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Pharmacogenomics

Faculty Presenter
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Scholars' Summaries

*Authored by **Michael N. Corradetti, MD, PhD,** Duke Department of Radiation Oncology, Durham, NC, USA*

Pharmacogenomics involves the study of genotypic variation in individuals which may define the phenotype of response or toxicity to a given drug. While the study of the genetic basis of disease and malignancy has defined many of the advances of the 21st century, the field of pharmacogenomics is understudied and often overlooked in the practice of clinical medicine.

Importantly, the FDA has published pharmacogenetic information on more than 140 drugs. Most oncology-related drugs have some pharmacogenetic data associated with them, although approximately 40% do not. Several examples of drugs for which there have been high profile published data include simvastatin, irinotecan, the mercaptopurines, and the fluoropyrimidines. While genotype-directed dosing can be performed for some of these drugs, in many instances it is unclear how and when patients should be screened. It is clear, however, that pharmacogenetics-based knowledge is underutilized in the clinic.

To remedy this shortfall, Dr. Peter O'Donnell outlined a prescription-checking system which integrates pharmacogenomics information from a custom panel into an existing electronic medical record system at the University of Chicago Medical Center. This system, termed GPS (which stands for "Genomic Prescribing System), is a knowledge base which distills pharmacogenomics prescribing information into a red-yellow-green "stop light" for individual prescriptions. It was piloted as a clinical trial and successfully identified multiple "red" and "yellow" conditions which could potentially cause harm in a subset of the 1425 patients enrolled in the trial. Physicians confronted with a "red" or "yellow" warning simply pointed and clicked for additional information on the severity and implications of the interaction. The GPS system represents a promising approach for the clinician who may be overwhelmed with individual assays or the field of pharmacogenomics in general. It remains to be seen whether such a system will be employed on a wider basis and whether payers will support it. Additional study is also needed in many areas, including outcomes measurement and the predictive power of individual markers.

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*Authored by **Olive Eckstein, MD,** Texas Children's Hospital and Baylor College of Medicine, Houston, TX, USA*

As the importance of precision medicine targeted drugs continues to expand, pharmacogenomics increasingly holds an important role in the understanding of individual differences in response to medication. The goal of pharmacogenomics is to understand drug response or toxicity in relation to genetic variations in individuals. With improved understanding of pharmacogenomics, patients can receive more effective and less toxic medications with potential for much less cost to the healthcare system overall by directing individuals away from ineffective or toxic drugs.

There are now over 140 different drugs which have drug labels containing pharmacogenomic information. Despite this rapidly expanding list, there are still quite a few barriers contributing to underutilization of available pharmacogenomic tests in the clinical setting. Lack of provider education and confidence is one such barrier. A large survey of physicians showed that most providers do not feel that they are adequately informed about pharmacogenomic testing options. In addition, the perceived cost of pharmacogenomic testing is much higher than the actual cost, especially when considering the net cost-benefit analysis of using more effective and less toxic drugs. Availability of pharmacogenomic testing, delays in obtaining

results, and physician unease with interpretation of results and their clinical relevance similarly hinder use of pharmacogenomic tests to guide selection of drugs for individuals.

Oncologists are inherently qualified and capable of seeking out and implementing pharmacogenomic testing. This was illustrated by another study which showed that their self-reported ability to interpret and discuss results with patients was much higher when compared to that of cardiologists or family medicine physicians.

Pharmacogenomic tests can identify differences in response rates, overall survival, and progression free survival as well as common toxicities. Genotype-directed dosing can be successfully implemented with knowledge of individual genetic variations and can subsequently impact outcomes of these individuals. An example of this has been well described in tests of *UGT1* polymorphisms and therapeutic efficacy of irinotecan.

Genome-wide association studies (GWAS) are an important strategy used to identify new pharmacogenomic markers. However, design of pharmacogenomic trials utilizing GWAS should ideally have a large discovery set of patients and historical controls for comparison and should consider both phenotypes and endophenotypes, use rigorous statistical methods, and be replicable and validated.

Genomic prescribing systems are being developed to maximize the number of individual pharmacogenomic tests provided to a patient while minimizing costs. Instead of choosing single pharmacogenomic tests which are essentially equal in cost, genomic prescribing systems can provide physicians with pharmacogenomic data for all drugs with known genomic variations, and this information can be used in the future for multiple prescribing decisions.

The future of pharmacogenomics will further reveal the prognostic use of individual markers, measure important differences in outcomes, include assessment of tumor and germline genomics, and become assimilated into the electronic medical record as part of routine clinical use.

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*Authored by **Keigo Komine, MD, PhD,** Tohoku University, Seiryo-machi, Aoba-ku, Sendai, Japan*

Pharmacogenomics (PGx) is the study of the effect of genetic variation on drug response or toxicity. Adverse drug reactions are a major cause of in-hospital death in U.S., and the efficacy rates for even the most common drugs treating the most prevalent diseases are ~50%. As a result, the health care system wastes millions of dollars on poor prescription drug choices. We need to proceed with PGx testing.

In the area of oncology, *TPMT* genotyping in administration of mercaptopurine and *UGT1A1* in irinotecan are famous. Recent attempts have been made to search for PGx markers by comprehensive analysis based on NGs. In addition, some prospective trials have been conducted to set the right dose according to the genotype. The study that compared *DPYD*2A* wild type patients administered standard 5-FU dose with *DPYD*2A* heterozygous patients administered genotype-guided 5-FU dose showed that *DPYD*2A* genotype-guided dosing resulted in adequate systemic drug exposure and significantly improved safety for the individual patient.

The University of Chicago has a genomic prescribing system (GPS) known as the 1200 Patients Project. They developed a PGx panel to analyze the risks of various drugs and established a system to display the results of analyses intelligibly. Over 1000 patients have currently enrolled and over 3000 clinic encounters have occurred. For the establishment of precision medicine, development of GPS is expected.

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*Authored by **Zachery Reichert, MD, PhD,** University of Michigan, Ann Arbor, MI, USA*

Dr. Peter O'Donnell introduced us to the field of pharmacogenomics through the familiar lens of personalized oncology. Instead of identifying genetically predicted tumor sensitivities to a targeted drug, pharmacogenomics is the study of how a patient's genotype predicts a unique drug sensitivity (e.g. toxicity). As adverse drug effects are the fifth leading cause of hospital admissions and prevalent in oncology, all methods to minimize these life threatening events should be pursued. He

challenged us as oncologists to champion this field of research and implementation, as we have familiarity with genetics and high risk therapies.

The first limitation in implementing pharmacogenomics broadly is recognition of its value (despite over 140 drugs including this information on labeling). Mercaptopurine processing with different thiopurine methyltransferase (TPMT) genotypes illustrated safety improvement and is recognized as standard of care. The genotypically influenced (via UGT1A1 polymorphisms) clearance of irinotecan allows for empiric dose adjustments to improve safety and treat a population that may have not tolerated standard dosing. Through pharmacokinetic monitoring, therapeutics levels of irinotecan in the serum were maintained and presented as a surrogate for maintained efficacy. He finished the case studies with a full pharmacogenomic clinical trial using DPYD deficiency and 5FU. Now that its value has been illustrated, broad population-based pharmacogenomics data is needed to support this growing field. We discussed the challenge of sample bias and the need for diverse population sets to create this database. The final step to implementation is the engagement of practitioners to utilize the information in a time/user friendly format. He shared his pharmacogenomics platform and prescribing tool (which is integrated into the electronic medical record ordering system) as a model. It was user friendly, graphically driven, and had clinically informative results with links to source information to improve an engaged user's knowledge base. Clinical outcomes of this platform at the University of Chicago are still pending (although preliminary data suggest it changed prescribing practices). With the drop in sequencing costs, integration of medical records systems, and better data security, pharmacogenomics may create a genetic foundation for every physician's creed of "first do no harm".

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*Authored by **Matthew J. Reilley, MD,** The University of Texas MD Anderson Cancer Center, Houston, TX, USA*

This lecture served as an introduction to the topic of pharmacogenomics and specifically how this field is relevant to oncology. Pharmacogenomics is the study of the effect of genetic variation on drug response or toxicity. At present, most drugs are prescribed with little or no regard to or knowledge of the unique genetic variations of an individual patient. Adverse drug reactions are the 5th leading cause of in-hospital death and lead to millions of wasted healthcare dollars due to poor prescription drug choices. Understanding how drugs will affect individual patients is a central tenet of the precision medicine initiative. Importantly, compared to other subspecialists, oncologists are uniquely prepared to lead other physicians into the pharmacogenomic era. Oncologists already regularly order genetic testing on patients and have conversations about therapeutic choices based on genetic variants. While most oncologists are keenly aware of the role of genetic variations in predicting effectiveness of newer targeted therapies, there are crucial genetic variations within common cancer types that affect the response or toxicities to standard chemotherapeutics. One of the well understood toxicities is that of mercaptopurine in patients with inactivation of TPMT. These patients will experience moderate to severe myelosuppression; however, with individualized dosing based on TPMT genotype, efficacy can be preserved while avoiding excess toxicity. Similar results were seen in genotype directed dosing of irinotecan in patients with UGT1A1 deficiency. One challenge is that the most frequently observed gene variant may differ between ethnic groups. This is a particular challenge if much of the literature has focused exclusively on a specific population and limited the ability to detect relevant variants among the broader population.

Dr. Peter O'Donnell spent the next part of the lecture describing a genomic prescribing system pilot that is being run at the University of Chicago. Patients who enroll in the study receive genomic profiling with reportable information for 37 genes, including over 100 germline variants and relevant prescribing information for 42 medications. This includes information for capecitabine/fluorouracil, doxorubicin, irinotecan, sunitinib, mercaptopurine, ondansetron, and tamoxifen. Clinicians are provided with decision support through their EMR regarding the possible effect of identified pharmacogenomics on drug choices. So far, the system has been well received and has helped guide prescription changes in situations in which extreme toxicity was likely. In summary, this lecture highlighted the practical utility of incorporating better pharmacogenomics into oncology practice. In a future where genomic profiling is likely to become more common place, it will be important to use this information to enhance the precision of novel and standard chemotherapeutic delivery.

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*Authored by **Despina Siolas, MD, PhD,** New York University Langone Medical Center, New York, NY, USA*

Pharmacogenomics is the study of the effect of patient genetic variation on drug response or toxicity. Oncologists are primed

to think about pharmacogenomics because they have educational or practical experience with genetics. Few US doctors have ordered a pharmacogenomics test, but the FDA has pharmacogenomics recommendations for a number of drugs. Different genetic alleles can cause enzyme deficiencies resulting in alterations of drug metabolism. Clinically relevant examples include 6MP, irinotecan, and 5FU toxicity. For the drug 6MP, the amount of TPMT enzyme can be quantified, and dosing can be individualized. However, it is unclear whom to screen for these rare alleles, with other problems including high cost and waiting for a send out test. One approach is to start these drugs at a low dose and titrate up the dose if necessary. The speaker presented a pilot project called the 1200 Patient Project, which is a genetic prescribing system whose goal is to get the right drug to every patient ASAP. Patients are tested upfront for genetic variation with a testing panel of hundreds of markers. The computer algorithm then gives the physician a pharmacogenomic alternative to the offending therapy. It also provides research evidence, level or grade of evidence, and FDA information. The program has 42 medications with >100 genetic variants in 37 genes. Of the 1200 patients enrolled, 1.5% received a red light regarding a medication. All the physicians who received a red-light message read the information, but only 61% changed the offending drug at that time. The reason behind this was patient preference to stay on an ineffective drug due to observed clinical improvement. This program may be expanded in the future.

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*Authored by **David B. Zhen, MD,** University of Michigan Medical Center, Ann Arbor, MI, USA*

Adverse drug reactions are the fifth leading cause of in-hospital mortality in the United States, and efficacy rates for many commonly prescribed drugs treating the most prevalent disease are suboptimal (~50%). This leads not only to poor patient outcomes but the wasting of millions of health-care dollars due to poor prescription drug choices. Pharmacogenomics is the study of the effect of genetic variation on drug response or toxicity and is a means that could better inform appropriate drug selection and dosing for individual patients. Examples of the use of pharmacogenomics in the clinical setting include assessing for thiopurine methyltransferase (TPMT) activity for patients prescribed mercaptopurine, UGT1A1 activity for patients treated with irinotecan, and dihydropyrimidine dehydrogenase (DPD) deficiency in patients receiving 5-fluorouracil. Despite such available testing, pharmacogenomic profiling is underutilized by physicians. Reasons for this are multifactorial and include lack of physician experience in interpreting and translating pharmacogenomic information, poor access to such testing, concerns for costs of the assay, and unclear benefit of widespread testing in unselected populations. We will need to address these concerns and further develop the breadth of pharmacogenomic assays to better evaluate for and understand the role of rare germline variants/haplotypes to drug response and toxicity in order to further advance the progress of making pharmacogenomics a clinically relevant tool. The 1200 Patients Project at the University of Chicago is aiming to tackle such issues through the development of the Genomic Prescribing System (GPS), a standardized system providing access to efficient and cost-effective pharmacogenomic testing and linking it with the appropriate infrastructure for the interpretation of results and generation of an easy-to-comprehend report for clinicians. It is the hope that such an endeavor will provide further insight into, and establish a foundation for, developing programs in pharmacogenomics with the ultimate goal of delivering more effective and safer treatment plans to patients.