Review Article

Pharmacogenomics in cardiovascular precision medicine

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Abstract: A significant portion of cardiovascular care is dependent on prescription drugs, which costs America over 300 billion every year. Cardiovascular disease medications are often influenced by genetically determined drug response. Better understanding of drug efficacy optimization may greatly improve cost-effectiveness and safety of cardiovascular health care. Inter-individual variability in drug actions include but not are limited to, the processes of absorption, distribution, metabolism, excretion, and interaction with target receptors and organs. This review focuses on how genetic testing of drug metabolism and response, has contributed toward cardiovascular precision medicine. The scope of this review covers the cardiovascular drug-gene pairs with the most evidence supporting implementation in clinical practice and with Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines available. These drug-gene pairs are, clopidogrel and cytochrome P450 family 2 subfamily C member 9 (CYP2C19) genotype; warfarin and both CYP2C9 and vitamin K epOxide reductase complex subunit 1 (VKORC1) genotypes; and simvastatin and solute carrier organic anion transporter family member 1B1 (SLCO1B1) genotype. Response to β-blockers involving metabolizing enzyme and drug receptors is discussed too. A number of institutions including our own have been implementing pharmacogenomics testing of these drug-gene pairs into clinical practice. A transition from the current model of pharmacogenomics testing post therapy initiation to a preemptive approach is desired to serve the needs of physicians and patients.

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Evolving role of pharmacogenomics in cardiology

Precision medicine aims to define diseases more precisely, to diagnose more accurately, and to treat patient more relevant to the disease subtype and an individual's unique condition. One of the key aspects of this movement away from one-size-fits-all patient management is the selection and dosage of medications. Human body's response to drug is mainly determined by two variable process, pharmacokinetics and pharmacodynamics. Pharmacokinetics describes the time course of drug concentration change during which drugs are deposited and cleared in body compartments through absorption, distribution, metabolism, and excretion. Pharmacodynamics refers to drug actions at a constant concentration including interaction with receptors, target cells and downstream signaling (1). The scope of pharmacogenomics covers genetic variants that contribute to differences in each of these steps, although up to date, most of clinically implemented pharmacogenomics testing focus on drug metabolism.

This review presents how precision medicine, specifically that surrounding genetic testing of drug metabolism, has influenced the practice in cardiovascular diseases in the clinic and in the laboratory. It is estimated that prescription drugs account for ~10% of annual cost of cardiovascular care in the United States, which exceeds 300 billion (2). Attempt to understand and optimize drug efficacy is expected to greatly improve cost-effectiveness and safety of cardiovascular health care.

The strategy to characterize genetic components in individual drug response was announced as a goal led by the National Human Genome Research Institute shortly after the completion of whole genome sequencing (3). Over

the years, significant progress has been made such as the International HapMap and 1000 Genomes projects, that enabled genome-wide association studies (GWAS) of drug response. Among the undesirable drug effects, the most impactful ones are failure of efficacy, serious adverse events that result in hospitalization or prolonged hospitalization, severe sequelae, disability, or death. Therefore, the most valuable benefits from pharmacogenomics testing are provided by finding that minimize the risk of these undesirable drug effects. Based on the data from GWAS, a number of genetic determinants of drug responses have been identified, including genetic contributors to statin-induced myopathy, clopidogrel effectiveness and warfarin dose requirement (4). Another NIH-funded initiative is the Pharmacogenomics Knowledge Base (PharmGKB), which provides a comprehensive resource of pharmacogenomic information for clinicians.

Despite the tremendous effort to generate and incorporate pharmacogenomic data into clinical care, there remains paucity in clear guidance on test result interpretation and translation into actionable prescribing decisions. In 2009, the Clinical Pharmacogenetics Implementation Consortium (CPIC) was formed to address this barrier to create guidelines on the clinical use of pharmacogenetic data (5). However, the scenarios presented in these guidelines are how clinicians prepare themselves to interpret the genetic testing results that patients already obtained previously, and to prescribe medications based on these results. Hence, CPIC guidelines recommend how to respond to available genetic test results instead of addressing if and what genetic tests to order. Currently CPIC guidelines were available for 24 drugs or drug classes in a number of therapeutic areas. The Dutch Pharmacogenetics Working Group also provides guidelines for interpretation and use of pharmacogenomic data, and both the Dutch and CPIC guidelines are freely available through PharmGKB.

In the field of cardiovascular medicine, the most prevalent pharmacogenomics testing are warfarin and cytochrome P450 family 2 subfamily C member 9 (CYP2C9)/vitamin K epOxide reductase complex subunit 1 (VKORC1) genotypes, clopidogrel and CYP2C19 genotype, and simvastatin and solute carrier organic anion transporter family member 1B1 (SLCO1B1) genotype. CPIC guidelines are available for each of these drug-gene pairs, and a number of institutions including our own are implementing these into clinical practice.

Warfarin—CYP2C9/VKORC1

The intra- and inter-individual variation in reaching optimal anticoagulation status through Warfarin therapy and its interaction with other drugs have long been recognized. Combination of CYP2C9 and VKORC1 genotypes are the underlying pharmacogenomics basis for such heterogeneity in warfarin dosing. The *CYP2C9* gene is involved in the clearance of S-warfarin, and genetic variation in the *VKORC1* gene regulating the oxidation state of vitamin K is associated with different sensitivity to warfarin. Institutions such as our own have designated pharmacists in cardiology medication therapy management to recommend initial warfarin dosage at safe and effective levels.

The warfarin label approved by United States Food and Drug Administration (FDA) targets individuals with CYP2C9 genotype leading to decreased drug clearance and VKORC1 genotype resulting in increased drug sensitivity. These patients are recommended to receive lower than typical warfarin dosage. CPIC has developed a pharmacogenomic algorithm for drug dosage based on CYP2C9/VKORC1 genotyping results and clinical data like age and weight to support medication decisions. Consequently, genotype-guided warfarin dosing has become the standard-of-care at a number of institutions including ours (6).

Clopidogrel—CYP2C19 genotype

As a prodrug, clopidogrel is metabolized to its active thiol metabolite which inhibits platelet activation and aggregation. There are two steps in the metabolism process of clopidogrel and the CYP2C19 enzyme is involved in both steps. Among the variants of CYP2C19, those that result in enzyme deficiency lead to decreased circulating concentrations of the active clopidogrel thiol metabolite, and subsequently suppressed inhibition of platelet activation and aggregation. Individuals inheriting the deficient CYP2C19 variant form have increased risk for major adverse cardiovascular events, particularly those with history of acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) (7). Other CYP2C19 polymorphisms include poor metabolizers inheriting two nonfunctional alleles and thus inactive enzyme, intermediate metabolizers with a single nonfunctional allele resulting in reduced enzyme activity.

The possibility for variable CYP2C19 metabolism of clopidogrel resulting in adverse clinical outcomes was

reported by the American College of Cardiology and the American Heart Association expert panel in 2010. This report eventually led to the FDA warning label targeting poor metabolizers by the FDA. The label warns about decreased active drug metabolite concentration leading to suboptimal therapeutic outcome in poor metabolizers. Pharmacogenomics testing is included in the label as an option to assess the patient's response to drug and alternative antiplatelet therapy is recommends for poor metabolizers. Examples of alternative agents are Prasugrel and Ticagrelor that are independent of metabolism via CYP2C19 enzyme. In the CPIC guidelines, both poor and intermediate Clopidogrel metabolizers with a history of ACS and PCI procedure were recommend to switch to alternative anti-platelet therapy (7).

Nevertheless, FDA did not recommend CYP2C19 polymorphism testing as a routine practice before the use of clopidogrel, even though about 1 in 5 patients undergoing PCI with stenting showed poor response to clopidogrel, and stent thrombosis often end up with severe morbidity and sometimes fatal outcomes (8). We have started our local protocol to screen patients undergoing cardiac catheterization with pharmacogenomics testing of CYP2C19 since 2015. Other institutions such as the University of Florida Health Personalized Medicine Program has launched universal CYP2C19 testing in certain patient populations as the standard-of-care.

Simvastatin—SLCO1B1 genotype

Statin is the major class of lipid-lowering agents with few adverse events. Given its popularity and potent effect, statin therapy has a common side effect, myopathy which limit its use in some patients. Symptoms range from mild myalgia to life-threatening rhabdomyolysis. Risk factors for myopathy include higher statin doses, concomitant use of drugs that inhibit statin metabolism or clearance, renal or liver dysfunction, and certain SLCO1B1 genotypes. Without sufficient comorbidity assessment and pharmacogenomics testing, it is difficult to predict which patient might develop myopathy. Thus a common standard is to start at a dosage and make changes if adverse events occur, which may have fatal consequence in rhabdomyolysis cases.

The SLCO1B1 gene encodes an organic anion polypeptide transporter 1B1, which transports most of statins to the liver. The 521T>C (p. Val174Ala) polymorphism was found to be related to myopathy caused by statins. Among the statin categories, Simvastatin has the most data on its association with genetic testing result, which is covered in the CPIC guidelines (9). For example, patients with 521CT or CC genotypes were recommended to be put on lower doses of simvastatin (usually 20 mg/day) or alternatives of statins such as pravastatin or rosuvastatin. In these patients who are on simvastatin, creatinine kinase is suggested to be routinely monitored for myopathy. With these association and clinical relevance evident, institutions such as the Vanderbilt University has incorporated SLCO1B1 genotyping into routine clinical practice. Patients with SLCO1B1 polymorphism that made them susceptible to myopathy are prescribed a very low dose of non-simvastatin statin drug or an alternate lipid-lowering agent.

β-blockers—CYP2D6/ADBR1 genotype

Beta-blockers are antagonists competing with catecholamine to bind to β-1-adrenergic receptors (ADBR1). They are widely used for hypertension, cardiac arrhythmia, angina, and myocardial infarction. A number of genes have been associated with inter-individual variation in β-blocker responses, including CYP2D6, ADBR1, and ADBR2.

Loss-of-function variants in CYP2D6 are associated with phenotypes of poor metabolizers for β-blockers such as propranolol, timolol, and metoprolol. About 5–10% of the population carry two or more loss-of-function CYP2D6 alleles, and thus will have elevated circulating drug concentrations. Notably, suppressed CYP2D6 metabolism does not always translate into clinical effects (e.g., carvedilol), and not all β-blockers are metabolized through CYP2D6 (e.g., atenolol and nadolol) (10). Inconsistent findings have been reported regarding the impact of common variants in ADBR1 on response to β-blockers. Homozygosity of Arg389 allele was linked to better left ventricular ejection fraction compared to carriers of the Gly389 allele in some (11), but not all studies (12). Common variants in ADBR2 were not found to be associated with altered clinical outcomes (13) despite evidence from cell studies (14).

The equivocal cause-effect relation between genetic polymorphisms in CYP2D6 and β-blocker response is reflected in the FDA label warning. For example, the label of Lopressor (metoprolol tartrate) states that the CYP2D6 dependent metabolism seems to have little or no effect on safety or tolerability of the drug. Nevertheless, heart failure patients that carry the loss-of-function CYP2D6 allele may be particularly vulnerable to high drug concentration

and thus need to avoid β-blockers. Given the evidence of pharmacogenomic interactions between β-blockers and ADBR1 polymorphisms, combining multiple risk alleles may be more informative in managing β-blockers therapy (15,16).

Methods of pharmacogenomics testing

Laboratory methods used in pharmacogenomics encompass a variety of techniques in molecular testing. Common sample types are buffy coat from whole blood and buccal cells. Most of pharmacogenomics testing target a specific region of interest, and the amplification is usually through polymerase chain reaction (PCR). To verify the identity and size of PCR amplification product, gel electrophoresis is often performed after PCR. Methods to determine genotype include PCR coupled with restriction fragment length polymorphism (RFLP) analysis, that is only capable of analyzing limited number of samples, pyrosequencing that uses a primer extension reaction coupled with a luciferase-based enzyme reaction, TaqMan technique that uses fluorescence-labeled probes in addition to PCR primers, the Invader method that uses fluorescence resonance energy transfer (FRET)-quenched cleavase probes, bead-based multiplex genotyping, and high-density microarrays. There are several more recent techniques such as mass spectrometry that differentiates DNA molecules based on defined mass, denaturing high-performance liquid chromatography that uses a reverse-phase ion-pair column to discriminate variant alleles, and whole gene sequencing when needed (17,18).

Further implementation of cardiovascular pharmacogenomics

As summarized above in this article, clopidogrel, warfarin, and statins (particularly simvastatin) are examples of how pharmacogenomics testing benefits patients with cardiovascular diseases. However, several other drugs and drug classes may soon join their ranks. The more desirable model of pharmacogenomics testing is the preemptive approach that has genotyping performed before the patient receives drug prescription and dosage. This way, the genetic test results are availability in the medical record when the physician needs to select and prescribe drug(s). Another advantage of the preemptive approach is the ability to batch samples and expand the target gene polymorphisms, so that it allows comprehensive coverage of potential variants involved in drug metabolism and response. Although this model actually improves the efficiency of genotyping and prepares the patient to have information ready at future occasions of medication selection and dosing, it is not supported by payment system in the United States (19).

There are two possible models for performing pharmacogenomics testing in the clinical setting: reactive (at the time of care) and proactive (test results obtained in advance). Limited by reimbursement structure in the United States, reactive genotyping methods are more likely to have insurance to cover the cost, because the genetic test can be linked to the current diagnosis (19). More recently, there have been insurance policies requiring evidence supporting change of dose, which favors the proactive model of pharmacogenomics testing. In other countries where government-funded healthcare is more dominant, the reimbursement of pharmacogenomics testing is dependent on national level guidelines and healthcare policy. Our institution has exercised a model that for certain patient population that are the recipients of certain therapy, pharmacogenomics testing is ordered as part of a routine care package to help guide the clinicians on drug prescription (20). Furthermore, an alert appears in the electronic health record would be instrumental to guide clinicians' decision making.

The apparent discrepancy between testing model efficiency and reality in practice can potentially be transformed through education of the current and next generation of clinicians and pharmacists. Provider education in pharmacogenomics needs to address how to apply genetic testing data clinically. Educational strategies that meet actual needs, such as the clinical value of pharmacogenomics testing, the integration of medical record test results, and test reimbursement are critical to facilitate the implication of pharmacogenomics testing (21). Innovative education methods such as clinical case demonstration, flipped classrooms and team-based learning should be encouraged (22). With accumulating data from clinical practice, more diverse and personalized recommendations are expected to be developed. Federal programs such as the Precision Medicine Initiative would promote basic and clinical research acceleration in this field. Endorsement from clinicians to support point-of-care education and electronic tools for clinical use of pharmacogenomics data is crucial to the advancement of this field (23). NIH and a number of other institutions have taken actions to support the development and awareness of such educational resources through the establishment of the

Inter-Coordination Committee of Genomics Pedagogical Education Associations and the Center for Competence in Genetics and Genomics (11, 12).

In summary, a multidimensional approach is required to meet the needs of clinical practice, research, and education in order to integrate pharmacogenomics testing in the optimization of patients' cardiovascular care.

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