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Pharmacogenomics in cardiology – genetics and drug response: 10 years of progress

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History of pharmacogenomics in cardiology: where have we been?

Following completion of the Human Genome Project in 2003, Dr Francis Collins and others on behalf of the National Human Genome Research Institute announced their vision for the future of genomics research [1]. A number of grand challenges were identified, and among these were developing strategies to identify genetic contributions to drug response, creating genome-based approaches to predict drug response, and applying discoveries to promote the use of genomic information into clinical practice. The NIH has invested significant resources in addressing these challenges, including funding the International HapMap and 1000 Genomes Projects, which have enabled genome-wide association studies (GWAS) of drug response. Through GWAS, investigators have identified genetic contributors to statin-induced myopathy, clopidogrel effectiveness and warfarin dose requirements. While most GWAS of drug response have been conducted in European populations, a recent GWAS in African–Americans revealed a novel association between the rs12777823 polymorphism and warfarin dose requirements in this population, demonstrating the importance of conducting pharmacogenomic studies in different ethnic groups [2].

Other NIH-funded initiatives include the Pharmacogenomics Research Network (PGRN), whose broad objective is to elucidate genetic variants contributing to drug response, and the Pharmacogenomics Knowledge Base (PharmGKB), which is a comprehensive resource of pharmacogenomic information for researchers and clinicians. Specific projects within the PGRN have focused on the pharmacogenomics of antihypertensive response, arrhythmia therapy, antiplatelet interventions and cardiovascular disease risk. The Translational

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Pharmacogenetics Project was formed as a network-wide PGRN effort to translate actionable pharmacogenetic discoveries into clinical practice. More recently, the NIH-funded Implementing Genomics in Practice Network was formed to further enhance and accelerate the incorporation of genomic information into clinical care.

In spite of these efforts, widespread incorporation of pharmacogenomic data into clinical care remains challenging. Lack of clear guidance on how to interpret pharmacogenomic test results and incorporate them into actionable prescribing decisions was identified as a significant barrier to clinical adoption. In 2009, the Clinical Pharmacogenetics Implementation Consortium (CPIC) was formed as a joint collaboration between the PGRN and PharmGKB to address this barrier. In addition to PGRN members and PharmGKB staff, CPIC members include external experts in pharmacogenomics and laboratory medicine who collaborate to create guidelines on the clinical use of pharmacogenetic information. These guidelines are founded on the assumption that patients will present commonly in the future with genetic test results at the time of drug prescribing, and thus clinicians will need to be prepared to handle these results. Therefore, CPIC guidelines recommend what to do with existing genetic test results rather than address whether or not to perform testing. As of early 2015, guidelines were available for 14 drugs or drug classes spanning a number of therapeutic areas. The Dutch Pharmacogenetics Working Group also provides guidelines for interpretation and use of pharmacogenomic data, and both these and CPIC guidelines are freely available on the PharmGKB website.

In his state of the union address on 20 January 2015, President Obama announced a new Precision Medicine Initiative signaling continued government support to accelerate progress toward individualized care that takes genetic variability into account [3]. The objective in the near term is to employ genetic approaches to better understand and treat cancers. Longer term objectives are to apply individualized molecular approaches to improve management of a wide range of diseases, and cardiovascular disease will likely be among them.

Current state of cardiovascular pharmacogenomics: where are we now?

The cardiovascular drug–gene pairs with the most evidence supporting implementation in clinical practice are clopidogrel and *CYP2C19* genotype; warfarin and both *CYP2C9* and *VKORC1* genotypes; and simvastatin and *SLCO1B1* genotype. CPIC guidelines are available for each of these drug–gene pairs, and a number of institutions are implementing these into clinical practice.

Clopidogrel–*CYP2C19* genotype

Clopidogrel is a prodrug that is metabolized via a two-step process to its active thiol metabolite that is responsible for inhibiting platelet activation and subsequent aggregation. The polymorphic CYP2C19 enzyme is involved in both steps of the process. Individuals with an inherited deficiency of CYP2C19 have reduced plasma concentrations of the active thiol metabolite, decreased inhibition of platelet aggregation and an increased risk for major adverse cardiovascular events, especially after an acute coronary syndrome and percutaneous coronary intervention (PCI) [4]. Poor metabolizers have two nonfunctional *CYP2C19* alleles and no active enzyme, while intermediate metabolizers inherit a single

nonfunctional allele and have reduced enzyme activity. The US FDA-approved clopidogrel labeling was revised in 2010 to include a boxed warning about reduced drug effectiveness in poor metabolizers. The labeling states that genetic testing is available and recommends alternative antiplatelet therapy in poor metabolizers. The CPIC guidelines recommend alternative anti-platelet therapy for poor or intermediate metabolizers who suffer an acute coronary syndrome and undergo PCI [4]. Prasugrel and ticagrelor are alternative agents whose effectiveness is not dependent on *CYP2C19* genotype.

In June 2012, The University of Florida Health Personalized Medicine Program launched *CYP2C19* testing for patients undergoing cardiac catheterization, with the expectation that many of these patients would subsequently undergo PCI and require antiplatelet therapy [5]. Genetic testing was initially paid for by grant support. The genetic test order was later moved to the post-PCI order set when clinical billing was initiated for the genetic testing. *CYP2C19* testing remains on the post-PCI order set today as the standard of care for patients undergoing PCI. A pharmacist reviews all genotyping results and contacts the treating physician for patients with the poor or intermediate metabolizer phenotype to recommend alternative antiplatelet therapy in the absence of any contraindications. An alert appears in the electronic health record (EHR) if clopidogrel is subsequently prescribed for a patient with the poor or intermediate metabolizer phenotype to warn the physician of reduced clopidogrel effectiveness and suggest alternative therapy with prasugrel or ticagrelor. Clinical outcome data, including the occurrence of major adverse cardiovascular events with this approach to antiplatelet therapy, are being collected.

Warfarin–*CYP2C9/VKORC1*

The *CYP2C9* and *VKORC1* genotypes are well recognized as contributors to interpatient variability in the dose of warfarin required for optimal anticoagulation. The *CYP2C9* gene affects *S*-warfarin clearance and plasma levels, and *VKORC1* genotype influences sensitivity to warfarin. The FDA-approved warfarin labeling recommends a lower starting dose for individuals with a *CYP2C9* or *VKORC1* genotype associated with reduced warfarin clearance or increased sensitivity, respectively. Pharmacogenomic dosing algorithms that incorporate both genotype and clinical data (e.g., age, body size, amiodar-one use) are available to assist with warfarin dosing, and CPIC guidelines recommend dosing warfarin via a pharmacogenomic algorithm when genotype results are available [6].

In order to more appropriately dose warfarin and prevent serious adverse consequences with inappropriate dosing, genotype-guided warfarin dosing became the standard of care at the University of Illinois Hospital and Health Sciences System (UI Health) in August 2012 [7]. Each new warfarin order for a hospitalized patient without a recent history of warfarin use triggered an automatic order for genotyping and consultation with the pharmacogenomics service. Electronic decision support was created to calculate an initial warfarin dose based on patient-specific clinical factors, which appears in an alert to the clinician at the time of the initial warfarin order. Genotype results were targeted to be available prior to the second warfarin dose, at which time the pharmacogenomics service provided a genotype-guided dose recommendation. The service continued to provide a daily dose recommendation, refined based on international normalized ratio (INR) response to previous doses, until the

patient reached a therapeutic INR or was discharged. Initial outcomes with the service were presented at the 2014 American Heart Association Scientific Sessions [8]. Compared with historical controls, individuals receiving genotype-guided warfarin dosing required less time to achieve a therapeutic INR value, had a lower incidence of sub- and supra-therapeutic INR values, were more likely to have a therapeutic INR at the time of hospital discharge, and had a shorter duration of low molecular weight heparin use.

In late 2013, two clinical trials examining the efficacy of genotype-guided warfarin dosing were published. EU-PACT trial was conducted in a homogenous European population and showed greater time spent in the therapeutic INR range with genotype-guided dosing compared with standard dosing [9]. The COAG trial was conducted in an ethnically diverse cohort and showed no difference in time spent in the therapeutic range with pharmacogenomic versus clinical dosing [10]. African–Americans made up 28% of the COAG trial population and were more likely to be overdosed with the pharmacogenomic approach.

The disparate fndings between the two trials led many clinicians to question the utility of pharmacogenomic dosing. The higher incidence of supra-therapeutic anticoagulation in African–Americans was especially concerning. Both the EU-PACT and COAG trials limited genotyping to the *CYP2C9*2, *3* and *VKORC1*– 1639G>A variants. These are the most common variants affecting warfarin dose requirements in Europeans but not African–Americans. Other genotypes occur commonly (e.g., *CYP2C9*8* and rs12777823) or almost exclusively (e.g., *CYP2C9*5, *6, *11*) in African–Americans and lead to significantly lower dose requirements. Recent evidence shows that failure to account for these variants causes significant overdosing of warfarin in African–Americans, thus providing a likely explanation for the COAG trial results in this ethnic group [11].

In response to the COAG trial findings, genotype-guided dosing is no longer the standard of care at UI Health. However, genotyping remains optional and is still ordered in approximately 50% of eligible patients (personal communication). The pharmacogenomics service continues to provide dosing recommendations to all patients, with recommendation based on clinical factors alone in those without a genotype order. This model provides a unique opportunity to compare anticoagulation-related outcomes between patients receiving genotype-guided dosing and contemporary controls receiving clinically based dosing.

Simvastatin–*SLCO1B1*

Myopathy is the most common side effect with statin therapy, with symptoms ranging from mild myalgias to life-threatening rhabdomyolysis. Risk factors for myopathy include higher statin doses, concomitant use of medications that inhibit statin metabolism or clearance, renal or hepatic dysfunction and *SLCO1B1* genotype. The *SLCO1B1* gene encodes the organic anion transporting polypeptide 1B1, which transports most statins to the liver. The c. 521T>C (p.Val174Ala) polymorphism is associated with statin-induced myopathy. The genetic association data are strongest with simvastatin, which is the focus of the CPIC guidelines [12]. In patients with the 521CT or CC genotype, the guidelines recommend using a lower simvastatin dose (e.g., 20 mg) or an alternative statin (e.g., pravastatin or

rosuvastatin), with consideration of routine creatinine kinase monitoring if simvastatin is used.

Vanderbilt University has implemented *SLCO1B1* genotyping into clinical practice [13]. Patients who have risk factors for cardiovascular disease or who may need future statin therapy are genotyped for *SLCO1B1* 521T>C, with results are placed in the EHR. If simvastatin is later ordered for a patient with the CT or CC genotype, an electronic alert appears to warn about the increased risk for myopathy.

Future of cardiovascular pharmacogenomics: where are we going?

Realizing a future vision in which patient outcomes are optimized through integration of pharmacogenomic data into cardiovascular care will require a multidimensional approach that addresses needs in practice, research and education.

Future practice

There are currently two approaches to genotyping that are used clinically: reactive (i.e., at the point of care) and preemptive (i.e., test results obtained for future use). The approaches to genotype-guided warfarin and clopidogrel dosing at UI Health and The University of Florida Health, respectively, are reactive in that genotyping is done in response to a drug order. In the current payment landscape, a reactive genotyping approach increases the likelihood of insurance reimbursement since genotyping can be linked to a current diagnosis for a defined patient and provider population [14] However, this approach requires significant technical time to process the genotype efficiently so that results are available early in the course of therapy. In addition, reactive genotyping is generally confined to variants affecting the drug of interest. Over time, repeated reactive testing for individual drug–gene variants quickly becomes relatively more costly than processing a single sample in a broader preemptive array, especially as broader preemptive testing approaches continue to decrease in cost.

The approach at Vanderbilt University is preemptive, with genotyping done in advance of the patient being prescribed simvastatin. There are a number of advantages with preemptive genotyping, including the availability of genetic test results in the EHR at the time of drug prescribing; the ability to batch samples to run at one time, improving the efficiency of genotyping (and therefore decreasing the cost per genotype) and the opportunity to simultaneously test for multiple genetic variants at once which may have implications for many different medications that a patient may be prescribed in the future. However, array-based preemptive genotyping is initially associated with increased costs and limited third-party reimbursement in the current payment landscape [14]. Should reimbursement strategies and/or rates for preemptive testing change, it would significantly affect the landscape for pharmacogenomic implementation.

Future research

Despite significant strides in pharmacogenomic research, there remains a paucity of data for minority populations, which could significantly hinder progress in the field as illustrated

with the warfarin pharmacogenomic studies. Important data on warfarin pharmacogenomics in African– Americans emerged after the COAG trial was initiated. Data are still lacking for other minority populations, including Hispanics. Yet, based on the COAG trial results, many have concluded that genotype-guided warfarin dosing is of limited clinical utility even though genotype-guided dosing that takes into account variants important for different minority groups has not been evaluated outside of the UI Health example above. For pharmacogenomics to benefit all populations, further research in minorities is needed.

Additionally, randomized, controlled clinical trial data are appropriately considered the gold standard for establishing clinical utility of medical interventions. These data guide most drug therapy decisions in cardiology, and there has been a demand for such data to support pharmacogenomic implementation. However, few randomized clinical trial data exist in this area, especially with clinical outcomes as a primary end point, and it may be unrealistic to expect such data. Pharmacogenomics, by definition, benefits a small portion of the population that is at risk for nonresponse or adverse effects due to the presence of one or more specific genetic variants. Most patients have a genotype associated with ‘good’ response to drug therapy. Clinical trial data supporting a ‘good’ response in most patients form the foundation of each drug's approval by the FDA without the use of a companion genetic test. It is the subset of the population with a variant genotype that stands to benefit clinically from pharmacogenomic testing. However, in order to detect a meaningful difference in clinical outcomes with population-based pharmacogenomic testing, a very large number of patients would need to be enrolled, which may be financially and logistically unrealistic. On the other hand, the cost of genotyping is comparable with many other tests routinely and often repeatedly ordered in clinical practice. Thus, clinicians and third-party payers will need to consider whether clinical trial data are truly needed to justify ordering a genetic test that provides a lifetime result and could identify someone at high risk for nonresponse, adverse effects and/or costly consequences with usual therapy.

Future education

Current evidence supports the need for concerted educational efforts among a variety of constituencies to translate emerging pharmacogenomic research findings into meaningful changes in clinical practice. Although clinician education competencies exist for pharmacogenomics and genomic medicine, they overwhelmingly emphasize awareness and knowledge of pharmacogenomic information, rather than how to apply these data clinically. Accordingly, although clinicians agree that genetic variability can influence drug response, most providers do not feel adequately knowledgeable, informed or equipped to make drug therapy choices that incorporate these data [15]. Traditional didactic lecture formats have shown limited benefit in improving practitioner understanding and knowledge retention of clinical pharmacogenomic information [16].

A future approach to provider education in pharmacogenomics and genomic medicine education must address these needs. Educational strategies that address practical needs such as the clinical value of pharmacogenomic testing, EHR integration of test results and reimbursement of testing will be essential in translating pharmacogenomic science to practice [17]. Innovative educational approaches such as applying personal genotype data to

clinical case scenarios and using flipped classroom and team-based learning models to support practitioner education have been explored and should be expanded [18,19]. Additionally, electronic or other tools that support point-of-care education and clinical use of pharmacogenomic and genomic data are needed for clinicians [15]. NIH has taken important steps in supporting development and increased awareness of such educational resources through establishment and support of the Inter-Society Coordinating Committee for Practitioner Education in Genomics and the Genetics and Genomics Competency Center [20]. The Institute of Medicine has also recently addressed these significant needs through a series of national workshops to identify best practices and pragmatic approaches to support practitioner education in genomics. Continued stakeholder involvement and multidisciplinary efforts will be needed to explore, document and disseminate innovative and effective educational strategies in pharmacogenomics.

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