As the incoming chair for the AAPS Drug Metabolism Focus Group (DMFG, http://www.aaps.org/Drug_Metabolism/) I would first and foremost like to offer great appreciation to Dr. Swati Nagar for her leadership and contributions as the chair of the DMFG over the past two years. Under Swati’s watch in addition to reorganizing the DMFG, she led the DMFG in contributing excellent programming to the AM’s, helped create “this” biannual Newsletter and was a proponent for an upcoming Webinar scheduled for the Spring of 2017 entitled: Advances in mechanistic TMDD and platform PBPK models for the pre-clinical and translational development of therapeutic antibodies. Swati leaves some “big shoes” to fill.

The DMFG is a primary focus group of the Pharmacokinetics, Pharmacodynamics, and Drug Metabolism (PPDM) section. The steering committee holds one monthly teleconference on the first Tuesday of each month. The mission of DMFG is to recommend policies and ideas to support state of the art lectures and speakers for PPDM / AAPS programming, support year round programming and provide learning opportunities to the scientific community. In order to accomplish this goal the steering committee NEEDS YOUR HELP. There are over 500 AAPS members that choose DMFG as their primary focus group and we would like to hear from you with ideas for AM programming, webinars, blogs, short courses etc... For those of you reading the committee Newsletter please send us your feedback – we’d love to hear it!

It is with the help of the AAPS community that we can make AAPS an exciting place to meet, discuss and learn. Please feel free to contact any member of the steering committee with your thoughts and ideas. Thank you!
Personalized or precision medicine is a medical terminology used to stratify patients into different groups by tailoring decisions about medical interventions, treatments and drug dosage based on the individual’s predicted response or risk of disease. The term is gaining tremendous popularity in recent years given the growth of new diagnostic and informatics approaches that provide understanding of the molecular basis of disease, particularly genomics. In the colloquial sense, “precision” implies a high degree of certainty of an outcome. However, precision medicine is likely to demand a greater tolerance of uncertainty and accommodation for calculating and interpreting probabilities.

In personalized medicine, diagnostic testing is often employed for selecting appropriate therapies based on the context of a patient’s genetic content or other molecular or cellular analysis. One of the early applications associated with personalized medicine is CYP2D6-mediated drug metabolism. CYP2D6 is responsible for the metabolism and elimination of approximately 25% of clinically used drugs. It shows the largest phenotypic variability among the CYPs, largely due to genetic polymorphism. The genotype accounts for normal, reduced, and non-existent CYP2D6 function. Pharmacogenomic tests are now available to identify patients with variations in the CYP2D6 allele and have been shown to have widespread use in clinical practice (1) The CYP2D6 function may be described as poor metabolizer, intermediate metabolizer, extensive metabolizer or ultrarapid metabolizer (2) and the drug dosage adjusted accordingly. A patient’s CYP2D6 phenotype is often clinically determined via the administration of debrisoquine (a selective CYP2D6 substrate) and subsequent plasma concentration assay of the debrisoquine metabolite (4-hydroxydebrisoquine) (3).

Statins are among the most widely used medications in the Western world. Despite their effective lipid-lowering effects, a large amount of residual risk remains in patients treated with statins. One explanation of this residual risk is variation in patients’ responsiveness to statin therapy. This variation has been investigated with genes associated with lipid metabolism, inflammation, thrombosis, and endothelial function as well as genes involved in uptake, distribution, and metabolism of statins (7). Statins exhibit active hepatic uptake mediated by the transporter OATP1B1. The SLCO1B1 gene encodes OATP1B1. OATP1B1 is expressed on the sinusoidal membrane of hepatocytes and facilitates liver uptake of statins. One variant, rs4149056, alters trafficking of the transporting polypeptide to the cell surface, resulting in elevated plasma levels of atorvastatin, simvastatin, and pravastatin (8). Clinically, this variant may decrease a statin’s cholesterol-lowering ability, and possibly enhances the risk of systemic adverse events such as myopathy.
Cancer treatment has seen the most application of personalized medicine. Over recent decades, cancer researchers have discovered large genetic variety in different tumors as well as a single tumor in different patients. These discoveries raise the possibility that drugs that have not been clinically effective in a general population may be useful for a proportion of cases with particular genetic profile. One such example is Trastuzumab (Herceptin), which is a monoclonal antibody that interferes with the HER2/neu receptor and is used to treat certain breast cancers. This drug is only used if a patient's cancer is tested for over-expression of the HER2/neu receptor. Two tissue-typing tests (immunohistochemistry and fluorescence in situ hybridization) are used to screen patients for possible benefit from Herceptin treatment (4, 5). Tyrosine kinase inhibitors such as imatinib (Gleevec) have been developed to treat chronic myeloid leukemia (CML), in which the BCR-ABL gene is present in >95% of cases and produces hyperactivated abl-driven protein signaling. These medications specifically inhibit the ABL protein and are a prime example of rational drug design based on knowledge of disease pathophysiology (6).

Personalized medicine could potentially intervene at all stages of disease progression beginning from the disease susceptibility, screening and diagnosis to prognosis and pharmacogenomics/ oncogenomics driven treatment. Health risk assessment, family history, and predictive biomarkers form the basis of identifying the disease susceptibility and screening. For example, family history-based risks for common disease conditions include type-2 diabetes, coronary artery disease, colon cancer, hypertension, breast cancer, lung cancer, ADHD, and obesity [9-11]. Therapy enabling and putative biomarkers are central to screening, diagnosis, and treatment. Some of these include, estrogen receptor (breast cancer), mutant K-Ras (non-small lung cancer), mutant K-Ras, BRAF, PIK3, and PTEN, (colorectal cancer), MGMT (glioma), TPMT (ALL), and UGT1A1 (colorectal cancer) [12]. Genetic testing identifies correct treatment for correct patients and form the basis for diagnosis (oncology monitoring), prognosis (cystic fibrosis genotype testing), and pharmacogenomics/ oncogenomics [11-12].

Recent advances in the imaging techniques such as molecular imaging with 18F-2-fluoro-deoxy-D-glucose (FDG)-PET and PET–CT in cancer has also revolutionized management of the cancer patients [12]. Moreover, advances in molecular diagnosis hold significant promise for clinical oncology. This includes testing for variations in genes, gene expression, protein expression, and metabolites. The test results are then correlated with clinical factors such as disease state, prediction of future disease states, drug response, and treatment prognosis to guide individualized treatment patients. For example, tumors with mutations in ALK (reported in 4% of lung tumor cases) or EGFR (noted in <10% of adenocarcinomas) have specific clinical presentations and targeted treatments [12] The current genetic screening interventions include (1) pre-conceptional screening (cystic fibrosis), (2) antenatal screening (major chromosomal abnormalities, and down syndrome), (3) neonatal screening (metabolic and endocrine diseases), (4) cascade screening (colorectal cancer, breast cancer, and lung cancer), (5) population/ sub-group screening, and (6) direct-to-consumer screening. Whole genome sequencing and exome sequencing are currently under development as clinical diagnostic intervention [9, 12].
Several policies are in place to support execution of genetic testing and reimbursement for patients. Regulatory policies supporting genomic and personalized medicine include (1) Guidance for Voluntary Genomic Data Submissions, (2) Draft guidance for pharmacogenetic and other genetic tests, including microarrays, (3) Concept paper for the co-development of pharmacogenomic drugs and diagnostics, and (4) Draft Guidance for In Vitro Diagnostics Multivariate Index. Reimbursement policies supporting genomic and personalized medicine include (1) The Advanced Laboratory Diagnostics Act of 2006, (2) The American Association of Health Plans, (3) CDC ACCE Project, and (4) Evaluation of Genomic Applications in Practice and Prevention. Lastly, the legislative policies supporting genomic and personalized medicine include (1) Genetic Information Non-Discrimination Act (GINA), (2) Health and Human Services Personalized Health Care Initiative, and (3) Genomics and Personalized Act [9-11]. However, the insurance companies have little to no incentive to support the genetic testing and receiving reimbursement is extremely cumbersome for patients at present.

Several challenges confound advancement and standardization of precision medicine. These include analytical and clinical validity, clinical utility, ethical, legal, and social issues [10, 11]. Analytic sensitivity and specificity, laboratory quality control, and assay robustness in terms of accurately and reliably measuring the genotype of interest confound the analytical validity. Clinical validity in terms of detecting and predicting the disorder of interest is hindered by clinical sensitivity and specificity of assays, prevalence of the disorder, false positive and negative predictive values, penetrance, and disease modifiers such as diet and environmental factors. The risk-to-benefit assessment in the clinic is limited by incomplete natural history of condition, availability and effectiveness of treatment or preventive interventions, patient and healthcare provider education patients’ economic status, and intermittent follow-up and disease monitoring. Lastly, the ethical, legal, and social factors include, but are not limited, patient privacy, stigmatization, discrimination, family/ social constraints, informed consent, ownership of data/ samples, licensing, patents, risk-mitigating safeguards, and cost-effectiveness [11].

In conclusion, the idea of personalized medicine as patient-tailored and precision medicine has still to realize its full potential, and its success, in the wake of unresolved and ever-staggering challenges, is deemed unrealistic by many. However, the application of genetics in stratifying screening approaches, with potential for tangible health benefit to patients is not only realistic, but also attainable.

References:


Senior Scientist Feature: Dr. Kathy Giacomini, PhD

– Sumit Basu, PhD

Professor, Co-Director UCSF-Stanford Center of Excellence in Regulatory Sciences and Innovation
Department of Bioengineering and Therapeutic Sciences, UCSF School of Pharmacy, CA, USA

Sumit Basu in conversation with Dr. Kathy Giacomini:

**SB: Briefly describe your background and experience in transporter biology and Pharmacogenomics.**

KG: I began studies of transporters while I was a postdoctoral fellow at Stanford. Working in the laboratory of Terry Blaschke, I initiated a joint research project with Rick Mamelok, an assistant professor, on the effects of diabetes on renal glucose transport in the proximal tubule. My purpose in working with Dr. Mamelok was to learn methods involved in the study of glucose carriers in the renal brush border membrane with the ultimate goal of applying those methods to the study of carriers for drugs in the kidney. As an assistant professor at UCSF, my first NIH grant, funded in the early 1980’s was focused on characterizing the mechanisms of transport of basic drugs in the kidney. During the molecular biology era, my group was the first to clone and characterize human transporters for basic drugs: Organic Cation Transporter 1, OCT1 (SLC22A1); and nucleosides and nucleoside analogs: Concentrative Nucleoside Transporter 2, CNT2 (SLC28A2). My graduate student, Lei Zhang, made the observation that the OCT1 we cloned had one amino acid difference from OCT1 cloned by Hermann Koepsell and colleagues. I proposed that we may have each cloned genetic polymorphisms of OCT1, one with one amino acid deletion, and this drew my interest to pharmacogenomics with a focus on membrane transporters. Together with Ira Herskowitz, I became the Principal Investigator of a large NIH center grant focused on the Pharmacogenomics of Membrane Transporters, which was funded between 2000 and 2015. Our project made enormous progress in understanding the function and clinical implications of genetic variants in membrane transporters in multi-ethnic populations.

**SB: What is the importance of influx membrane transporter in determining the clinical pharmacology of a new drug candidate?**
KG: Influx transporters are critical for the absorption, distribution, and elimination of drugs (ADME, pharmacokinetics); they also play a role in pharmacologic effect as well as drug toxicity by controlling access of drugs and their metabolites to tissues and subcellular compartments. Transporters mediate drug-drug interactions, and also may be drug targets. That is, certain drugs are designed to interact with particular transporters to achieve their desired pharmacologic effects.

SB: What are the major hurdles in determining the influence of influx transporters on the drug disposition?

KG: Though drug transporter interactions can be readily characterized in cellular assays, in vivo, it is difficult to discern which transporters are truly playing a role in a drug's disposition. To aid in determining the transporters that truly play a role in vivo, investigators can study drug disposition in: (a) genetically engineered mice in which particular transporters may be knocked out or expressed; (b) individuals who harbor human genetic polymorphisms in transporters; and (c) individuals receiving interacting drugs which are selective inhibitors of transporters. Biomarkers for transporters may also be employed to aid in these studies. Each of these tools has certain limitations however, and different data types must be combined together to understand the influences of influx transporters on the disposition of drugs. Pharmacokinetic modeling, particularly, physiologically based models, may also aid in identifying the transporters relevant in vivo.

SB: How can pharmacogenomics impact regulatory drug approval?

KG: Pharmacogenomic factors may underlie variation in drug response. Often drugs are not approved because of variable response or toxicity in a subset of individuals. Pharmacogenomic factors may identify good and poor responders to a drug, or patients likely to experience a toxicity. Thus discovering genetic variants that associate with drug efficacy and toxicity is important for rational drug administration and for drug approval.

SB: Will be there any impact of modeling tools to accelerate the progress in the field?

KG: Yes, modeling will be key in predicting drug concentrations at sites of action and toxicity through incorporation of transporters in models. Further modeling will play a key role in predicting the effects of genetic variants and potential drug-drug interactions on drug response and toxicity. As data sets become larger and more diverse, again modeling will play a key role in combining data sets to better understand the factors that control drug disposition, response and toxicity.

SB: Over the years, what changes have you witnessed in the field? And how do you think this field will be changing in the future?

KG: For the near future, drugs that target transporters will be discovered and developed for the treatment of rare and common disease. Through human genetic studies
including genome-wide association studies, GWAS, we now know of over 80 transporters in the Solute Carrier Superfamily (SLC) implicated in rare diseases. Polymorphisms in over 150 transporters play a role in human disease. These transporters all represent potential targets for new drugs in the treatment of disease. We will begin to understand the role of transporters in biological pathways and their endogenous roles in both human physiology and pathophysiology. This latter area is very under-studied, and transporters characterized primarily as drug transporters may have important roles in human disease, which have not yet been revealed. Similarly, transporters characterized primarily as transporters for vitamins, amino acids, etc. may play important roles in drug disposition. The function and substrates of orphan transporters including transporters on subcellular membranes will be revealed. For pharmacogenomics, there is a dearth of human genetic studies and those have been limited to a genetic study of a few drugs. More genome-wide association studies with greater numbers of samples will be conducted in the area of pharmacogenomics. We have just completed and published a large GWAS on response to metformin in over 10,000 metformin users. These large numbers are needed to reveal genes for transporters and for other proteins that play a role in drug disposition, response and toxicity.

SB: Please give your opinion on how students and young students can contribute in this field.

KG: Apologies for preaching here, but my answers are as follows. Right now, you are the individuals in the laboratory doing the experiments. Be passionate and absolutely obsessed about research. Do experiments and carefully examine your data, and with a fresh perspective. Though you may set out to go from point A to B, don’t forget to do side experiments based totally on your curiosity. Scientific discovery depends on your experiments, your observations and the hypotheses and perspectives you bring to your research. And those depend on your passion for your research. Pursue research because it is fun; it is interesting; and it is your obsession. Spend your time in creative activities.
Pankajini Mallick in conversation with Dr. Sook Wah Yee:

**PM: Briefly describe your background and experience in the field of Pharmacogenomics.**

**SY:** Working as pharmacist and through my PhD in Medicinal Chemistry from Cardiff University, UK, I learned about the clinical use of prescription drugs, their pharmacological targets and the differences in their clinical efficacy and side effects. These understandings have made an impact on me to be a better scientist and pharmacist, so as to help patients obtain right drugs with better efficacy and less side-effects. This simplistic motivation and interest to learn pharmacogenomics, made me keen to pursue postdoctoral opportunity in School of Pharmacy in US. I feel fortunate to be mentored by Dr. Giacomini. As a postdoc in her laboratory, I have gained pharmacogenomics experiences ranging from identifying genetic polymorphisms in membrane transporters, performing functional studies to associate effect of polymorphisms with drug response related phenotypes. I am grateful that she exposed me to a variety of challenges that helped me acquire ample knowledge over the last several years under her mentorship. Having successfully lead large collaborative projects to gather clinical samples and phenotypes for genomewide association studies related to response to metformin, I have gained experiences in performing data analysis and utilizing bioinformatics and genomics tools, which are important areas in the field of pharmacogenomics. Given the opportunities by Dr. Giacomini, I am actively involved in coordinating several network activities within the Pharmacogenomics Research Network (PGRN) and the PGRN-RIKEN Collaborative Studies. The interactions with the PGRN and PGRN-RIKEN are an important part of my research and career development, as I am motivated by the new challenges and opportunities in the field of pharmacogenomics.
PM: What made you pursue research interest in Pharmacogenomics?

SY: The interest came across to me from my training as a pharmacist and my research thesis in medicinal chemistry. When I was a pharmacist, many patients complained to me about their drugs not working or giving them problems. In the meantime, as a graduate student in the field of Medicinal Chemistry, I was aware of many drugs that have multiple targets and was interested in determining their off-target effect. Based on this perspective, I married my motivation to helping patients with my enthusiasm in discovering drug targets and off target effects. I came across the intuition to pursue and to learn pharmacogenomics, i.e. to find the right drug to target the right patients.

PM: Could you please briefly describe the role of pharmacogenomics in early clinical trials vs drug discovery and development?

SY: Knowledge about pharmacogenomics is important for scientists involved in early clinical trials, drug discovery and development. This can be well described through following scenario. Before a new drug enters Phase-I clinical trial, pharmaceutical company already knows if their drug X is a substrate of drug metabolizing enzyme (DME) and/or transporter. Currently, FDA has established a list of genetic polymorphisms in drug target and disposition genes, including DME and transporters, which have been incorporated in drug labels. Genetic polymorphisms in these genes are known to cause the protein to function differently in humans, which can lead to differences in drug efficacy or adverse events. Thus, the company can incorporate polymorphism knowledge and propose genotyping of volunteers during early clinical trials for specific key genetic polymorphisms. These results could provide valuable information about the response and/or toxicities that the volunteers may have during clinical trial and inform early design of the next clinical trial.

Similarly, discoveries from genomewide association studies (GWAS) related to disease/human traits and candidate gene studies related to genetic contribution to variation in drug response and adverse events could be particularly valuable to drug discovery and development. There are several successful targets identified through human genetic studies that leads to drug target by pharmaceutical companies. To name a few examples: genetic variations in PCSK9 and CD40 are strongly associated with LDL cholesterol level and risk for rheumatoid arthritis respectively. These have led pharmaceutical companies to pursue these as drug targets for treatment of the respective diseases. Therefore, human genetic studies whether it is pharmacogenomics, human disease or traits could bring valuable information to scientists in drug discovery and development.

PM: What are the potential limitations or challenges in genome-wide association study (GWAS) for establishment of personalized medicine?

SY: In my opinion there could be three limitations or challenges.

(1) Most of the GWAS published to date were conducted in European populations. Information about other ethnic groups, particularly African Americans and Hispanics are very limited. There are reports on differences in response to drugs and also genetic differences by different ethnic groups. These pose a challenge when implementing
genotype-guided warfarin dosing in this ethnic population. This brings us to the next challenge in GWAS, i.e. “Replication”.

(2) Though several studies have shown replicative data for genetic polymorphisms in certain DMEs and transporters, however there are many more studies that lacked replications. This is often due to small sample size or due to limited access to clinical cohort. Even though those studies have clinical implications, the findings from GWAS with smaller sample size will be a challenge for the establishment of personalized medicine.

(3) Third challenge that I feel is “Implementation” in GWAS. I see and hear about researchers who are challenged in convincing their institutions to set up genetic testing to guide therapy choice, common reason being that a physician doesn’t see the need for genotyping patients before initiation of therapy. Physicians believe that patients will come back for a visit and if the drug does not work, a dose change or add-on a new therapy can then be suggested. Thus support from clinicians and institution is very important to set up the initial genotype to dosing clinic.

Hopefully, with the effort of large consortia, some of these challenges could be resolved.

PM: What are the ethical considerations for pharmacogenomic testing in pediatric clinical care and research?

SY: I think we need to ask the question “What are the specific benefits and risks to the child?” when it comes to ethical considerations for Pharmacogenomic testing in children for clinical care and research. A few considerations that I am thinking about are (i) how to proceed with secondary genomic information. For example, a child will have a genetic testing done for a gene associated for the current treatment, but what about the information relevant to other drug or disease that the current genetic testing could provide? This secondary information could have implications for family members or on the child once they reach adulthood. (ii) potential discrimination for specific test for example, risk of denials for disability, long-term care and insurance as a result of the testing that the child will be seeking. These are my considerations, however there are many other specific benefits to the child where genotyping guided therapy has saved a lot of children’s lives and has helped avoid side effects.

PM: Will focus on the polymorphisms of the nuclear receptors be more effective for targeted therapy?

SY: Nuclear receptors (NRs) are known to regulate ligand-activated transcription factors of genes. They played important endogenous roles and genetic polymorphisms in these genes. They have also been identified for their associations with phenotypes related to lipid levels, inflammation and diabetes. Among few successful examples of drugs that target the NRs, Fibrate which is used to treat hyperlipidemia, is an activator for peroxisome proliferator-activated receptor (PPAR) alpha. Currently, there is interest within pharmaceutical companies to develop drug to target NR, farnesoid X receptor (FXR) for treatment of metabolic disease. I am not sure it is fair for me to judge whether we should focus on nuclear receptors for more effective targeted therapy. I think there are other targets that are also effective but will require a number of years in development and in human studies to evaluate their effectiveness. Certainly, with human genetic and
mouse studies, we could be informed about whether they are potential new targets within the nuclear receptor family.

**PM: What have we learned from genome-wide association findings from your recent publication “Variation in the glucose transporter gene SLC2A2 is associated with glycemic response to metformin”? and why is it important to know about pharmacogenomics considerations for metformin therapy?**

SY: This is a very exciting collaboration for us with our colleagues from University of Dundee. There are 3 key take home messages. First, a genetic variant associated with lower expression levels of SLC2A2 in the liver, is associated with better response to metformin, i.e. greater reduction of hemoglobin A1c from baseline, in patients with type 2 diabetes. Second, the effect of the variant is relatively large and particularly in patients who are obese. This effect is equivalent to having an additional 500 mg dose of metformin in individuals who have two copies of the variant allele compared to individual without the allele in obese patients. Third, we also observed similar effect of this variant in SLC2A2 in other ethnic populations. Overall, we feel this can have important clinical implications and provide further information to understand about metformin pharmacological action with SLC2A2 in the liver. Moving to the next question, “why this finding can be important?”, currently, a patient diagnosed with type 2 diabetes (T2D) will likely be prescribe metformin as first line therapy for T2D. The doctor will start patient on a low dose of metformin and follow up about a month later to see whether their hemoglobin A1c level have begun to decrease as desired. If the initial dose does not work, the doctor is likely to gradually increase the amount until the patient response. It’s often trial and error and it can sometime take more than a year for doctor to determine that the patient needs an additional second-line therapy or to eliminate metformin. Based on current treatment guidelines, there is no way for a doctor to know when a patient comes in, if they are going to be responsive to metformin or not. Imagine that if genotyping of this SLC2A2 variant became available in a clinic, based on a patients genotyping, the physician could potentially increase patients dose or add-on another therapy earlier on for those patients with two copies of the major allele and could keep patients at a lower dose if patients have two copies of the minor allele. If the first group switches to a higher dose or add on another drug sooner, patients will achieve the target sooner. If the second group maintains a lower dose to achieve the target for a longer period of time, this group will result in patients experiencing fewer gastrointestinal side effects.

**PM: What are some of the hurdles to perform and interpret these genetic tests for practical recommendations for pharmacogenomics-based prescription?**

SY: Let’s start with the hurdles related to performing the genetic tests. If you know which specific genotype you would like to determine for the pharmacogenomics-based prescription, probably the hurdles are finding out which companies offer the test and then to compare their prices, turnaround time, availability and quality of the genetic test results and reports, amount of samples (blood or saliva) required for genetic tests. All of these factors could influence the decision you will make for selecting the right one. Moving to hurdles to interpret these genetic tests; I feel it could be overwhelming with the amount of data from literatures for the different genetic variants associated with various drug response phenotypes. Furthermore, literatures could be using other
nomenclature for the different genetic polymorphisms and this can add on to further confusions and hurdles to interpreting the results. Information gathered by Clinical Pharmacogenetics Implementation Consortium (CPIC®) on many commonly used prescription drugs, class of drugs and the genetic information has helped me in making careful interpretation.

**PM: Being actively involved in promoting understanding of pharmacogenomics in scientific community, what are the hurdles/challenges you face in propagating such interest among scientists?**

SY: I believe there are a few hurdles or challenges that may affect a scientist’s interest in pharmacogenomics. These include ethnical issues in regards to maintaining participants’ privacy, funding and resources in conducting pharmacogenomics-based prescription or for research, lack of expertise and a person’s experience in the work environment, affected by decision maker and time.

**PM: How do you envision the future directions of pharmacogenomics?**

SY: I envision the future directions of pharmacogenomics in three interfaces: (i) discovery, (ii) clinical practice (iii) tools and technologies. In the era of big data, I envision that more capabilities of integrating large datasets from patient’s electronic health records together with other types of datasets will speed up the discovery of pharmacogenomics research which will fuel discovery of more potential targets that will result in novel targets for disease treatment or reducing side effects. In terms of clinical practice or implementation, there will be more easy access and interpretable genetic testing guidelines to facilitate bench-to-bedside to improvise treatment methods and improve patient’s healthcare. Last but not least, I envision that more new and cost effective tools and technologies will become increasingly available which can enhance discovery rate, allowing easy interpretation of the results and the ability to integrate the data to clinical practice for patients and healthcare providers.
Pharmacogenetic tests are based on the identification of genetic variants that influence the individual’s response to a particular drug. The utilization of pharmacogenetic testing may contribute to optimize drug therapy by improving clinical outcomes while reducing potential drug toxicities. The term preemptive pharmacogenetics refers to the incorporation of genetic information (i.e. genotypes) for a given set of pharmacogenetic markers into the individual’s medical record (EMR). Thus, test results are already available in the EMR to assist in pharmacotherapeutic decision-making. If the patient were to be prescribed a high-risk drug, the clinician will be able to identify potential drug-gene interactions or toxicity risks prior to administration. A few institutions have been pioneering the implementation of preemptive pharmacogenetic strategies.

In a recent study, Dunnenberger et al. reviewed the implementation of clinical preemptive pharmacogenetic testing in a set of medical centers across the United States (1). These sites included the Mayo Clinic, St. Jude Children’s Research Hospital, University of Florida, Vanderbilt University Medical Center, and Mount Sinai Medical Center. For example, the “Right Drug, Right Dose, Right Time—Using Genomic Data to Individualize Treatment” (RIGHT) protocol aimed to: 1) identify patients that would likely benefit from pharmacogenetic testing, 2) integrate genotyping results for 85 pharmacogenes into EMRs, and 3) develop and implement clinical decision support systems (CDS). CDS tools were developed in order to assist clinicians during the utilization of pharmacogenetics information. The protocol involved 1,013 subjects, and actionable pharmacogenetic variants in five genes (CYP2D6, CYP2C19, SLCO1B1, CYP2C9, and VOKOC1) were integrated into the CDS. When considering the five genes together, 99% of subjects were carriers of at least one potentially “actionable” pharmacogenetic variant (2). This showed the prevalence of genetic variants with the potential to impact drug disposition in this population.

St. Jude Children’s Research Hospital developed the PG4KDS protocol to implement preemptive pharmacogenetic services. Through this protocol, 1,016 patients were preemptively genotyped for 230 genes. Of those genes, only tests result for four genes (TPMT, CYP2D6, SLCO1B1, and CYP2C19) were released to the patient’s EMR. These four genes were of particular interest because they are linked to interactions with 12 “high risk drugs” (e.g. codeine, tramadol, mercaptopurine, and amitriptyline) (3). A total of 56 active CDS alerts were implemented to assist clinicians making pharmacotherapeutic decisions. In this case, CDS alerts described the risk to the patient, offered a therapeutic recommendation, and required the prescriber to modify, cancel, or continue with the current medication order.

Barriers for implementing the use of preemptive pharmacogenetic strategies in the clinical setting do exist. Such barriers include the lack of a uniform consensus for defining clinical utility, the need for integrated infrastructure to accommodate various processes (e.g., sample genotyping, data warehousing, incorporation of data into EMRs,
and development of CDS tools), and uncertainties related to costs and reimbursements (4). It remains to be determined whether the use of preemptive pharmacogenetic tests would contribute to improvements in clinical outcomes.

References


“It’s far more important to know what person the disease has than what disease the person has.”
– Hippocrates

Over the last century, the rise of genetics, imaging and data mining has led to tremendous advances in the pharmaceutical industry. As a result of the identification of key drug-metabolizing enzymes and the understanding of how the genetic differences in these enzymes lead to individual differences in response to a drug, the field of pharmacogenetics/pharmacogenomics (PGx) evolved. The sequencing of the human genome has further paved the path for personalized medicine to become a reality.

Chemotherapeutic agents usually have narrow therapeutic indices with more severe toxicities than other drugs; and therefore, understanding and implementing PGx becomes more crucial for cancer therapy. For cancer therapies, both tumor and germline genomic systems need to be studied for better efficacy and reduced toxicity. According to the report in 2013, PGx information is available in the drug labels for 30 Food and Drug Administration (FDA)-approved anticancer drugs (Weng L 2013). These include 24 biomarkers, either germline variants or tumor specific gene variants (which include functional deficiencies, expression changes and chromosomal abnormalities) (Weng L 2013).

A germline variation is any heritable variation in the lineage of germ cells, such as polymorphisms in the drug-metabolizing enzymes encoding genes. For example, CYP2D6 for tamoxifen, UGT1A1 for irinotecan, and TPMT for 6-mercaptopurine (Huang 2009). Whereas, a tumor genetic mutation, also known as somatic mutation, is a tumor-specific accidental change in a genomic sequence of DNA. In case of somatic mutations, pathways considerations are critical to select an appropriate targeted therapy (Wheeler H 2013). A classic example is epidermal growth factor receptor (EGFR), which can be activated either due to mutations in different genes within the pathway or itself have mutations. Some of the somatic associations that appear on FDA-approved drug labels include (i) Imatinib - BCR-ABL fusion gene (philadelphia chromosome) for chronic myeloid leukemia (CML); (ii) Lapatinib, Trastuzumab - ERBB2, also known as HER2 or NEU for breast cancer; (iii) Tamoxifen – ESR1 for breast cancer; (iv) Cetuximab, Panitumumab – EGFR and KRAS for colorectal cancer (Wheeler H 2013). Incorporation of these PGx markers in tailoring the therapy has improved efficacy or reduced toxicity, as well as, shown pharmacoeconomic advantages.
The International Cancer Genome Consortium and the Cancer Genome Atlas are excellent public resources of large-scale genome data in thousands of patient-derived tumors of more than 50 cancer types at the genome, transcriptome and epigenome levels for somatic mutations (Went L 2013). The location and the allele frequencies of genomewide SNPs in various human populations are also publicly available from many online resources, such as the NCBI dbSNP(www.ncbi.nlm.nih.gov/projects/SNP) and University of California at Santa Cruz (UCSC) genome browser (http://genome.ucsc.edu/).

It is important to note that genome-wide association PGx studies also help identify novel drug targets or pathways related to the cancer or drug. This can in turn stimulate drug discovery. A classic example of this phenomenon is imatinib, a tyrosine kinase inhibitor used to treat CML, which was developed using the genetic knowledge of the disease and the target (Collisson E.A 2012).

Despite the phenomenal advances in the medical fields, we still have some work to do to practice personalized medicine. In order to apply PGx more widely to cancer therapies, we need comprehensive, high-throughput and cost-efficient prognostic tools to analyze the tumor samples with a quick turn-around time. Also, there needs to be more alternative therapies, based on different targets, for each type of cancer, to design a “tailored dosing regimen” for each individual patient. Eventually, we hope that every patient’s drug-related germline variants will be readily available, and these will be combined with somatic mutations found in the cancer sample as well as the patient’s personal data from the medical records (including comorbidities and co-medications) by well-designed and validated algorithms to provide clinicians with treatment recommendations in a timely manner.

References:
# Upcoming Meetings

## January – July 2017

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<td>Apr 2 - 6</td>
<td>ACS</td>
<td>253rd National Meeting and Exposition</td>
<td>San Francisco, CA</td>
<td><a href="https://www.acs.org/content/acs/en/meetings.html">https://www.acs.org/content/acs/en/meetings.html</a></td>
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<td>Apr 22 - 26</td>
<td>ASPET</td>
<td>Experimental Biology</td>
<td>Chicago, IL</td>
<td><a href="https://www.aspet.org/EB2017/">https://www.aspet.org/EB2017/</a></td>
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<td>Jun 13</td>
<td>DVDMDG</td>
<td>Rozman Symposium</td>
<td>Bucks County, PA</td>
<td><a href="http://www.dvdmdg.org">www.dvdmdg.org</a></td>
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<tr>
<td>Jul 9 - 14</td>
<td>GRC</td>
<td>Drug Metabolism</td>
<td>Holderness, NH</td>
<td><a href="https://www.grc.org/programs.aspx?id=11188">https://www.grc.org/programs.aspx?id=11188</a></td>
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Recent publications related to “Personalized/ Precision Medicine”

- De Andres F et. al., To Genotype or Phenotype for Personalized Medicine? CYP450 Drug Metabolizing Enzyme Genotype-Phenotype Concordance and Discordance in the Ecuadorian Population OMICS. 2016 Nov 16
Aneesh Argikar, Ph.D
PK/PD associate director working
KinderPharm LLC

Javier Blanco, PhD
Associate Professor, School of Pharmacy and Pharmaceutical Sciences.
The State University of New York at Buffalo, NY
Years with AAPS: 11

Ken Cassidy, PhD (Chair)
Senior Research Advisor, Drug Disposition, Eli Lilly and Company
Years with AAPS: 5

Nimita Dave, PhD
Senior Clinical Pharmacokineticist II,
Abbvie, North Chicago, IL
Years with AAPS: 8

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Associate Scientist, Preclinical and Translational PK/PD, Genentech,
South San Francisco, CA
Years with AAPS: 5
Pankajini Mallick, PhD
Postdoctoral Fellow
ScitoVation, LLC
Years with AAPS: 5

Punit Marathe, PhD
Executive Director, Metabolism and Pharmacokinetics, Bristol-Myers Squibb, Princeton, NJ
Years with AAPS: Over 25 years

Swati Nagar, PhD (Past-Chair)
Associate Professor, Department of Pharmaceutical Sciences, Temple University School of Pharmacy
Years with AAPS: 16

Prathap Shastri, PhD
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Years with AAPS: 8
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