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PERSONALIZED MEDICINE: EXAMINING THE CURRENT AND FUTURE APPLICATIONS OF PHARMACOGENETICS AND PHARMACOGENOMICS

by

SWARNA VEERAMANI

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Approved by

First Reader _____

Gwynneth Offner, Ph.D.
Associate Professor of Medicine

Second Reader _____

Carl Franzblau, Ph.D.
Professor of Biochemistry

PERSONALIZED MEDICINE: EXAMINING THE CURRENT AND FUTURE APPLICATIONS OF PHARMACOGENETICS

SWARNA VEERAMANI

ABSTRACT

There have been many scientific developments in the last century including the atomic bomb and DNA sequencing. Moreover, when human genome was sequenced in the early 2000s, it opened a new avenue to study disease and human development. Genetic tests have become an integral part for cancer diagnosis. Still, cancer therapy is decided based on the tumor genotype, the very definition of pharmacogenetic testing. More specifically, pharmacogenetics or pharmacogenomics is defined as variations in genes that can affect drug response. There has been great deal of research into pharmacogenetics and its potential fields for application. One such field is cardiology and cardiovascular disease. There are some promising researches that indicate genetic influence over drug response, such as the role of CYP2C19 over metabolism of a drug used for treating acute coronary disease and other cardiovascular issues. This is a great tool in the transition toward personalized medicine; however there are some logistical and social concerns over genetic tests; test administration, result accuracy and validity, data storage and security. Also, many patients were concerned with confidentiality, payment method and timely intervention. Also, implementation plans should include all areas, not just cities. Although there is potential for pharmacogenetic testing, many challenges have to be considered and addressed to ensure public confidence and proper use of the technique. Pharmacogenetics is a step towards individualized or

personalized medicine; in-depth research prior to implementation will help tackle any challenges that may arise.

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LIST OF ABBREVIATIONS

AFIJI.....Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention

ARG.....Arginine

BP.....Blood Pressure

COX-1.....Cyclooxygenase-1

CSKT.....Confederated Salish and Kootenai Tribes

DNA.....Deoxyribonucleic acid

FAST-MI.....French Registry of Acute ST-Elevation and Non-ST- Elevation Myocardial Infarction

FDA.....Food and Drug Administration

GLN.....Glutamine

GLU.....Glutamate

GLY.....Glycine

HLA.....Human Leukocyte Antigen

HR.....Heart Rate

IT.....Information Technology

IVF.....In-Vitro Fertilization

LDL.....Low Density Lipoprotein

LEU.....Leucine

MHC.....Major Histocompatibility Complex

MI.....Myocardial Infarction

MTM.....Medicine Therapy Management

NAT2.....N-acetyltransferase-2

PCI.....Percutaneous Coronary Intervention

PPI.....Proton Pump Inhibitor

SER.....Serine

SNP.....Single Nucleotide Polymorphism

TRP.....Tryptophan

INTRODUCTION

Among the many developments in the biological sciences in the last century, the ability to sequence DNA is arguably the most profound breakthrough (Sanger et.al, 1977). Sanger's initial work, sequencing the DNA of a bacteriophage, paved the way for sequencing the human genome in the early 2000s (Sanger et.al.1977; Int'l HGS Consortium 2004). A compilation of genome sequences, especially DNA sequences differentiating normal and cancer cells has been discovered through the help of Sanger sequencing and other modern sequencing techniques (Hood and Rowen, 2013).

In recent years, genome sequencing has become an integral part of research. However, the transition to application in medicine is slow. In a review by Hood and Rowen, they mention key research developments that can help advance patient care. For example, the article mentions there are variants in 70 genes that account for rate of clearance of drug from the body (Hood and Rowen, 2013). Moreover, databases of gene variants associated with disease have been created (Hood and Rowen, 2013). The data available through sequencing and other molecular techniques had created a need for a new way to categorize this information. To address this challenge, the U.S. National Academies published the National Research Council report (Toward Precision Medicine, 2011). The report highlights many scientific discoveries and developments to justify creating a new category (Toward Precision Medicine, 2011). As part of the report, the council defines the term "precision medicine" as choosing a patient population that has a common factor for diseases which would benefit from a particular treatment (Toward Precision Medicine, 2011). The report postulates that use of this new categorization

would help gain a deeper understanding of the biology of diseases in addition to sign and symptoms in patients (Toward Precision Medicine, 2011). In short, sorting the research discoveries under precision medicine provides a new avenue or perspective in treating diseases.

As stated earlier, research in academia and industry has accumulated a wealth of knowledge about various normal and disease states. However, a clear way to implement the information is yet to be determined. Many aspects have to be considered such as finances, effective way to implement the techniques to routine medicine, etc. In an editorial Dr. Desmond-Hellman has stated that it only costs $1000 to sequence a genome in a day (Desmond-Hellman, 2012). As advanced sequencing techniques emerge, there is no doubt that the money and time to sequence any genome, including the human genome, would be a fraction of the numbers today. Soon, sequencing genomes and other techniques have the potential to become common tests in normal practice such as checking blood counts or vitamin levels during a physical. These techniques would greatly improve patient care as well as help further knowledge about diseases and human physiology (Figure 1).

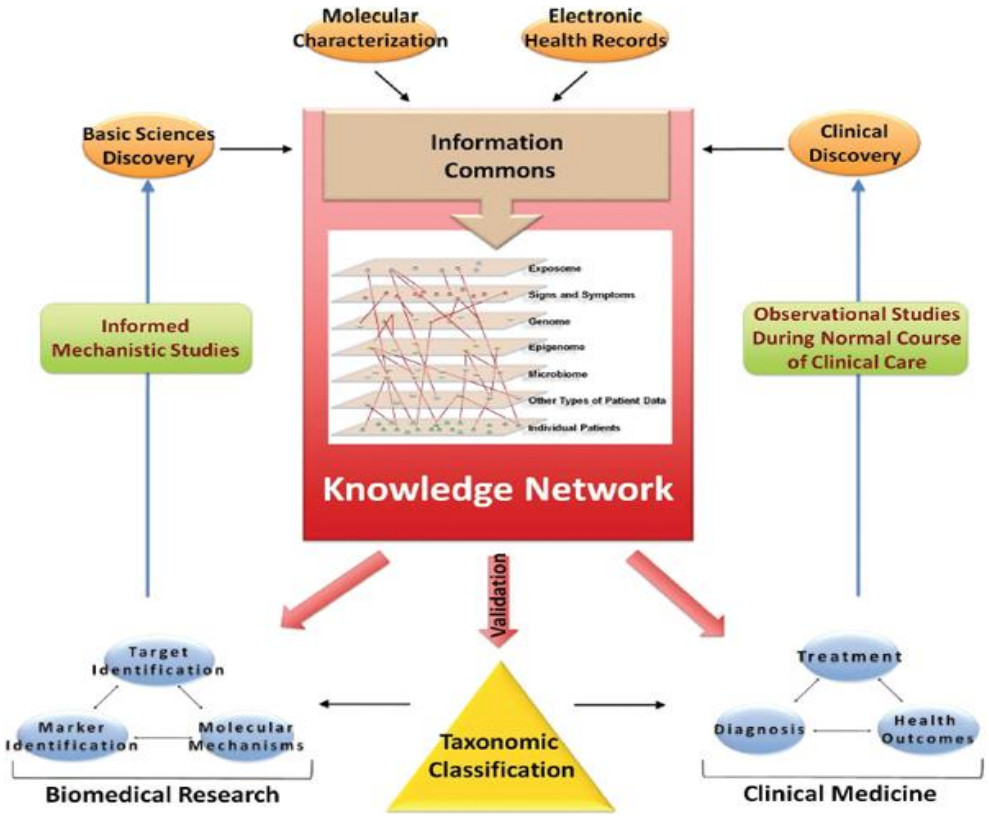

Figure 1. Flow chart displaying connection between biomedical research and clinical medicine. (reproduced Toward Precision Medicine 2011)

SPECIFIC AIMS

The goal of this paper is to assess various aspects of research, clinical trials and clinical medicine to determine the future status of pharmacogenetics as a form of precision or personalized medicine. The various aspects include validity of results from research and clinical trials; feasibility of implementation the technique and public concerns present in practice of medicine.

LITERATURE REVIEW

The implementation of Pharmacogenetics can be very valuable in the practice of medicine. The laboratory techniques used to determine a genetic impact on a patient's reaction to medicine can help physicians develop a better treatment regiment for their patients; one with minimal side effects. There is a wealth of information about this branch of pharmacology in the literature and more to come. In order to gain a deeper understanding of Pharmacogenetics and develop a method of implementation in everyday medical practice, a few things must be considered: What are the specific benefits of Pharmacogenetics?, Is this technology ready to be used in a clinical setting?, Are there any gaps in our knowledge?, How to implement Pharmacogenetics in clinics?, and Public response and concerns to this novel idea.

Benefits of Implementation:

Pharmacogenetics or in more broad terms pharmacogenomics, arose from a genome-wide analysis that has given the ability to find potential drug reactions in patients treated for a particular disorder (Wang, et.al, 2011). For example, through the use of pharmacogenomics, it was determined that hypersensitivity to the drug carbamazepine, an anticonvulsant, in patients of European descent is associated with HLA allele (McCormack, et.al, 2011). Based on genomic studies, the FDA has changed drug label requirements to include pharmacogenomic variations that could affect drug response, emphasizing the need for further research into genomics and implementation of genomic studies in a clinical setting (Wang, et. al, 2011).

Most, if not all, branches of medicine can benefit from pharmacogenomics. In particular, cancer diagnosis and treatment has greatly benefitted from pharmacogenomics. Pharmacogenomics helped determine the difference in normal and tumor genomes (Wang, et.al, 2011). This genomic difference has altered the treatment regiment for certain types of cancers. For example, researchers determined that response to trastuzumab in breast cancer patients with HER2 heightened expression of the protein (Slamon, et.al, 2001). Another example would be the increase survival rate of melanoma patients, with a mutated serine-threonine kinase, when treated with an inhibitor specific for that mutation (Flaherty, et.al, 2010).

Another such area of medicine that has been revolutionized through pharmacogenetics is the treatment of infectious diseases (Wang, et.al, 2011). In some cases, patients might be sensitive to certain medications or suffer adverse side effects; genome-wide studies were helpful in finding associations between the medication and side effect. For example, the antibiotic floxacillin, used to treat staphylococcal infections, is associated with a rare form of hepatotoxicity known as cholestatic hepatitis (Daly, et.al, 2009). In an association study, it was determined that the single nucleotide polymorphism in the MHC complex is associated with the liver side effect (Daly, et.al, 2009). This study is an indication of further research into this antibiotic and shows another potential reason for implementation of genetic testing prior to starting a regiment.

Apart from the field of oncology and infectious diseases, another area in medicine has become the focus of pharmacogenomics. In recent research, cardiovascular drugs are the focus of many pharmacogenomic research studies. Common cardiovascular

medications, such as warfarin and clopidogrel have the focus of pharmacogenomic research due to their narrow therapeutic indexes (Wang, et.al, 2011). The FDA has altered the drug label of these medications in light of the knowledge gained in genomic studies (Wang, et. al, 2011).

Recent research shows that treatment of cardiovascular diseases would greatly benefit from the implementation of genetic testing prior to prescription. Through modern sequencing abilities, genetic testing for detection of inherited disorders is now part of the routine (George, 2014). There are three time/situational points for requiring a genetic test for cardiovascular problems; diagnositic, presymptomatic or postmortem. More specifically, diagnostic tests are used to screen an array of genes known to be associated with a specific disease, presymptomatic testing is more targeted toward a specific variation due to familial presence of a disease, such as familial cardiomyopathies, and postmortem testing is used to determine the reason for the cardiac outcome (George, 2014). Also, genetic testing in embryos during IVF procedure has shown success in diagnosing certain cardiovascular diseases (George, 2014)

There are many drugs that are prescribed for cardiovascular disease and each treatment involves a trial and error to determine the effective dosage, sometimes with severe side effects (O'Donnell and Sorrentino, 2015). Clopidogrel, an anticoagulant commonly used to treat certain coronary disease, is shown to have no effect in roughly half of the patients in clinical studies (O'Donnell and Sorrentino, 2015). It is suggested that the variation in drug response could be caused by variations in the formation of the metabolite, since clopidogrel is administered as a prodrug, a drug that is converted in the

body to an active drug (O'Donnell and Sorrentino, 2015). Clopidogrel is converted to its active form in the liver by CYP2C19, an enzyme in the cytochrome P450 family (O'Donnell and Sorrentino, 2015). Through research, it is suggested that the lack of response to the medication could be due to a mutation in the gene coding CYP2C19 that results in a defunct enzyme (O'Donnell and Sorrentino, 2015). If this information is known prior to treatment, alternatives can be prescribed without trying this medication. More specifically, there are two medications, prasugrel and ticagrelor, that target the same entity in the body as clopidogrel and are shown to reduce cardiac events (O'Donnell and Sorrentino, 2015).

Similarly, pharmacogenetics could help determine efficacy of a drug in a population based on patient genotype. An example that illustrates this point is the use of beta blockers to treat hypertension. It is shown that variations in a G-protein coupled receptor, GRK4, in African Americans results in a lower response to metoprolol (O'Donnell and Sorrentino, 2015). Also, another study by The Pharmacogenomic Evaluation of Antihypertensive Response Trial indicated that a variation in GRK4 results in decreased response to atenolol in both Caucasians and African Americans. Furthermore, variations in other targets and proteins that help clear the medication can affect the efficacy and clearance of beta blockers in patients with hypertension and other cardiac issues (O'Donnell and Sorrentino, 2015).

As life sciences evolved, there have been many great discoveries and developments, from discovery of DNA as the genetic material to sequencing DNA. As we now usher in the age of precision or personalized medicine, such as targeted

treatments used for cancer therapy, we are branching to other areas of medicine, especially cardiology and cardiovascular disease. The transition to individualized medicine will happen slowly, as new information gathered and validated and arm physicians and patients with the knowledge required for determining the best course for treatment.

Pharmacogenetics in Cardiovascular Disease Treatment:

The benefits to implementing pharmacogenetic testing becoming a routine in clinical practice are numerous, even though the research for this field is still at its infancy. The area of medicine that has greatly benefited from genotyping is cancer, which has helped to specify the treatment for the specific cancer in a specific patient. However, one will not immediately think that cardiology would benefit from genetic testing, apart from fetal testing to determine potential cardiovascular risk.

Although treatment of cancer has been revolutionized by genetic testing, other areas of medicine could benefit from genetic data. When discussing pharmacogenetics, variability of a drug response in various patients indicates the possibility of a genetic factor affecting the drug reaction (Voora and Ginsburg, 2012). More specifically, a genetic test is recommended when family members react similarly to a medication or if there is a drastic difference in drug response across ethnic groups for a particular drug (Voora and Ginsburg, 2012). Genetic influence can be determined through two approaches; a targeted screening or genome-wide. Targeted screening refers to the testing for a known gene or a set of genes that could affect drug metabolism or effect, while a genome-wide screening looks for potential candidates (Voora and Ginsburg, 2012). The

genetic screening might reveal variations that are categorized into affecting pharmacokinetics, pharmacodynamics or part of a disease mechanism (Voora and Ginsburg, 2012). Through further research, the genetic variations determined through screening might be the reason behind the varied drug response in patients. Many drugs used to treat cardiovascular diseases have been the subject of much research including statins, thienopyridins and diuretics.

Research has revealed many genetic markers associated with these drug classes and potential clinical implications. Statins are used for cholesterol reduction; they have four effects in the body: reduce LDL, prevent cardiovascular incidents, musculoskeletal side effect and adherence to the medication (Voora and Ginsburg, 2012). Statins lower LDL levels by affecting targets of *HGMCR* and APOE genes (Voora and Ginsburg, 2012). A low frequency variation in *HGMCR*, that produces a protein that is resistant to pravastatin and simvastatin, only lowering LDL levels by 5% to 20%, while research on other statins is still underway (Chasman, et.al, 2004; Krauss, et.al, 2008; Voora and Ginsburg, 2012). There are two variants of *APOE* that give rise to three different haplotypes that have great influence on a patients' response to statins (Voora and Ginsburg, 2012). It has been established that the haplotype designated ε2 confers the greatest advantage in lowering LDL through statins. Also, it is determined that the effect is consistent with all types of statins, even if the reduction in LDL is only modest, <15% (Voora and Ginsburg, 2012). Although other genes could influence statin effects, HGMCR and APOE proteins play a significant role in LDL reduction and decrease in cardiovascular events.

Although statins are relatively safe, there is a minor risk of having musculoskeletal side effects. More specifically, genetic variations in a liver transporter gene, *SLCO1B1*, have an effect on the risk of adverse effects (Voora and Ginsburg, 2012). A particular variation, designated as *5, leads to a transporter protein with improper localization sequences that prevents the transporter from reaching the plasma membrane, resulting in decreased ability to clear the statin from the body (Voora and Ginsburg, 2012). The effect on *5 variation of *SLCO1B1* depends of the specific statin; the highest risk for myopathy is with simvastatin, followed by atorvastatin and lastly pravastatin and other statins (Link, et.al, 2008; Voora and Ginsburg, 2012). In particular, simvastatin increases the risk of a creatine kinase positive myopathy by four to five folds, and a two to three fold increase in creatine kinase negative myopathy in patients carrying *5 (Voora, et.al, 2009;Voora and Ginsburg, 2012). As a result of this side effect, patients do not adhere to or continue their statin regiment, especially *5 *SLCO1B1* carriers.

Aspirin, widely used for pain management and fever reduction, is also used to treat certain cardiovascular issues. Aspirin targets the prostaglandin G/H synthase (COX-1), irreversibly inhibiting the enzyme, and also inhibits the conversion of arachidonic acid to thromboxane (Voora and Ginsburg, 2012). Aspirin is a good candidate for pharmacogenetic studies because of interpersonal variability that is heritable and high dosage of aspirin could lead to cardiovascular events (Voora and Ginsburg, 2012). Since, aspirin binds to COX-1 indiscriminately; the pharmacogenetic research is focused on platelet function (Voora and Ginsburg, 2012). There are many platelet associated genes that affect platelet function in the presence of aspirin; however two genes in particular are

noteworthy. A variation in *ITGB3* and *PEAR1* increases platelet function in response to aspirin (Faraday, et.al, 2011; Voora and Ginsburg, 2012). On the other hand, research on *LPA* revealed a protective effect of aspirin on patients. That is, a variation in the non-coding region of the gene elicits a two-fold increase in protection against cardiovascular diseases, when carriers are on an aspirin regiment compared to non-carriers (Chasman, et.al, 2009).

One of the most prevalent cardiovascular issues is hypertension, with many patients taking one or more medications to maintain their blood pressure at near normal levels. A diuretic is used to reduce the volume of fluid in the body through urine. There is a specific gene that is associated with fluid levels. The gene adducin 1 alpha (*ADD1*) is shown to be involved in adjusting sodium levels (Cusi, et.al, 1997). A mutation in this gene that alters the amino acid glycine to tryptophan in a specific position (Gly460Trp) renders the protein more sensitive to sodium levels in the body, and augments the effects of using a class of diuretics named thiazides to reduce blood pressure to ideal levels (Cusi, et.al, 1997). Furthermore, in some cases, it is shown that thiazides could offer the highest protection from heart attacks and stroke in Trp460 carriers versus Gly460 carriers (Psaty, et.al, 2002).

Another class of medications used to treat hypertension and other cardiac issues are beta blockers. Beta blockers inhibit the beta-adrenergic receptor, coded by *ADBR1*, which results in changes to heart rate (HR), blood pressure (BP) and other responses to prevent heart attacks, heart failures and death (Voora and Ginsburg, 2012). The patient's response to beta blockers is affected by *CYP2D6*, *ADBR1*, *ADBR2* and *GRK5* (Voora and

Ginsburg, 2012). The beta blocker metoprolol is metabolized by CYP26D; there is a mutation, *CYP2D6*4* that decreases the activity of the protein, resulting in longer exposure to the medication, increases the effects (Voora and Ginsburg, 2012). There are two variations in the *ADBR1*that changes Ser49Gly and Arg389Gly; carriers of Arg389 greatly benefit from metoprolol, with the highest HR and BP reduction compared to Gly389 (Liu, et.al, 2003). Moreover, patients with systolic or left ventricular heart failure showed improvements in left ventricular function when treated with either metoprolol or carvedilol and are carriers for Arg389 compared to carriers with Gly389 (Perez, et.al, 2003; Voora and Ginsburg, 2012). On the other hand, homozygous carries of Arg389 did not benefit from treatment with bucindolol and resulted in re-hospitalization or even death (Voora and Ginsburg, 2012). Also, patients with chronic coronary artery disease who are treated with verapamil and are Ser389/Arg389 heterozygotes had a poor prognosis, 9 versus 2 fold risk, compared to patients with the same genotype treated with atenolol (Voora and Ginsburg, 2012). Similarly, there are two variants in the other beta-adrenergic receptor (*ADBR2*), Arg16Gly and Glu27Gln, that indicate acute coronary syndrome patients (ACS) patients who are homozygous carriers of both Arg16 and Glu27 have a increased risk of death compared to Gly16 and Gln27. Lastly, *GRK5* variation that leads to Glu41Leu was shown to be sensitive to beta-blockers in mouse models; however there was such indication in humans (Voora and Ginsburg, 2012). Furthermore, one study has shown better recovery for patients with Leu41 compared to Glu41; further research can help gain more information about this variation (Voora and Ginsburg, 2012). In summary, patients with Arg389 have great decreases in HR and BP, improved heart

function and overall survival on beta blockers and use of other beta blockers instead of metoprolol in *CYP2D6*4* carriers would prevent adverse events associated with metoprolol over exposure (Voora and Ginsburg, 2012).

Arrhythmias are irregular heartbeats. Many drugs, such as digoxin and calcium channel blockers are used to prevent cardiac events (Voora and Ginsburg, 2012). There has been research done on *ABCB1* encoded receptors, which are targets for medications such as verapamil, diltiazem and digoxin, however, variations in the receptor have not been shown to have any clinical significance (Voora and Ginsburg, 2012). Yet, there are two medications that show promise and require further research. Procainamide is metabolized in the liver via acetylation (Voora and Ginsburg, 2012). There are four particular variants that reduce the activity of a specific acetyltransferase, NAT2, leading to slower conversion of the drug into a metabolite and inducing autoantibody production (Voora and Ginsburg, 2012). The second medication alluded to earlier is propafenone. This medication is also metabolized in the liver by CYP2D6 and the variation discussed above, *CYP2D6*4*, lowers the amount of drug cleared from the body (Voora and Ginsburg, 2012). The CYP2D6 gene mutation has both positive and negative effects. Carriers of *CYP2D6*4* treated with low doses of propafenone have the highest reduction of HR due to exercise or other stresses; however there is no such effect with higher doses of the drug (Voora and Ginsburg, 2012). Also, this mutation is shown to augment the ability of the drug to reduce both atrial and ventricular arrhythmias in some studies (Voora and Ginsburg, 2012). A huge draw back to the use of the drug in carriers of the

mutation is central nervous system toxicity and excessive target inhibition that results from high propafenone in the system (Voora and Ginsburg, 2012).

So far, hypertension, cholesterol and antiarrhythmia drugs were discussed. Still, there are two medications that have been extensively studied; Clopidogrel and Warfarin. Clopidogrel is a thienopyridine that is used to prevent stent thrombosis, heart attack or death in patients suffering from acute coronary syndrome; especially patients who have had percutaneous coronary intervention (Voora and Ginsburg, 2012). Clopidogrel is an ideal candidate for pharmacogenetic research due to the variability in affecting platelet function, which a trait shown to be heritable and the efficacy of the drug could predict future cardiovascular incident (Voora and Ginsburg, 2012). Two genes that affect the response to clopidogrel treatment are *CYP2C19* and *ABCB1* (Voora and Ginsburg, 2012). The first gene mentioned above, *CYP2C19*, is a liver enzyme that converts the medication into an active metabolite that will interact with its target, P2RY12 (Voora and Ginsburg, 2012). There is a specific variant, *CYP2C19*2*, that greatly reduces the enzymes function, which leads to low concentration of the active metabolite of the drug (Voora and Ginsburg, 2012). There is another variant, *CYP2C19*17* also known as ultra metabolizers, that has the opposite effect, resulting in rapid conversion of clopidogrel into its active metabolite; however this increases the risk of bleeding (Voora and Ginsburg, 2012). The *2 carriers are defined based on the number of alleles of this mutation present, or by the activity of the enzyme (Voora and Ginsburg, 2012). Furthermore, the number of alleles affects the level of enzyme inhibition, with carriers of 2 alleles of *2 will be poor metabolizers of clopidogrel and other medications modified by CYP2C19

(Voora and Ginsburg, 2012). To compensate for the diminished enzyme activity, the patient would be prescribed a higher dosage. However, if this information is known prior to treatment, there are alternate medications such as ticlopidine, prasugrel and ticagrelor, which are not affected by CYP2C19 activity (Voora and Ginsburg, 2012). Similarly, ABCB1 also affects the availability of the active drug. This protein is a transporter located in the liver and intestines that absorbs many things including clopidogrel (Voora and Ginsburg). There are three single nucleotide polymorphisms or SNPs and if each of them is a T, that is the haplotype would be T-T-T on both alleles, then the protein would have a reduced activity, leading to low drug concentration in the body (Voora and Ginsburg, 2012). Prasugrel or ticagrelor would be good alternates for this genotype as well since they are not shown to be affected by this genotype (Voora and Ginsburg, 2012). Clopidogrel is a great medication that helps prevent excessive clotting in people prone to acute coronary events and knowing the genotype of the patient would greatly improve patient care.

Another common medication used to control clotting is warfarin. The variability in patient response to warfarin results from three molecular entities: *CYP2C9, VKORC1* and *CYP4F2*. The first gene, *CYP2C9*, is responsible for drug clearance from the body. More specifically, the enzyme CYP2C9 is responsible for clearing an active form of the drug, the S-warfarin (Voora and Ginsburg, 2012). There are two variations of the gene, *CYP2C9*2* and *CYP2C9*3*, that produces an enzyme with low activity. Specifically, *3 variant reduces the drug clearance by 90%, whereas *2 only decreases the clearance by 30% (Voora and Ginsburg, 2012). This wide range results in dose decreases by 19-33%

per allele (Voora and Ginsburg, 2012). The second gene, *VKORC1* or vitamin K epoxide reductase complex subunit 1, is the target protein for warfarin (Voora and Ginsburg, 2012). There are two haplotypes, A and B, which affect the gene expression and therefore the dose of warfarin for the patient (Voora and Ginsburg, 2012). In particular, the A haplotype is located in the promoter region of the gene and reduces gene expression; this warrants a 30% lower dose of warfarin for each A allele present (Voora and Ginsburg, 2012). Lastly, a variation of *CYP4F2* leads to low levels of CYP4F2 in the liver resulting in higher vitamin K levels and higher warfarin dose to decrease the vitamin K levels (Voora and Ginsburg, 2012). In short, the variants of all three genes above increase a patient's risk of having a high INR, with values greater than 4.0, or even delay the response to warfarin (Voora and Ginsburg, 2012). More specifically, carriers of either variant in *CYP2C9* increase the risk of bleeding (Voora and Ginsburg, 2012).

There have been many studies comparing the effectiveness of clopidogrel and its alternatives. One such study investigated the effect of *CYP2C19* on drug response in patients treated with clopidogrel or ticagrelor. As mentioned earlier, there is variability in patient responses to clopidogrel, with strong indication toward loss of functions variants of *CYP2C19* (Tantry, et.al, 2010; Voora and Ginsburg, 2012). On the other hand, ticagrelor is a drug that is an active metabolite and does not require enzymatic activation (Tantry, et.al, 2010; Voora and Ginsburg, 2012).

A study by Tantry, et.al investigated the effect of CYP2C19 genotype on platelet reactivity in patients treated with clopidogrel or ticagrelor as well as comparing platelet reactivity between treatments in patients with specific genotype. This group designed two

studies, ONSET/OFFSET and RESPONSE and enrolled 174 patients in total (Tantry, et.al, 2010). More specifically, 92 of these patients received ticagrelor and the remaining 82 received clopidogrel and all these patients had been genotyped (Tantry, et.al, 2010).

The ONSET/OFFSET was a randomized, double-blinded, parallel-group multicenter study focused on the start and end time effect on platelet reactivity in patients treated with ticagrelor, clopidogrel or placebo for the duration of 6 weeks (Tantry, et.al, 2010). The patients received a starting dose of 180 mg of ticagrelor and 600 mg of clopidogrel or a placebo and maintenance doses of 90mg/day ticagrelor, 75mg/day of clopidogrel or placebo; patients given ticagrelor received a booster of 90 mg 12 hours after the starting dose (Tantry, et. al, 2010). After 6 weeks the patients received a final dose of the drug and monitored for changes after 10 days (Tantry, et.al, 2010). For this ONSET/OFFSET study, blood was drawn prior to loading dose, 8 hours after the loading dose and 8 hours after the last dose 6 weeks later and 10 days after the last dose (Tantry, et.al, 2010).

The RESPOND study is a multicenter, double blinded crossover study that compared platelet reactivity in patients treated with ticagrelor or clopidogrel who were categorized as responsive or nonresponsive to clopidogrel treatment (Tantry, et.al, 2010). These patients were treated with either 600 mg of clopidogrel loading dose followed by 75 mg/day maintenance dose for 2 weeks or 180mg of ticagrelor loading dose followed by 90 mg/day for 2 weeks (Tantry, et.al, 2010). After the two week period, the patients classified as nonresponders switched treatments, while only half of the responders

switched treatments for another 2 week period (Tantry, et.al, 2010). Blood was drawn in similar pattern to the ONSET/OFFSET study (Tantry, et.al, 2010).

The patients who consented for genotyping were screened for the loss-of-functions variants of *CYP2C19*, specifically *CYP2C19*2*, and other variants including *CYP2C19*17*, the gain-of-function variant as well as *ABCB1*variant (Tantry, et.al, 2010). This information was part of the discussion to see whether the data supported the hypotheses. Furthermore, both treatment groups had balanced genotype frequencies with exception of the intermediate metabolizers and the all of the ultrametabolizers in ticagrelor group (Tantry, et.al, 2010). In addition to the genotype frequencies the patient demographics were similar between two groups, except more hypertensive patients were placed in the ticagrelor group.

Given all of these data, the authors made several observations. First, the genotype of the patient did not affect platelet function in patients treated with only aspirin (Tantry, et.al, 2010). Second, they determined that the *ABCB1* genotype did not influence platelet function prior to or during either treatment regiments (Tantry, et.al, 2010). Also, patient treated with ticagrelor had a significantly reduced platelet function compared to patients treated with clopidogrel across all *CYP2C19* genotype, including the ultrafast metabolizers and extensive metabolizers (wild type genotype); however the authors could not validate this result in patients classified as poor metabolizers due to the small number of participants in that group (Tantry, et.al, 2010). Furthermore, there was no indication that patient genotype played a role in platelet function in ticagrelor treatment group after the loading dose or during treatment (Tantry, et.al, 2010). Conversely, the influence of

genotype was seen in the clopidogrel treatment group, with the greatest influence seen during the maintenance dose period of the studies (Tantry, et.al, 2010). That is, patients who have the loss-of-function genotype and who are intermediate metabolizers do not respond to clopidogrel therapy, resulting in high platelet function (Tantry, et.al, 2010). Also as an important observation, the authors mentioned that the platelet function was similar between patients who carried the wild type *CYP2C19* alleles (*1/*1) and patients who are heterozygotes with a gain-of-function allele (*1/*17) (Tantry, et.al, 2010).

Based on these observations the authors surmised that loss-of-function alleles had a higher influence on platelet function in patients treated with clopidogrel compared to patients carrying gain-of-function alleles (Tantry, et.al, 2010). Moreover, the authors cautioned readers by stating that although CYP2C19 is shown to play a significant role in converting clopidogrel, the prodrug, into an active metabolite and other enzymes such as CYP1A2, CYP2B6, CYP2C9 and CYP3A4 are also involved in the "drug activation" process (Tantry, et.al, 2010). Additionally, the authors mentioned that only 12% of the variability in response to clopidogrel could be attributed to *CYP2C19* variants; hence more research into other hepatic enzymes and other factors could reveal a more complete picture (Tantry, et.al, 2010).

Another group, Simon et.al in 2009, designed a study to find genetic influence on response to clopidogrel and cardiovascular events. Their study focused on determining genes that could affect the clinical outcome of patients treated with clopidogrel after suffering an acute myocardial infarction (acute MI). The authors focusing on clopidogrel, since aspirin and clopidogrel combination therapy is the standard treatment to prevent

future atherothrombotic events after an acute MI (Simon, et.al, 2009). The authors designed a study to evaluate the influence of the polymorphisms of *ABCB1*, *CYP3A5*, *CYP2C19*, *P2RY12* and *ITGB3* on clinical outcomes such as ischemic events or death in one year (Simon, et.al, 2009). The study consisted of patients registered in the French Registry of Acute ST-Elevation and Non-ST- Elevation Myocardial Infarction (FAST-MI) from October 1 to December 24, 2005 (Simon, et.al, 2009). The patients were at least 18 years of age who had twice the normal serum levels of creatine kinase, creatine kinase MB, troponin I or troponin T (Simon, et.al, 2009). Moreover, the subjects chosen were admitted to the ICU with 48 hours of symptoms (Simon, et.al, 2009). The patient treatment was not affected by participation in the study; 10ml of blood was drawn from the patients in addition to the amount drawn during admission for genotyping (Simon, et.al, 2009).

The studies consisted of 2430 patients, of whom 2208 were treated with clopidogrel, with an average loading dose of 300 mg/day and an average maintenance dose of 75mg/day (Simon, et.al, 2009). During the one year follow up, 225 patients died and 94 patients suffered for a nonfatal MI or a stroke (Simon, et.al, 2009). Furthermore, the 294 patients who experienced an ischemic event were older patients with certain preexisting conditions such as hypertension, diabetes or heart failure (Simon, et.al, 2009). The authors reported that the allele frequencies of the genes mentioned above were not different between the patient who had a clinical event and those who did not; however the authors did mention that there was a difference in *ABCB1* variant in combination with *CYP2C19* loss-of-function between these two groups (Simon, et.al, 2009). The authors

discovered that variants of *CYP3A5*, *P2RY12* and *ITGB3* did not contribute risk of death, a nonfatal MI or a stroke (Simon, et.al, 2009). Conversely, there was an increase in risk of events in patients with *ABCB1* variant (CT or TT genotype) compared to patients with the wild-type genotype (CC) or having two loss-of-function alleles of *CYP2C19* compared to one or none of those alleles (Simon, et.al, 2009). Furthermore, patients with two alleles with TT variant in *ABCB1*had a higher event rate in one year compared to those with wild type genotype; 15.5% and 10.7%, respectively (Simon, et.al, 2009). Also, patients with two loss-of function alleles of *CYP2C19* had a higher event rate compared to patients with wild type genotype; 21.5% and 13.3% respectively (Simon, et.al, 2009). In accordance with the difference seen when comparing the combined presence of *ABCB1* and loss-of-function allele of *CYP2C19*, one or two *ABCB1* variant alleles and two loss-of-function alleles of *CYP2C19* were associated with high risk of clinical outcome (Simon, et.al, 2009).

Similarly, another group lead by Dr. Simon in 2011, designed a study to investigate clinical outcomes in patients treated with clopidogrel and proton pump inhibitors. The patients were selected based on the criteria mention in the above study and registered in the FAST-MI registry mentioned earlier (Simon, et.al, 2011). There were 3670 patients in the registry and of these patients, 2744 patients were not previously treated with clopidogrel or proton pump inhibitors (PPIs) (Simon, et.al 2011). Moreover, 2353 of 2744 patients received clopidogrel with 48 hours of symptom onset (Simon, et.al, 2011). In these patients treated with clopidogrel, the odd ratio for having a clinical outcome was 0.90 in patients also using PPI compared to non-PPI users (Simon, et.al,

2011). However, this was not associated with a significant increase in risk of in-hospital mortality or one-year mortality in patients with a wild-type *CYP2C19* genotype (Simon, et.al, 2011).

Another study also investigated the influence of *CYP2C19* in young patients treated with clopidogrel after MI. Although MI in patients younger than 45 years is uncommon, it is a series of thrombotic event that is treated with percutaneous coronary intervention (PCI) and antiplatelet therapy (Collet, et.al, 2009). The authors of the paper studied the effect of *CYP2C19*2* on long-term prognosis of the patients on clopidogrel therapy (Collet, et.al, 2009). The study involved 378 patients, between 18 and 45 years of age who survived a MI, registered in the Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention (AFIJI) between April 1, 1996 and April 1, 2008 (Collet, et.al, 2009). Moreover, the patients must have been on clopidogrel regiment, 75 mg/day, for a minimum of one month (Collet, et.al, 2009). Each patient's medical history and vitals were gathered along with blood sample drawn for DNA and other analyses (Collet, et.al, 2009). The patients were contacted every 6 months to collect information on drug treatment and whether or not the patients continued clopidogrel (Collet, et.al, 2009). The blood sample mentioned above was used to determine *CYP2C19* genotype and measure biomarkers such as plasma fibrinogen levels (Collet, et.al, 2009). Of the 259 patients who were on clopidogrel, only 213 patients were continuing the dose until the end of the study (Collet, et.al, 2009). Furthermore, 186 of 259 patients had a homozygous wild type genotype (*1/*1), 64 patients were heterozygotes (*1/*2) and the remaining 9 patients were homozygous for the variant (*2/*2) (Collet, et.al, 2009).

The authors indicated that there were 32 major adverse cardiac events in 26 patients who were on the maintenance dose of clopidogrel, with 6 patients experiencing more than one cardiovascular event; 12 patients suffered from stent thrombosis (Collet, et.al, 2009). The effect of *2 was evident in the early stage of clopidogrel treatment and present throughout the treatment; the primary outcome (MI, death or stroke) occurred in 10 patients with wild type genotype and 9 patients who were *2 carriers (Collet, et.al, 2009). The main risk associated with the *2 variant was the significant increase in the rate of myocardial infarction; along with an increase in stent thrombosis in patients with stents (Collet, et.al, 2009). In summary, the authors concluded that there is a strong correlation between the presence of *2 variant and recurring cardiovascular events in patients treated with clopidogrel; especially patients who are of European descent and survived a MI before the age of 45 (Collet, et.al, 2009).

Implementation of Pharmacogenetic Testing:

Even though the field of pharmacogenetic is still young and requires further research, the feasibility and process of implementing such testing in clinical practice requires its own investigation. The studies to be discussed below list the pros and cons of implementation.

In a review article, the authors researched many studies and compared the costs of pharmacogenetic testing. In this article the authors compared the cost of testing to the year of the test (Berm, et.al, 2016). The authors argue that since genotyping technology is always evolving, so does the cost of testing; for example, the authors listed the cost of genotyping done in studies in 2009, 2010 and 2012, with cost of screening in 2009 and

2010 ranging from US $175-$575 whereas cost of screening in a study done in 2012 was US$72 (Berm, et.al, 2016).

Apart from cost there are other barriers that prevent smooth implementation of pharmacogenetics into clinical practice. One of the major reasons is lack of substantial evidence to support the use of genetic testing for pharmacogenomics (Berm, et.al, 2016). Another reason is the lack of diversity in the sample of patients in their study (Berm, et.al, 2016).

In a review by Haga, et.al, the authors discuss some of the current challenges of pharmacogenetic testing implementation in clinical practice. They divided the challenges into six categories: 1) Timing and Accessibility of Testing, 2) Number of Appointment Sessions, 3) Use of Technology, 4) Training, 5) Standard and 6) Insurance (Haga, et.al, 2015). The challenges with timing are to determine the best time point for a pharmacogenetic testing; prior to starting a particular regiment, or having the information on file obtained when the patient was healthy (Haga, et.al, 2015). When considering access, a pharmacist in a clinic would have quick and easy access to the results from the test and the patient's medical records, while a store pharmacist can only get the information for the patient and have a copy of the results sent over from the physician (Haga, et.al, 2015). However, the authors argue that patients may not be able to remember the results accurately and it would be difficult to have results sent over to a store pharmacist from the physician's office (Haga, et.al, 2015). The authors offer a solution by suggesting the use of a health information exchange (HIE) to share test results between the physician and pharmacist (Haga, et.al, 2015).

The appointment timings are also play a role when discussing pharmacogenetic testing. Typically, an appointment with a pharmacist can last between half hour and one hour (Haga, et.al, 2015). When a pharmacogenetic test is recommended, the appointment has to be extended to explain the details of the test such as purpose, risks, etc (Haga, et.al, 2015). Also, a follow-up appointment would be necessary to explain the results and options available (Haga, et.al, 2015). Recognizing this growing need, there are over-the-phone consultations, however it is still unclear whether it would be a good option for pharmacogenetic testing discussions (Haga, et.al, 2015).

Another challenge with pharmacogenetic implementation is the handling of all the data; that is storing and transferring the information (Haga, et.al, 2015). The field of information technology (IT) can help facilitate data sharing including prescription history and test results (Haga, et.al, 2015). Still, genetic testing results are attached to a patient's health records and not part of the prescription list and related tools; the information can be entered manually into the system, but this information might not be available in other locations of the same franchise of a community pharmacy (Haga, et.al, 2015). The authors suggest research into a potential tool into integrate all aspects of patient's record into one system, so that medical records and prescription list are in one place (Haga, et.al, 2015).

In addition to challenges with patient records, pharmacists lack training for pharmacogenetic testing (Haga, et.al, 2015). The Accreditation Council for Pharmacy Education mandates that colleges and pharmacy schools provide fundamental training in medicine therapy management (MTM) (Haga, et.al, 2015). In order to order and explain

pharmacogenetic tests, pharmacists need advanced training (Haga, et.al, 2015). Also, physicians, physician assistants and nurses also need training to understand pharmacogenetics and decide when to use it (Haga, et.al, 2015). Defining standards for implementing pharmacogenetic testing into treatment management is an extension of training. The standards have to define the information to be communicated prior to testing and the proper method to discuss test results with patients (Haga, et.al, 2015). Also included in standards is defining liability for pharmacists to include genetic testing (Haga, et.al, 2015).

The last of the challenges laid out by the authors is reimbursement (Haga, et.al, 2015). The billing for the services can vary based on the scenario; for example, in urgent care clinics, the bill maybe filed as an incident-to-physician care charge (Haga, et.al, 2015). In other cases, the pharmacist may bill directly for the services rendered (Haga, et.al, 2015). Also, payer fee schedules and insurance reimbursement rates further complicate the issue (Haga, et.al, 2015). Since inclusion of pharmacogenetic testing increases the service provided by a pharmacist, insurance plans need to broaden medication plan to include proper reimbursement for pharmacists (Haga, et.al, 2015).

Apart from the science and the feasibility challenge of integrating pharmacogenetic testing into clinical practice, a great challenge involves updating insurance plans to accommodate the evolving field of medicine. When a pharmacogenetic testing is ordered, the bill will be sent by the laboratory company; however a pharmacist requires training to address such concerns with patients (O'Connor, Ferreri and Michaels, 2015). In general, Medicaid does not reimburse for pharmacogenomic testing (O'Connor,

Ferreri and Michaels, 2015). Medicare part B does reimburse of pharmacogenetic testing with a co-pay paid by patients (O'Connor, Ferreri and Michaels, 2015). On the other hand, private insurance companies' response to pharmacogenetic testing varies based on individual plans, ranging from no coverage to complete coverage (O'Connor, Ferreri and Michaels, 2015). However, people who have a health savings account (HSA) can use the money from that account to cover the test if their insurance does not cover the test (O'Connor, Ferreri and Michaels, 2015). Also, contacting the testing company about payment information can help patients with low coverage (O'Connor, Ferreri and Michaels, 2015).

There have been clinical studies that explore the feasibility of implementing pharmacogenetic testing for primary care. One such study is by Haga, et.al where the authors explore the role of pharmacists in test administration. The study design involves two models where the pharmacogenetic testing is either ordered by the physician or the pharmacist and physicians and patients were surveyed at two time points in the study (Haga, et.al, 2014). The study was conducted in two clinics part of Duke University in Durham, NC (Haga, et.al, 2014). The patients in the study were placed in two categories based on who asked for the genetic test; 24,000 patients in the pharmacist recommended group and 21,000 patients in the physician recommended group (Haga, et.al, 2014). Furthermore, the patient population was diverse age, sex, race and even payment method (Haga, et.al, 2014). Also, patients were prescribed medications such as warfarin, metoprolol, clopidogrel and simvastatin that have been shown to be influenced by genetic variations (Haga, et.al, 2014). Through the patient and physician surveys the authors

evaluated four factors; effectiveness of the delivery models on physician attitude toward pharmacogenetic testing orders and prescription changes, physician knowledge, attitude, opinion and use of pharmacogenetic testing, patient behavior toward pharmacogenetic testing through adherence to medicine, awareness of side effects and willingness to learn about their treatment, and costs associated with each model group and medications(Haga, et.al, 2014).

For three of the factors analyzed, the authors developed three hypotheses. The authors suggested that the pharmacist-initiated pharmacogenetic testing will have the greatest, resulting in an increase in proper use of pharmacogenetic testing (Haga, et.al, 2014). Also, they argued that use of pharmacogenetic testing will increase through physician awareness of drugs associated with genetic influence as well as having a pharmacist with expertise in pharmacogenetic testing will benefit the patients (Haga, et.al, 2014). Lastly, the authors hypothesized that patients will have a negative perception of drug safety and efficacy if they are either low or high metabolizers, hence affecting therapy adherence (Haga, et.al, 2014). The results for this study are yet to be published.

There is another study that investigated that incorporating pharmacogenetics in areas beyond cities (Dorfman, et.al, 2015). The goal of the study was to analyze the views of physicians in western Montana including rural areas and Confederated Salish and Kootenai Tribes (CSKT) regarding pharmacogenetic testing (Dorfman, et.al, 2015). The authors interviewed 10 physicians and 7 other healthcare providers between September 2011 and May 2012 (Dorfman, et.al, 2015). Furthermore, the participants were given $100 for their time (Dorfman, et.al, 2015). The participants in the study

accepted the possibility of genetic influence on drug response and pharmacogenetic tests have the potential to benefit patients (Dorfman, et.al, 2015). This view was shared by participants who have previously ordered pharmacogenetic tests and those who have not (Dorfman, et.al, 2015). However, some physicians and other who participated indicated that patient adherence to treatment is an issue that might require more attention that personalized medicine through pharmacogenetics (Dorfman, et.al, 2015). When questioned about their opinion on pharmacogenetic testing, the participants did not consider this test as a genetic test, which is used for clinical diagnosis or disease susceptibility (Dorfman, et.al, 2015). However, the participants did agree that patients might not see this difference (Dorfman, et.al, 2015). Also, the participants differed in their view on patient response to pharmacogenetic testing, ranging from no questions to confusion and non acceptance, especially Native American patients (Dorfman, et.al, 2015).

There were three main barriers to implementation of pharmacogenetic testing in rural areas; access, logistical and prioritizing patients (Dorfman, et.al, 2015). Furthermore, the participants indicated that cost of testing is a major concern (Dorfman, et.al, 2015). Also, participants mentioned the wait for results since there is only one genetic testing lab in Montana (Dorfman, et.al, 2015).

Public Response:

The following articles explore public views of pharmacogenetics. Issa, et.al investigated patient understanding and knowledge of personalized medicine and pharmacogenetics and how patients view pharmacogenomics in relation to standard care.

The authors used patient focus groups to gauge patient opinions and understanding of personalized medicine and pharmacogenetics (Issa, et.al, 2009). Specifically, the authors used four focus groups, each consisting of eight to ten individuals, with a moderator for each group (Issa, et.al, 2009). The participants were at least 18 years of age, spoke English, had an experience in the health care system and were fit to participate (Issa, et.al, 2009). The authors established a protocol for the groups; patients were welcomed, study explained and the patient gave a written consent (Issa, et.al, 2009). Then, sociodemographic information was gathered through a questionnaire to determine group dynamics (Issa, et.al, 2009).

The focus groups consisted of 32 patients with 60% between the ages of 45 and 64 (Issa, et.al, 2009). The participants had an understanding of the term "personalized medicine" through media outlets, however they was less aware of pharmacogenetics (Issa, et.al, 2009). Moreover, all the participants had a limited grasp on the role of genetic variation in drug metabolism, response and toxicity (Issa, et.al, 2009). Although the idea of pharmacogenomics or pharmacogenetics was beyond understanding for the participants, roughly 68% of these patients preferred the use of pharmacogenetic testing to improve treatment decisions and outcomes, specifically adverse effects of drugs (Issa, et.al, 2009). The participants also shared concerns about validity and use of this technology. For example, Focus Group 2 asked "How does it work for me? I would want to know how it would work for me, How is it going to work for me as opposed to something else you've shown through testing that isn't going to work for me?" (Issa, et.al, 2009). Also, participants in Focus Group 4 mentioned, "Well, the only thing I really

care about is how accurate the test is" (Issa, et.al, 2009). Participants were also concerned about test accessibility and availability of associated diagnostic and therapeutic resources; Focus Group 3 asked, "But important too is: Who gets the test? Is it only people with money? Who is excluded from the test?"; Focus Group 2 stated, "The cost and availability… certain technologies many only be at certain places, like here at the medical center? And not in more rural areas…? It's not like you can go to a community clinic with no insurance and say, 'I want this test, Do it now'" (Issa, et.al, 2009). There were also concerns about privacy; Focus Group 1 indicated that "The privacy issue's gonna be a major priority, major priority" (Issa et.al, 2009). Participants also voiced concerns about cost and insurance coverage; a person in Focus Group 1 said, "… If we can cure your high blood pressure by finding the right pill, even if that pill costs 50 bucks a day, versus… having a massive stroke, need 6 months of rehab and…renovate your house so you can get around, insurance companies ought to get on board and say 'We can save ourselves a pile of money by finding out now how to treat him to prevent that'" (Issa, et.al, 2009). Most of the participants indicated they would be willing to pay out of pocket for pharmacogenetic testing; however, they might not be willing to pay for such a test unless the condition was severe; Focus Group 4, "Some illnesses that, even for high cholesterol, I don't think I would test for that. But as it gets more serious, it's more likely that I would have it done" (Issa, et.al, 2009). As a last point, approximately 68% of the participants expect a consumer demand for pharmacogenetic testing (Issa, et.al, 2009). This study gathered public opinion and reception of personalized medicine and pharmacogenetic.

There is another study that aimed to gather consumer views on pharmacogenetics (Haddy, et.al, 2010). Similar to the study detailed above, Haddy, et.al used focus groups to study the public views on pharmacogenetic testing. The participants were at least 18 years of age who have suffered from a chronic medical condition or witnessed an immediate family member suffer (Haddy, et.al, 2010). The participants were divided by age, 18-35 in Group A, 36-60 in Groups C and D and 60 years of age or older in Groups E and F to ensure a comfort environment for discussion (Haddy, et.al, 2010). Each focus group had a moderator and each session lasted for an hour (Haddy, et.al, 2010).

Through this study, the authors gathered information on various participant perceptions. First, there was a consensus on the definition of medicine; an entity that improves quality of life including prescription, over-the-counter medications, alternative therapies and other therapies such as music and acupuncture (Haddy, et.al, 2010). When considering a new therapy, the main concern was side effects, both short-term and long-term (Haddy, et.al, 2010). Also, the participants were concerned about dosing instructions, type of medication (tablet or intravenous), size of tablet or capsule and taste of medication (Haddy, et.al, 2010).

When discussing the source of information on a particular medication, most participants sought multiple sources, from pharmacist and physician to internet and friends (Haddy, et.al, 2010). One participant in particular raised the idea of a short, user friendly pamphlet, raising the question on the effectiveness of dissemination of information to consumers; another participant echoed this feeling by saying “If I didn’t have some education in health, I would probably be too lazy to read the pack insert and

would just ask someone else on the same medicine, similar to what my parents do" (Haddy, et.al, 2010).

Most of the participants defined personalized medicine as individualized treatment or life-style changes and holistic approach; Focus Group D associated personalized medicine with pharmacogenetics, with one person indicating the use of genetics to design medications for individuals and another suggested the use of genetic to determine dosage (Haddy, et.al, 2010).

When questioned about appropriate access to their file, the participants agreed that those who have access to their general medical information should also have access to their genetic information; this included physicians and other medical personnel, hospitals and pharmacists (Haddy, et.al, 2010). However, sharing genetic information outside the healthcare system depended on personal preference and disease; for example, information on mental illness would only be shared with those close to the patient (Haddy, et.al, 2010). The participants were concerned with discrimination in the work place should employers learn about certain medical histories or genetic predispositions; from Group D "… I wouldn't want to have to disclose things at an interview as it may alter if you get a job" (Haddy, et.al, 2010). There is a strong negative response to whether insurance companies should have access to genetic information, which might lead to low or no coverage and exploitation by other companies; from Group D, "…if you can determine if you will get Huntington's or whatever, there are huge ramifications. It could mean that the 'perfect'people' could get insured and everyone else couldn't… I wouldn't

want it on some central database. That would be highly dangerous. It may even affect government strategies-what they give money to or not..." (Haddy, et.al, 2010).

The participants expressed concerns of confidentiality and security when discussing storing genetic information; from Group D, "What is secure? There is no such thing as secure anymore. Bury it!" (Haddy, et.al, 2010). Furthermore, participants believed storing the information in hard-copy was more secure that electronic filing (Haddy, et.al, 2010). There were two participants who did not want to store the information; Group A participant stated, "Is it necessary to be stored?" and Group D participant stated, "Maybe it shouldn't be stored- use it, then destroy it. Recollect it on an as-needs basis" (Haddy, et.al, 2010). There was polar opinions on whether the doctor or the patient should keep the information; Group A said, "I don't now think twice about blood test results being stored-wouldn't be any different. I trust doctors", while Group D said, "I could keep it myself- Doctor could have on request" (Haddy, et.al, 2010).

Also, there was a consensus among most participants on payment for genetic testing. That is, many participants suggested that the government should fund the testing as it would benefit the whole community by decreasing sick days, lowing adverse drug reactions and drug waste and decreasing the number of doctor visits (Haddy, et.al, 2010). This model also would be blind to socioeconomic status of the patient and improve overall well-being (Haddy, et.al, 2010). On the other hand, there were a few participants against government funding; Group F indicated that screening the whole population would be a "criminal waste of money" if the test cost $1000 per person and that the test should be the patient's choice by stating "I have never agreed with total government

control of knowledge, even if it will help me and my family" (Haddy, et.al, 2010). Group C was supportive of government funding if the test was only for disease diagnosis or treatment decision, not for frivolous things such as trying to determine the genotype of the child for reasons other than disease screening (Haddy, et.al, 2010).

The participants were given a scenario prior to discussion on genetics or genetic testing, a doctor visit to discuss treatment options for hypertension; participants indicated that a holistic approach in treating high blood pressure is necessary since the disease is not governed by one factor (Haddy, et.al, 2010). There were concerns about blood test results turnaround time and the halting of treatment until results arrived (Haddy, et.al, 2010). When the idea of pharmacogenetics was added to the scenario, many responded positively, from Group D "Sounds amazing!" and Group F " That would be great" (Haddy, et.al, 2010). However, some participants were upset about using the test and waiting for the result to be treated (Haddy, et.al, 2010).

Apart from the hypothetical scenario, the participants completed a survey, addressing value of efficacy and tolerance to adverse reactions and situation where side effects can be tolerated; the majority of the participants answered that if they were being treated for a life-threatening disease such as cancer, they would accept a medication with side effects as long as the treatment cures the disease (Haddy, et.al, 2010). This study covered a wide range of questions and gathered information on mind set of people in the healthcare system.

In this section, two studies were detailed to show the response of physicians and the general public to the notion of personalized medicine and pharmacogenetics. These

studies and others have valuable insight into public perception and can help create a smooth transition to personalized medicine via genetic approach.

DISCUSSION

There have been many milestones in biological sciences in the past century, one of which is the ability to sequence DNA. The work by Sanger led to sequencing the human genome in the early 2000s (Sanger, et.al, 1977; Int'l HGS Consortium, 2004). Sequencing is a routine part of research and in cancer therapy; however there has been little progress in implementing genome sequencing in all areas of medicine. To facilitate the transition, the United States National Academies published a National Research Council report that defined precision or personalized medicine laid down ideas to connect research and clinical medicine (Toward Precision Medicine, 2011). Although it is expensive to sequence genomes, with the evolution of sequencing technology the cost will surely drop to an affordable value (Berm, et.al, 2016).

When considering genetic testing, pharmacogenetic testing is a valuable resource to discuss. A pharmacogenetic test can help narrow genetic influence on a patient's response to a medication and provide physicians with the knowledge to tailor a regiment for that patient; one with little to no side effects. The goal of this paper is to explore literature to find specific benefits of pharmacogenetics, whether the technology is ready for implementation and are there any gaps in our knowledge, how to implement this technology in clinics and what is the public response and concerns to this novel technique.

There are many benefits to successful implementation of pharmacogenetics or more generally pharmacogenomics. As mentioned earlier, many adverse events or ideal patient populations can be identified through pharmacogenetics, such as hypersensitivity to carbamazepine associated with HLA allele in European descendants (Wang, et.al, 2011). Furthermore, pharmacogenomics will help in the diagnosis and treatment of cancer; an example would be the use of trastuzumab to treat breast cancer patients with a heightened expression of HER2 (Slamon, et.al, 2001). Apart from cancer, pharmacogenetics will revolutionize the treatment of infectious diseases; predicting patient sensitivity or severe side effects to medications such as the liver toxicity associated with floxacillin (Daly, et.al, 2009). Another area of medicine that has been shown to potentially reap benefits from pharmacogenetic testing is cardiology or treatment of cardiovascular diseases. Medications such as warfarin and clopidogrel have been the focus of research due to the narrow therapeutic indexes of these drugs (Wang, et.al, 2011). The FDA has changed the drug labels of these medications to include information from genomic studies (Wang, et.al, 2011).

The factor which indicates genetic influence over drug efficacy and side effect profiles is the variability in drug response in a diverse patient population; specifically if all family members react similarly to a medication or if there is a vast difference in response to a drug across ethnic groups (Voora and Ginsburg, 2012). Pharmacogenetic testing might reveal variations in the genome of the patient or patient population that might affect the pharmacokinetic, pharmacodynamic or the disease pathway and result in an unexpected drug response (Voora and Ginsburg, 2012).

Many drugs used to treat various cardiovascular diseases have been the focus of research; mainly statins, thienopyridins and diuretics. Statins are widely known medications used for treating patients with high cholesterol (Chasman, et.al, 2004; Krauss, et.al, 2008; Voora and Ginsburg, 2012). They work by reducing the LDL or bad cholesterol levels; however they carry a risk of a musculoskeleton side effect (Link, et.al, 2008, Voora, et.al, 2009; Voora and Ginsburg, 2012). Through genetic research, many genes associated with drug efficacy and myopathy risk have been elucidated and applying this data in clinical practice can improve adherence to treatment, and predict and prevent adverse events.

Another common class of drug used to treat cardiovascular issues, namely hypertension, is a diuretic. Variations in genes associated with sodium transport in the kidneys will affect the efficacy of diuretics. A specific variation in adducin 1 alpha gene (*ADD1*) increases the protein's sensitivity to sodium levels in the body and increases the effect of thiazide diuretics, reducing blood pressure levels quickly (Cusi, et.al, 1997; Voora and Ginsburg, 2012). Since this mutation has the effect of a diuretic, prior knowledge will signal the physician to prescribe a lower dose, to prevent the patient from reaching low blood pressure levels.

A medication that has been extensively researched is clopidogrel. Clopidogrel is an antiplatelet drug, in the class of thienopyridine, used to prevent clinical outcomes such as stent thrombosis, cardiac arrest or even death in patients with acute coronary syndrome who have had a percutaneous coronary intervention (Voora and Ginsburg, 2012). Clopidogrel is an ideal candidate for pharmacogenetic research and testing since there is

variability in inhibition of platelet function, which is shown to be heritable (Voora and Ginsburg, 2012).

One gene in particular has been the focus of research when comparing the efficacy of clopidogrel and other drugs in its class; *CYP2C19* (Tantry, et.al 2010). CYP2C19 is a hepatic enzyme involved in conversion of clopidogrel into an active metabolite, an entity that will interact with the target protein (Voora and Ginsburg, 2012). The gene has two loss-of-function variants, denoted *CYP2C19*2* and *CYP2C19*3* and one gain-of-function allele, *CYP2C19*17* (Voora and Ginsburg, 2012).

A study by Tantry, et.al studied the effect of CYP2C19 genotype on platelet reactivity in patients treated with clopidogrel versus ticagrelor and comparing the platelet reactivity between the treatment groups given a specific genotype (Tantry, et.al, 2010). The study included two sub-studies, ONSET/OFFSET and RESPONSE with 174 patients (Tantry, et.al, 2010). The study revealed that patients treated with ticagrelor had a significantly lower platelet function compared to patients treated with clopidogrel across all CYP2C19 genotypes; furthermore there was no indication that the patient genotype affected platelet function in patients treated with ticagrelor (Tantry, et.al, 2010). The converse was true for patients treated with clopidogrel, with carriers of even one loss-of-function allele did not respond to the therapy indicated by high platelet function (Tantry, et.al, 2010). Given the information in this study, it can be concluded that ticagrelor might be a good alternative for patients with a CYP2C19 loss-of-function allele, and pharmacogenetic testing can remove trial and error for this treatment and avoid adverse outcomes from a nonresponsive clopidogrel therapy. However, the authors caution that

other enzymes do play a role in conversion of clopidogrel into an active metabolite and suggest further research to gain a complete picture (Tantry, et.al, 2010). Another study by Paré et.al has shown contradictory results, regarding the influence of loss-of-function allele on clopidogrel therapy (Paré, et.al, 2010).

Another study, by a group led by Dr. Simon, investigated genetic influence on response to clopidogrel treatment and clinical outcomes. Specifically, the study focused on clinical outcomes in patients who survived an acute MI (Simon, et.al, 2009). The study screened for variations in many genes including *CYP2C19* and their influence on outcomes such as ischemic events or death in a one year time frame (Simon, et.al, 2009). The authors discovered an increase in risk of events in patients with a TT or CT genotype in *ABCB1* and two loss-of-function alleles of *CYP2C19*. More specifically, patients with two alleles of TT genotype in *ABCB1* had a 15.5% event rate in one year compared to the 10.7% event rate in one year in patients with a wild type genotype (Simon, et.al, 2009). Also, patients with two loss-of-function alleles of *CYP2C19* had a 21.5% event rate compared to the wild type genotype at 13.3% event rate (Simon, et.al, 2009). Overall, the variants of these two genes greatly increase the risk of an adverse clinical outcome, and knowing this information will be a factor in having a good prognosis.

Dr. Simon led another group that investigated the clinical outcomes in patients treated with a combination of clopidogrel and proton pump inhibitors. The study revealed an increase in clinical outcomes in patients treated with a combined therapy of clopidogrel and proton pump inhibitors (Simon, et.al, 2011). However, this observation was not associated with an increase in risk of mortality in patients with CYP2C19 wild-

type genotype (Simon, et.al, 2011). Similar to the other studies above, there is a strong indication of genetic influence over clinical outcomes; however, further research is required to establish a firm association.

Yet another study investigated the influence of *CYP2C19* on clopidogrel therapy in young patients who suffered from an MI (Collet, et.al, 2009). The *2 variant had the greatest influence over clopidogrel from the start of therapy, with 9 patients having stoke, MI or had died (Collet, et.al, 2009). More specifically, the authors observed an increase in the rate of MI and stent thrombosis (Collet, et.al, 2009). These observations are promising and relevant; knowing the *CYP2C19*genotype of patients can signal doctors to recommend an alternate therapy that will have a better prognosis.

Although research, shows potential benefits, there is another aspect that is of equal importance; transition from research to clinical practice. More specifically, how to make the transition easier on patients, ensuring they have all the resources they need to understand and utilize pharmacogenetic testing. On a positive note, one article indicated that the prices of pharmacogenetic testing has been steadily falling (Berm, et.al, 2016). On the other hand, there are many avenues to consider when integrating a new test into the system such as when to order the test; who will have access to the test; increase in appointment duration and need of a follow-up, and more (Haga, et.al, 2015). Also, included in this list of barriers is insurance coverage (Haga, et.al, 2015; O'Connor, Ferreri and Michaels, 2015). Addressing each of these concerns will ensure a smooth integration into clinical practice.

There have been several field tests to explore the possibility of pharmacogenetic testing in primary care. A group led by Dr. Haga in 2014 started an experiment that explores the role of pharmacists as the contact person for pharmacogenetic testing. The study investigated whether there was a higher chance of appropriate and timely administration of pharmacogenetic testing if ordered by a pharmacist or a physician. The authors developed three hypotheses: 1) pharmacist-ordered pharmacogenetic testing will result in an increase in proper use of the tool; 2) physician awareness of drugs associated with genetic influence and having a pharmacist with pharmacogenetic testing expertise will greatly benefit patients; and 3) patient perception of drug safety and efficacy will be affected by their metabolism phenotype, either low or high (Haga, et.al 2014). The results of this study will provide a path for integration of this form of genetic testing into mainstream medicine.

Yet another study investigates incorporation of pharmacogenetic testing in suburban and rural areas. The goal of that study was to gather the views of physicians in western Montana including rural areas and Native American tribes, CSKT (Dorfman, et.al, 2015). All the participants in the study agreed on the potential of pharmacogenetics; however, many were concerned about patient adherence to treatment over genetic influence over that treatment (Dorfman, et.al, 2015). This information is important because even if an alternate to standard therapy is suggested, it is up to the patient to follow the guidelines from the physician and stay on the regiment. This study also revealed patients might have varying views of pharmacogenetic testing; the idea of genetic testing might be a sensitive topic to discuss with Native Americans such as CSKT

(Dorfman, et.al, 2015). The physicians who participated in the study also pointed out accessibility and logistical issues of including pharmacogenetic testing in rural areas as well as prioritizing patients for genetic testing (Dorfman, et.al, 2015). Also, physicians indicated that patients might become frustrated due to the delay in starting treatment from the wait for these results; especially since Montana is home to only one genetic testing laboratory (Dorfman, et.al, 2015). As another concern, the participants also mentioned cost of testing might deter patients from accepting the test order (Dorfman, et.al, 2015). This study in particular has given great insight into the state of clinics and hospital in rural areas and a clear plan will help address all the obstacles.

Although physicians are able to judge patients well and voice concerns on their behalf, there is a difference in ideas and perceptions between professionals and the general population. Two studies discussed earlier delved into consumer or patient perceptions on pharmacogenetic testing and challenges associated with implementation. In one study, the authors indicated that consumers had an understanding of personalized medicine from media coverage; however they were not as aware pharmacogenetic testing and had a limited understanding of genetic variation and its influence on drug metabolism, response and toxicity (Issa, et.al, 2009). Even if patients did not completely understand the idea of pharmacogenetics, 68% of the participants were excited about the use of such testing to improve treatment decisions and outcomes and potentially limit adverse events (Issa, et.al, 2009). Still, the participants were cautious about this new technology and questioned the validity and utilization (Issa, et.al, 2009). Patients shared concerns about patient priority by discussing accessibility and cost; the same concern

voiced by the physicians in the other study (Issa, et.al, 2009; Dorfman, et.al, 2015). A major concern was confidentiality and authorization to access their test results (Issa, et.al, 2009). These participants gave an insight into basic concerns and these should be and can be adequately answered by standardizing pharmacogenetic testing, talking to insurance companies about coverage, improving data security in healthcare and evolving testing technology to make the test affordable for all.

A similar study was conducted by another group, gathering views from participants who have a chronic medical condition or who have a close family member with a medical condition (Haddy, et.al, 2010). The participants were divided by age groups and provided an understanding of perceptions from different age groups. The study indicated that not many people have an understanding of pharmacogenetics and its use in personalized medicine, since only one group had made the connection (Haddy, et.al, 2010). Similar to the participants in the other study, these participants were concerned about privacy; they did not want to share the information outside their providers; they especially did not want the information to be accessible by insurance companies, fearing the information might lead to loss of coverage (Haddy, et.al, 2010). This is an interesting idea and could affect coverage, especially if a person has to take a medication that is not part of standard practice due to a genetic variation, affecting treatment and outcome in groups of patients in similar situations. Furthermore, these participants were also concerned about information security, considering hard-copy filing more secure than digital storage (Haddy, et.al, 2010). There is some credit to this idea,

since electronic files can be hacked, while someone has to go to a room and take the information in-person.

When discussing paying for pharmacogenetic or genetic testing in general, most participants strongly advocated for government funding citing overall community well-being as their main reason (Haddy, et.al, 2010). There were a few people who were against government funding, indicating that screening the entire population will be a huge waste of money and that people should have the choice to be tested (Haddy, et.al, 2010). I agree with the patient's right to accept or deny treatment further research is necessary to determine whether government funding might be the best option.

Many of the participants were enthusiastic about the use of pharmacogenetic testing; yet, there were some who did not want to wait for the test results to be treated, similar to the concern raised in the other study (Haddy, et.al, 2010; Dorfman, et.al, 2015). Pharmacogenetic testing will be a valuable tool that will improve quality of life, however the concerns mentioned above need to be analyzed and addressed properly and increase public awareness to ensure a seamless addition of pharmacogenetic test to the available tests.

The idea of pharmacogenetic testing is extremely exciting and promising. Further research into validating observations and associations will increase our knowledge on the role of genetics in another aspect of life; treatment. Also, studying implantation options and public opinions will help evolve the field of medicine as new tools are developed to better combat diseases.

CONCLUSION

In summary, there is a general movement towards genetics; characterizing disease based on genetic differences and choosing therapies based on that information. Given this trend, routine pharmacogenetic testing seems inevitable. However, there are many hurdles to cross before successful implementation and utilization of this technology. Additional research is necessary to validate present observations. There should be more focus on various challenges associated with introducing a new test, such as proper time to administrate the test; timely result turnover, information storage and protecting patient privacy. Moreover, there should be an effort to increase public awareness of the theory behind pharmacogenetics and clearly explain risks and benefits. That is, patients should have confidence in this test and believe the results will help them receive the appropriate treatment. Pharmacogenetic testing is the next step towards personalized medicine; so answering academic and social concerns will allow for smooth integration into mainstream medicine.

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CURRICULUM VITAE

SWARNA VEERAMANI

Year of Birth: 1993
2 Kinsman Lane
Merrimack, NH 03054
Cell - 603 377 6350
E mail: swarnaveeramani@gmail.com

Education:

Boston University School of Medicine, Boston, MA
Candidate for Master of Science in Medical Sciences Expected Graduation: 2017
GPA: 3.13/4.0

University of Massachusetts, Amherst, MA (May 2015)
B.S. in Biochemistry & Molecular Biology, Cum Laude
Secondary Major: Microbiology Minor: Chemistry
Commonwealth Honors College, Great Distinction - GPA: 3.731/4.0

Research Experience:

Jesse Mager Animal Science Laboratory, University of Massachusetts Amherst,
Independent Study/Honors Thesis September 2012 –May2015

Conducted protocols to determine the imprinted status of genes during mouse development. Training in laboratory techniques such as DNA/RNA extraction from tissues, Primer design, PCR setup, Gel Electrophoresis, Studying DNA and RNA sequencing data. Presented data at lab meetings and at research conference in April 2015

Momenta Pharmaceuticals, Cambridge, MA, Summer Intern
May 2013-August 2013

Conducted ELISA protocols to determine cytokine levels in mice serum. Analyzed ELISA results, presented results on poster at the end of the internship

Medically Relevant Experiences:

Boston Medical Center, Food Pantry Volunteer
February 2016- Present

Gathered necessary groceries needed for the patients and helped patients with packing the groceries. Conversed with patients to ensure they have the items they needed.

Southern New Hampshire Medical Center, Volunteer
September 2010-December 2012

As a Messenger/Escort, conducted errands throughout the hospital, helped transport patients throughout the hospital, helped discharge patients to patient pick up at the main entrance and deliver flowers to patients. In the ER, attended patient calls, sanitized rooms after patient discharge or relocation to in-patient floors, stocked rooms with supplies and transported patients throughout the hospital