are homozygous for the wild type allele CYP2C9*1 will typically have normal metabolism of warfarin. Individuals with one of the abnormal SNPs (i.e., either CYP2C9*2 or CYP2C9*3) metabolize warfarin more slowly and are prone to higher international normalized ratios (INRs) during the induction of warfarin therapy. These individuals are also about 2.6 times more prone to hemorrhage during the initiation of therapy than individuals with the normal allele (Gage & Eby, 2003). These two SNPs are the primary variations found in those of European descent and are found less often in people of African descent (Johnson & Cavallari, 2015). Other SNPs of CYP2C9 occur most often in people of African descent, and the presence of the CYP2C9*2 allele is rare in those of Asian descent.

In addition, the presence of the single polymorphism A allele of VKORC1 is associated with lower dosage requirements for warfarin and a higher risk of hemorrhage. The abnormal A allele is most commonly found in Asians followed by Europeans, and is least frequently seen in people of African descent. The impact of the VKORC1 abnormal allele on the risk of hemorrhage is apparent only in the first month of therapy; however, the presence of the CYP2C9*2 and CYP2C9*3 alleles carries a risk of bleeding that is ongoing throughout treatment. The CYP2C9 genotype carries a risk for major hemorrhage, with the highest risk being in the first three to six months after initiation of therapy.

The variant alleles of CYP2C9 and VKORC1 can explain 10%–45% of the dosage requirement variations for warfarin (Johnson & Cavallari, 2015). For example, the presence of the CYP2C9*2 allele may lead to a 1 mg per day reduction. However, the presence of the VKORC1-1639AA allele may result in a 2–3 mg per day reduction, whereas the VKPRC1-1639GG allele may cause a 1 mg per day increase.

Clinical Guidelines

The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends that genotype information, when available, be used in determining warfarin dosage, noting that data support the predictive value of genetic information in warfarin dosing (Johnson & Cavallari, 2015). In addition, the CPIC recommends that algorithms detailed by Gage et al. (2008) and Klein et al. (2009) be used for dosage determination instead of the U.S. Food and Drug Administration (FDA) drug label data. Both algorithms use demographic data (e.g., age, height, weight, gender, race), clinical history, and genotype to recommend initial dosages for warfarin (Gage et al., 2008; Klein et al., 2009; PharmGKB, 2014). Gage et al. (2008) developed a website that allows healthcare providers to easily access the algorithms (www.warfarindosing.org).

The FDA advises that when pharmacogenetic testing is used, it must be used cautiously and in collaboration with INR (Institute of Medicine, 2010). The clinical studies reported by Johnson and Cavallari (2015) used INR as the standard test to determine patients' therapeutic status of warfarin, regardless of the use of the genotype in setting initial dosage requirements. Zineh, Pacanowski, and Woodcock (2013) noted that the extensive use of INR in these studies may have actually contributed to the difficulty in determining the effectiveness of the use of genotype results. Measurement of INR is, and likely will continue to be, the standard of care in determining and monitoring the therapeutic range of warfarin.

The package insert for Coumadin®, a brand name for warfarin sodium, suggests that the initial and maintenance dosages of warfarin be adjusted depending on the presence of gene variations of CYP2C9 or VKORC1, if known (Bristol-Myers Squibb Pharma Company, 2011). In a statement that announced the addition of genetic information to warfarin packaging, the FDA (2007) noted that it supports the use of personalized medicine and pharmacogenomics to help identify optimal dosages for individual patients. However, the FDA (2007) also explained that more studies are needed to determine the precise drug dosages for patients with genetic variations. Although the FDA has approved some test kits for warfarin pharmacogenetic testing, the drug label does not overtly

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Table 1. Pharmacogenetic Testing Educational Resources for Patients and Healthcare Providers

Resource	Website	Content
ARUP Laboratories: Warfarin Sensitivity: Clinical Background	http://bit.ly/1fhNyra	Resource for laboratory test selection and interpretation
ARUP Laboratories: *Warfarin Sensitivity (CYP2C9 and VKORC1) 3 Mutations*	http://bit.ly/1Ulqh70	Information about indications for warfarin sensitivity genotype testing, available tests, epidemiology, and risk factors associated with abnormal alleles, as well as dosing implications
Genetics Home Reference	http://1.usa.gov/1ELufvw	Searchable information about genetic variations related to warfarin response
Genetic Testing Registry	http://1.usa.gov/1CLSrnr	Searchable information about tests for alleles related to warfarin sensitivity (e.g., indications, how to order tests, result interpretation), as well as links to clinical and consumer resources
Lab Tests Online: Warfarin Sensitivity Testing	http://bit.ly/1Oi9a26	Simple, plain language explanations of reasons for undergoing testing; frequently asked questions about testing; and links to other resources about warfarin therapy and pharmacogenomics
National Genetics and Genomics Education Centre: Pharmacogenomics in Healthcare	http://bit.ly/1CLS8sP	Videos, online courses, and written content, among other resources, provided by the National Health Service in the United Kingdom
National Human Genome Research Institute: Frequently Asked Questions About Pharmacogenomics	http://1.usa.gov/1CHPQ6B	Information about pharmacogenomics and its applications, as well as links to related resources

recommend testing for everyone. The label merely acknowledges that CYP2C9 and VKORC1 affect dosage requirements, as well as that genotype information, when available, can aid in selection of the starting dose (Kitzmiller, Groen, Phelps, & Sadee, 2011). Those most likely to benefit from genetic testing are individuals who are initiating warfarin therapy for the first time (Dean, 2013).

Johnson and Cavallari (2015) reported that the American College of Chest Physicians does not recommend genetic testing to help with determining the optimal dosage of warfarin. The CPIC does not address testing recommendations but instead suggests using genotype to determine warfarin dosages. Consequently, Johnson and Cavallari (2015) determined that, based on the results of two large studies in the United States and Europe, "the data at present do not support the clinical utility of ordering a warfarin pharmacogenetic test prior to therapy initiation" (p. 37). In addition, the Centers for Medicare and Medicaid Services ([CMS], 2015) have stated that the use of pharmacogenetic testing for warfarin dosing does not improve health outcomes. Therefore, pharmacogenetic testing for CYP2C9 and VKORC1 is covered only if the individual has not been tested before, is receiving new therapy, and is enrolled in a prospective, randomized, controlled clinical study (CMS, 2015). Table 1 provides various resources regarding pharmacogenetic testing for patients and providers.

Ethical Considerations

The use of pharmacogenetic testing carries with it positive and negative implications that are similar to those associated with genetic testing. In a study by Rogausch, Prause, Schallenberg, Brockmöller, and Himmel (2006), patients and physicians were surveyed about their attitudes regarding pharmacogenomic testing. About 63%–75% of patients said they were hopeful that pharmacogenetic tests could help with choosing the drug with the best dosage and efficacy, as well as the lowest side effects. Sixty-nine percent of patients also expressed concern that the disclosure of adverse test results could result in discrimination when seeking employment, and similar concerns were expressed by 71% of physicians surveyed. Patients and physicians also were concerned about health insurance discrimination. However, the study was published prior to the passage of the Genetic Information Nondiscrimination Act, which protects most Americans from genetic discrimination in the areas of health insurance and employment (GINAhelp.org, 2010a, 2010b).

Pharmacogenetic testing makes potentially important and medically useful information available to those who undergo it; however, many insurance companies do not cover warfarin sensitivity testing under normal circumstances (Wertz, 2003). For example, Aetna considers genotyping for warfarin sensitivity and other CYP450 testing to be experimental and investigational because the clinical value of the tests has not been clearly established (Aetna, 2015), and Medicare does not cover testing unless the individual is enrolled in a clinical trial (CMS, 2015). These types of policies leave the individual with the responsibility of paying for pharmacogenetic testing, putting such testing out of reach to all but those with the means to afford it. This issue contributes to the disparity in healthcare resources available to the affluent versus what is available to those without financial means (Wertz, 2003).

Conclusion

Rapid advances in pharmacogenomic research will continue to lead to improvements in the pharmacologic

management of disease processes. For some disease treatment protocols, clinical practitioners may come to rely on genetic and pharmacogenetic testing as a routine standard of care when initiating and managing drug therapy.

However, whether genetic testing is warranted in the initiation of warfarin therapy is undetermined. Genetic information may serve to inform clinical practitioners of a patient's increased risk of bleeding or metabolism of warfarin, but it should not be used as a substitute for more traditional means of monitoring the initiation and ongoing management of warfarin therapy. Clinicians should educate patients about the pros and cons of pharmacogenetic testing before recommending it as a tool in the pharmacologic management of warfarin therapy.

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Genetics & Genomics

This feature aims to educate oncology nurses about the emerging role of genetics and genomics in cancer care. Possible submissions include, but are not limited to, application of genetics and genomics in clinical practice, screening and surveillance, case studies to present new ideas or challenge current notions, and ethical issues. Manuscripts should clearly link the content to the impact on cancer care. Manuscripts should be 1,000–1,500 words, exclusive of tables and figures, and accompanied by a cover letter requesting consideration for this feature. For more information, contact Associate Editor Lisa B. Aiello, RN, MSN, AOCNS®, APN-C, at lba34@drexel.edu.