



Editorial

Special Issue – Pharmacogenomics & personalized medicine, Journal of Applied and Translational Genomics[☆]



In 1892, Sir William Osler noted that “If it were not for the great variability among individuals, medicine might as well be a science, not an art” (Osler, W., *The Principles & Practice of Medicine*, Appleton, NY, 1892). The observation is noteworthy not only for its depth of perception but also for its place in time, namely before the advent of penicillin and other important medicines that have produced cures and eliminated lethal diseases. Yet, despite that significant progress, the efficacy of medicines prescribed for common ailments hovers around 50–60%, and only 20% for cancer therapies. Approximately 1.5 million preventable adverse drug events, estimated to cost \$4 billion, occur annually in the US (<http://www.fda.gov/Drugs/DrugSafety/ucm188760.htm>). Prescription is always a trade-off between benefits to the patient and side-effects. The latter can lead to non-compliance, which is particularly important in areas with a high prevalence of communicable disease as this may lead to the emergence of resistant microorganisms. Worldwide statistics do not formally exist, though the societal burden is clearly formidable. This is largely the result of the fact that the vast majority of medicines are taken in dosages assumed to be safe and effective for all, irrespective of whether they are pediatric or adult patients. In other words, for the past century physicians have known when they prescribe that a particular medicine may not be safe and effective for an individual patient, yet have had no alternative but to adopt a trial and error approach to prescribing.

Only relatively recently has science been able to understand the great variability in individuals' responses to drugs. In the 1950s scientists first discovered that genetic variation is associated with individual variation in the activity of drug metabolizing enzymes. Variance in enzymatic activity was then thought both to demonstrate that inheritance plays a role in drug response and also to explain adverse drug events. Current knowledge is advancing these principles.

The ability to understand drug response at the molecular level is enabling pharmacogenomics and personalized medicine to remedy the ill effects of trial and error prescribing. Pharmacogenomics employs pharmacology and genomics to study how genes influence an individual's response to pharmacotherapy. Personalized medicine allows one to identify an individual's unique molecular characteristics in order to more precisely diagnose disease and prescribe specific treatments which are targeted to those characteristics, thereby having a greater likelihood of being safe and efficacious, and thus improving outcomes and reducing adverse drug events. Together, pharmacogenomics and personalized medicine are

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revolutionizing drug development and the practice of medicine. This Special Issue – ‘Pharmacogenomics & Personalized Medicine’ of Applied and Translational Genomics provides discrete examples of current challenges and opportunities in the field.

We begin with Fatima Barmania and Michael Pepper's article entitled “C-C chemokine receptor type five (CCR5): An emerging target for the control of HIV infection”. Understanding the molecular basis of immune system dysregulation is pivotal to understanding precise causes of a broad range of diseases and is crucial to identifying potential treatment targets. HIV infection is a prime example of immune dysregulation and is well known for having ravaged the lives of people in global proportions for decades. Arguably, the most clinically successful use of pharmacogenetics (genotyping to predict drug response) is the genotyping of HLA-B*5701 for hypersensitivity to antiretroviral drugs used to treat HIV, such as abacavir. CCR5, the HIV co-receptor, has recently emerged as a potential target in gene therapy aimed at “curing” HIV/AIDS. Identifying targets for drug development represents a substantial advance in controlling failure of the immune system. So it is fitting to begin with exciting new research that offers promise for developing a treatment targeted at the underlying cause of a disease that is particularly devastating amongst the economically active in the developing world.

Promising drug targets require clinical trials to determine the viability of a potential new therapeutic. Understanding the complex genotype–phenotype interactions that influence drug response and the detailed characterization of potential drug target genes is one of the significant challenges to advancing personalized medicine. Developing precision medicines challenges conventional trial design and execution, and with it the pharmaceutical industry's one size fits all blockbuster business model. Trials must be designed to identify not only population variations but also sub-population variations, requiring more advanced algorithms and appropriate study designs to include genetic predictors and the multi-factorial nature of drug response phenotypes. Nimita Limaye's “Pharmacogenomics, therapeutics and personalized medicine – The complexities of clinical trials: Challenges in the developing world”, walks us through the breadth and depth of the challenges to pharmacogenomic trial design and execution, demonstrating why these challenges are arguably greatest in the developing world.

The development of precision medicine is evident in a broad range of therapeutic modalities, including but not limited to stem cell technologies. Advances in stem cell technologies have generated hope for those who but a few years ago had none. Both adult and pluripotent stem cells offer the possibility of replacement of diseased cells and tissues to treat a myriad of diseases, conditions and disabilities. Regrettably, seemingly dramatic stem cell breakthroughs, particularly those that are not fully

validated, are offered by hucksters as miracle cures and have made their way to areas lacking appropriate regulation and legislation to protect the public from untoward practices, such as in Mexico and South Africa.

While hope exists that stem cells can one day cure such diseases, conditions and disabilities, that day decidedly has not yet arrived. Madelein Meissner-Roloff and Michael Pepper's article "Curbing stem cell tourism in South Africa" examines the ethical concerns and scientific impact of a rush to establish the field of stem cell therapy in the absence of governing legislation. The harm is particularly acute for a country like South Africa because of its history of exceptional medicine and its large population of individuals harboring cultural beliefs, rituals and superstitious practices that make them arguably gullible targets. Understanding how the absence of protective regulation and legislation can permit unproven medicine to flourish exposes not only illegal and unethical practices but also a real danger to scientific progress. As the authors poignantly argue, neglecting the proper procedure for establishing stem cell therapies is likely to result in a long delay in gaining public support for the field, thus hindering important work and further delaying validated and clinically useful treatments. Global awareness of this danger is necessary if society is to put into place the proper barriers to ensure the legitimate advancement of the field as well as the protection of vulnerable patients.

From there, we introduce the importance of sharing resources, building consensus and establishing standards in order to realize the promises of genomic technologies for routine patient care. The path from bench to bedside involves complexities associated with developing specific molecular diagnostic technologies for clinical use in a regulated environment. The challenges are particularly acute given the rapidity with which new molecular technologies are adopted in regulated clinical laboratories. As Neng Chen discusses in her article "Incorporating gene signature profiling into routine molecular testing", gene profiling and gene expression profiling illustrate how sophisticated molecular technologies are increasingly an important part of disease management. She further discusses how gene signature profiling will change the way molecular laboratories currently operate. Establishing data collection standards, analysis methods and proper communication between all stakeholders remains a challenge for laboratories aspiring to keep pace with the technological advances and deliver gene signature tests for routine clinical care.

We end this series with Gholson Lyon and Jeremy Segal's discussion of stakeholder concerns in clinical sequencing and the promise of affordable whole genome sequencing. They begin their article "Practical, ethical and regulatory considerations for the evolving medical and research genomics landscape" by discussing the importance of practical as well as ethical and regulatory considerations as they impact personalized medicine's ability to become a standard of care and not a just mere luxury for the rich or a "burdensome" cost center. They argue that it is equally important to protect the well being of patients and research subjects, to the extent that these categories are now functionally

different. Lyon and Segal discuss how and why it is imperative that sequencing be performed in appropriately regulated environments, such as CLIA-certified laboratories cleared for high complexity testing. Next generation sequencing is discussed for its ability to highlight the evolving overlap between patient and research subject regarding clinical care and dissemination of genetic test results, including "incidental" results. Whole genome sequencing represents an even greater degree of research/clinical care overlap and highlights the increasing shift to patient centric research initiatives as well as care.

Further, new information technologies and social media continue to alter privacy norms. Dissemination of genomic data, they claim, is becoming viewed as less unique and more like laboratory and imaging data. This shift, they claim, is evident in the public's greater willingness to share longitudinal phenotypic and genotypic data in publicly accessible online forums. For example, one can now register as an organ donor on Facebook in much the same way as registering as a donor at the motor vehicle registry department when renewing a driver's license. Or one can register with PatientsLikeMe.com and post private medical information about any clinical or research experience. The authors argue for the need for a distributive model of information sharing, such as these, which optimize cost and safety issues though greater reliance on work sharing designed to leverage specific strengths of genomic centers and clinical interpretation teams. Such a model promises to mitigate against many of the data sharing and other barriers preventing the full realization of personalized medicine and to pave the way for personalized medicine to be accessible to all.

We would like to express our deep gratitude to the authors and reviewers of this Special Issue. We hope that you will find these articles instructive and thought provoking.

We welcome your opinions and feedback about this issue as well as Letters to the Editor. Please send your comments to the editorial office: m.shivakumar@elsevier.com.

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