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Potential Role of Pharmacogenetic Testing in Clinical Care: Warfarin and Clopidogrel

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Human Genome's Potential Role in Reducing Health Care Costs and Saving Lives

The numbers are staggering.According to the Institute of Medicine (IOM), at least 1.5 million Americans are injured each year by medication mistakes and every hospital patient is exposed to at least one medication error each day (National Institute of Medicine. Preventing Medication Errors. Washington, DC: National Academy of Sciences; 2007). An estimated 7,000 people die each year from a medication error.In addition to the health toll this takes on the patient and the cost of human life, this situation is costing the healthcare system an estimated $21 billion annually in wasteful spending.The average senior is taking anywhere from 8-12 different medications per day. One possible, yet controversial solution to this problem has been the use of DNA testing to determine who is most at risk of suffering an Adverse Drug Event (ADE) based upon the way they metabolize the nation's most popularly used medications.

"Variability is the law of life and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under abnormal conditions which we know as disease" [1]. The study of pharmacogenetics serves to explain variability in pharmacological response resulting from genetic differences. Pharmacogenetics is based on the observation of phenotypes and investigates variations in genes as they relate to drug metabolism. It allows for better comprehension of pharmacodynamics and pharmacokinetics in order to reduce potentially harmful side effects [1]. The mainstay of pharmacotherapy involves giving the right medication at the right dose to the right patient in order to treat a specific disease state or condition. Personalized medicine is achieved through having a comprehensive understanding of how a drug works the pathology of the disease state, and drug response within individuals [1]. The idea of individualized medicine has been around for centuries. Notably, the Egyptian Papyrus Ebers contained more than 800 prescriptions, which were used to treat individual patients suffering from various conditions such as asthma and cancer.

The goal of individualizing therapy is to reduce the quantity and severity of side effects and toxicities while reaching the desired therapeutic effect for the patient, yielding the most beneficial health outcomes. Pharmacogenetics allows for selection of pharmacological therapy based on a patient's specific genetic makeup, therefore it has the potential to become an invaluable resource in certain fields of medicine to provide patients with tailored medication therapy.Studies propose that pharmacogenetic testing is the missing link to better health outcomes. However, some evidence also exists that suggest it is of little clinical relevance [2].

Despite this conflicting evidence, the Food and Drug Administration (FDA) has approved more than 100 drugs with pharmacogenetic information included within their labels [3]. Also, there are a multitude of pharmacogenetic tests available to identify genes that may affect drug metabolism. Pharmacogenetic testing remains a topic of controversy with conflicting evidence. The objective of our analysis is to examine the literature-based evidence and determine the relevance of pharmacogenetic testing in clinical practice. This discussion will focus on warfarin and clopidogrel as medications of interest in clinical pharmacogenetic research that are attracting significant attention.

Warfarin

Warfarin is an anticoagulant, which does so by inhibiting vitamin k epoxide reductase complex subunit 1 (VKORC1), thereby decreasing the formation of vitamin K dependent clotting factors. It is indicated for prophylaxis and treatment of thromboembolic disorders such as atrial fibrillation, deep-vein thrombosis, pulmonary embolism, prosthetic heart valves, stroke, and myocardial infarction. Although warfarin is widely used and effective for many, it does possess the risk for serious bleeding. As a result, it has been assigned a Black Box Warning by the FDA. Dosing is complex and must be individualized and adjusted per patient specific lab values regarding coagulation. Genetic polymorphisms of interest pertaining to warfarin are CYP2C9 and VKORC, both of which result in variability in therapeutic response among individuals.

Warfarin is a racemic mixture containing an S-isomer and an R-isomer. Of the two isomers, it is the S-isomer that exerts the majority of warfarin's therapeutic effects. The S-isomer is primarily metabolized by CYP2C9. Polymorphisms of CYP2C9 have the potential to affect the metabolism of S-warfarin, leading to decreased clearance. Based on the decreased clearance of the medication those individuals that possess the polymorphism would require lower doses of warfarin to achieve their therapeutic goal as compared to those with normal or "wild type" enzymatic activity.According to a meta-analysis of 12 studies, variations of the CYP2C9 genotype account for 12% of the variability in dosing requirements between individuals [4].

The second gene of interest pertaining to warfarin is the gene that encodes for VKORC1. Different polymorphisms of this gene result in either higher dosing requirements or lower dosing requirements.A meta-analysis of 10 different studies concluded that polymorphisms of VKORC1 account for 25% of inter-individual variability in dosing requirements [4].

Identifying a patient's VKORC1 haplotype and CYP2C9 genotype are of clinical relevance as it may prevent adverse bleeding events and provide for improved medication efficacy.Currently, there are a number of different pharmacogenetic tests available for warfarin.

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Examples include, Rapid Genotyping Assay, Nanosphere Verigene Warfarin Metabolism Nucleic Acid Test and the Warfarin Dose Advise Genetic Test, all of which have been approved by the FDA [5].

Several pharmacogenetic based treatment algorithms have been proposed for Warfarin. Table 1 illustrates an example algorithm which includes examples of maintenance daily doses of warfarin according to different genotypes. Depending upon an individual's specific genotype, a dose reduction of 10% to 90% may be required [6,7].

Warfarin is one of the most extensively studied medications in the field of pharmacogenetics and several studies have shown that the use of pharmacogenetic testing in patients taking warfarin is clinically relevant. Despite this, the FDA does not yet recommend routine pharmacogenomic testing to determine dosing, but they do acknowledge that dose requirements are indeed influenced by CYP2C9 and VKORC1 and that when genotype information is available, it can be used to assist in the selection of a starting dose.

Clopidogrel

Clopidogrel is an oral antiplatelet agent indicated for the treatment and prevention of acute coronary syndromes, prophylaxis of thrombotic events, and unstable angina. It is a prodrug requiring metabolism via hepatic enzymes to its active form in order to exert its therapeutic effects. The enzyme CYP2C19 is greatly involved in the metabolism of clopidogrel to its active form. Polymorphisms of this enzyme have shown to have an effect on the therapeutic response of clopidogrel.

Polymorphisms of CYP2C19 can render an individual a poor metabolizer, meaning they have little to no CYP2C19 activity and therefore are unable to metabolize clopidogrel to its active form when compared to those with normal or "wild type" enzymatic activity. Individuals with polymorphisms of CYP2C19 who are receiving clopidogrel will have lower levels of the active metabolite resulting in decreased platelet inhibition and are therefore at a higher risk of cardiovascular events. Figure 1 illustrates an algorithm proposed to initiate antiplatelet therapy in patients with acute coronary syndromes. A recent multicenter, randomized, double blind trial of 333 patients with cardiovascular disease concluded that patients with specific polymorphisms of CYP2C19 needed a dose increase from the typical 75mg of clopidogrel to 225mg to achieve similar anti-platelet activity as compared to those with normal CYP2C19 function [8,9].

Clopidogrel currently has an FDA boxed warning stating that poor CYP2C19 metabolizers may not benefit from this therapy and should consider an alternative treatment.Although evidence exists that this may be clinically relevant, routine testing is not yet recommended and there are no clear recommendations regarding dose adjustments in those who are poor metabolizers.

Problem

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7mg	5-7mg	3-4mg	3-4mg	3-4mg	0.5-2mg
AG	5-7mg	3-4mg	3-4mg	3-4mg	0.5-2mg	0.5-2mg
AA	3-4mg	3-4mg	0.5-2mg	0.5-2mg	0.5-2mg	0.5-2mg

†Ranges are derived from multiple published clinical studies. VKORC1 −1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose.
[a]Data from: http://packageinserts.bms.com/pi/pi_coumadin.pdf [7]

Table 1: Three Ranges of Expected Maintenance Coumadin (warfarin) daily doses Based on CYP2C9 and VKORC1 Genotypes†[a]

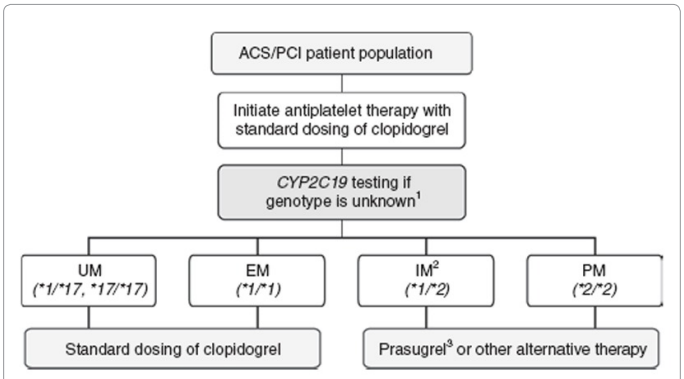

Figure 1: Algorithm to Initiate Antiplatelet Therapy Based on CYP2C19 Genotype[a] [a]Data from Johnson, Gong, Whirl-amillo et al [9]

While the inventors of this technology sing its praises for its high efficacy and its unique window into the ways in which drugs are metabolized differently based upon one's genetic make-up, can these tests actually help prevent medication errors and in turn save lives and the healthcare industry billions in wasted revenues and the cost it takes to rectify the complications stemming from these reactions? Or do the ethical questions raised from doing such a pharmacogenetic test, as well as concerns over malpractice through making pharmacogenetic testing a standard of care, outweigh the potential benefits?

The nation's largest payer for hospital care, the Centers for Medicare &Medicaid Services (CMS), has one primary objective: cost containment through best practices and evidence-based medicine. With an unprecedented number of people turning 65 and Americans living longer than ever, it has been well documented that the current healthcare conditions are unsustainable.Any and all cost containment measures that also have potential for improved patient outcomes stand to have great impact on cost containment.Pharmacists are on the frontline of medication distribution and therefore make an ideal clearinghouse for capturing and collecting this data for smarter medication dosing and adherence.

Ethical considerations

Due to the ethical concerns associated with pharmacogenetic testing, not only will this clinical study abide by IRB standards but will also adopt the National Institutes of Health's confidentiality agreement in order to ensure that any and all pharmacogenetic testing is relegated/limited to the clinical pathways in which certain cardiac drugs are metabolized.

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