Pharmacogenomics and Drug Development

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With the convergence of advances in multiple disciplines, including bioinformatics, the field of pharmacogenomics has emerged during the past decade as a promising platform for drug discovery and clinical development with significant therapeutic and psychosocial implications.

Pharmacogenomics refers to the study of the relationship between specific DNA-sequence variation and drug effect, for example, variation in haplotype versus variation in therapeutic outcome. Pharmacogenomics holds the promise that medications and diagnostic interventions may be tailor-made for individuals and adapted to each person’s unique genetic makeup, considering that individual’s environment, diet, age, lifestyle, and current state of health as significant modifiers. Therefore, pharmacogenomics combines traditional pharmaceutical sciences, such as biochemistry, pharmacology, or toxicology, with annotated knowledge of genes, proteins, and their variations that are capable of defining relationships across variables.

These data, as well as more traditional phenotypic information, result in an individualized profile of disease risk or a potential drug response. In few other disciplines of medicine are the clinical examples of the application of the art more striking than in oncology. In oncology, the treatment of patients is often accomplished by using chemotherapy characterized by narrow therapeutic indexes (ie, the difference between the toxic and therapeutic dose is small). Proper target identification and dosage/regimen selection are keys to successful therapeutic outcome.

Benefits and Challenges

What are some of the anticipated benefits and challenges of discovery, development, and commercialization efforts that are built on a pharmacogenomics platform from the perspective of multiple stakeholders?

Advanced risk stratification for disease. Knowing one’s genetic code and how it affects the risk for eventual illness will allow a person to make adequate lifestyle and environmental changes at an early age to avoid or lessen the severity of a disease. Similarly, advanced knowledge of specific disease susceptibility will allow the creation of a personalized health plan, careful monitoring with sophisticated assessments (eg, the use of specialty biomarkers), and will facilitate the introduction of treatments at the most appropriate stage to maximize the therapeutic impact.

Improvements in the drug discovery and development process. Pharmaceutical companies will be able to identify specific molecular targets for “lead” identification and optimization, potentially identifying radically unique therapeutic strategies. Previously failed drug candidates, based on toxicity or lack of efficacy in an unselected disease population, may be resurrected when matched with a niche population prospectively defined by using clinical and genetic information.

The drug approval process will be radically transformed when the impact of genetic-based procedures for proper patient identification for treatment are appreciated. For example, the need for genetic/phenotypic risk-modeling tools, modifications in the consenting process, or restrictions in drug labeling to a genetically defined population would be part of a challenging portfolio of issues addressed during the development and commercialization process.

More accurate methods of determining appropriate drug dosage/regimen. Current methods of dosage and regimen selection that are based on empiricism or on an individual’s weight and age may be augmented by algorithms that also consider a person’s genetics and the impact of the environment and diet on genetic expression (ie, epigenetics). At minimum, this process will rationally address individual variations in drug absorption, distribution, metabolism, and elimination as has been successfully demonstrated for warfarin dose-finding. This will maximize a therapy’s value by decreasing the likelihood of toxicity as a result of over-exposure, while enhancing the time until optimal efficacy can be achieved.

Decrease in the overall cost of healthcare. A reduction in the number of failed drug trials, the time it takes to get a drug approved, and the overall expenditures associated with clinical development may dra-
matically alter the cost/benefit equation for investment within the pharmaceutical industry. Similarly, decreases in potential toxicity, in the length of time patients are taking medication, or in the number of medications taken to find an effective therapy may, in theory, promote a net reduction in healthcare utilization.

Decreases in potential toxicity, in the length of time patients are taking medication, or in the number of medications patients must take to find an effective therapy may, in theory, promote a net reduction in healthcare utilization. In contrast, an explosion in potential drug targets would accelerate the number of compounds available in any therapeutic armamentarium. Difficult decisions regarding reimbursement, prior authorizations (eg, expensive diagnostics for expensive therapeutics), and formulary design can introduce an increasingly complicated metric into the cost equation.

Expanding Implications
Is pharmacogenomics information in use today? To a limited degree, particularly regarding issues of drug disposition and safety, pharmacogenomic-based research strategies exist. What is in ascendancy, however, is an expanded appreciation of the impact of pharmacogenomic initiatives across multiple stakeholders in an increasingly complicated healthcare environment.

Pharmaceutical research and development will be concerned with issues of development efficiencies, as well as with cost incentives (an implied market segmentation suggests a limited space for recouping research costs); regulatory policy will need to grapple with issues of evidentiary standards and appropriate labeling; healthcare providers will require actionable data, with a full appreciation of potential liabilities associated with genetically based pharmacotherapy, and patients will need assurance regarding privacy, insurability, and the overall economic value of an intervention. In essence, increasing the use of pharmacogenomic platforms for drug discovery and development will be characterized by increasing sophistication not only in medical and scientific domains but also by a commensurate mastery of implications in healthcare economics and psychosocial issues.

References