Challenges and Opportunities in Pharmacogenomics and Therapeutics

The use of a patient's genetic data to inform decisions related to diagnostic and prognostic health care represents the ultimate achievement of 50 years of genomic research. The technology to realize this vision has emerged and continues to evolve. An emerging vision of the future involves deriving patient-specific genomic data before birth, which includes an exhaustive sampling of genomic information. In this envisioned future, genetic data will be periodically updated throughout a patient's lifetime on a tissue-specific basis to screen for genetic changes associated with age-related diseases. A patient's genotypic data will be further integrated with dedicated databases/warehouses harboring genetically linked health and adverse drug response risk information that will be utilized at the point of care for patient-specific therapeutic interventions.

Current and near-term uses of genomic information provide a glimpse of its future potential. For example, drugs are metabolized endogenously by a series of enzymes collectively referred to as the cytochrome P450 system. These enzymes are further characterized into subgroups, such as CYP1A1 and CYP2D6. It has been demonstrated that the metabolic activity and oral clearance of the immunosuppressant, sirolimus, is significantly decreased in patients with CYP3A5*3 single-nucleotide polymorphism (SNP). Furthermore, it is suggested that dose adjustments should be made in patients that harbor this SNP to reduce the risk of drug toxicity. In this context, an SNP refers to a single-nucleotide base change within the gene sequence of a P450 enzyme in the patient's genome, which decreases the enzyme's expression level and/or activity level.

This is distinct from a nucleotide base change commonly referred to as a “mutation” in which a change in the genome results in a disease state; this SNP predisposes the patient to an adverse drug response. Thus, patients who harbor this allele are at risk of drug toxicity associated with higher drug plasma levels if the “standard” dose is prescribed. Pharmacogenomic data could be used to suggest a more effective dose (in this case, a reduced dose) by predicting the metabolic capability of the patient.

Numerous current and near-term potential methods for DNA analysis support both SNP discovery and detection. The term SNP discovery refers to the utilization of biotechnology methods to uncover new SNPs in a subset of the population, which becomes more difficult (costly) if a specific SNP is rare in humans and inherently dependent upon DNA sequencing in human samples. SNP detection involves the use of laboratory testing to determine the allelic profile of a patient's sample within known polymorphic locations in their genome. Many known SNPs have been discovered within phase-1 metabolic enzymes, and some of these have been genetically linked to altered drug clearance and drug safety. These “drug safety” SNPs are best positioned to benefit the health care community in the near term because they are not inherently biomarkers of genetic illness in humans and may serve to reduce the incidence of adverse drug effects in the clinic.

The use of SNP information to identify drug safety issues could potentially produce a cultural shift in pharmaceutical drug development whereby new drug product development would require genomic screening to ensure safety and efficacy. Ultimately, clinical drug development (Phases I-IV) could be limited to patients with specific SNP genotypes to increase the overall safety and efficacy of new drug entities. This might benefit pharmaceutical firms by providing increased clarity in the creation of patient inclusion criteria for clinical dosing studies, thus reducing the variability in response that would occur without pharmacogenomic information. As a result, it might be anticipated that fewer promising drug entities will be abandoned due to erratic pharmacokinetics as well as safety and efficacy issues.

Future potential, however, does not equate to current reality. In a previous issue of JMCP, Morrow presented a thorough review of the literature focused on the clinical utility of pharmacogenomics in asthma. In addition, he considered the economic implications of pharmacogenomics, highlighting issues of importance to managed care pharmacy as the technology develops. We agree with Morrow that the developing field of pharmacogenomics represents an area of great opportunity for pharmacy in general and for managed care pharmacists in particular. Yet, Morrow reports that in regard to clinical utility, pharmacogenomic evaluation is not sufficiently developed to implement individualized asthma therapy on a population-wide basis. We concur with Morrow's assessment based on several points.

We suggest that the path to an optimal future in genomics-based health care is obscured by several independent factors that must be recognized and overcome to fully exploit genomic content in human health care. Ultimately, a functioning system for clinical genotyping requires (1) an information management system and data standards, (2) a secure interface between DNA analysis biotechnology and the clinical genotyping information system, (3) management of costs and opportunities to ensure that the clinical genotyping system provides value to health care, and (4) the education of pharmacy students and other health care professionals in the biological interplay between genomics and disease pathology.

At the heart of a large-scale clinical genomics implementation would be an information management system that can accommodate many different analysis methods (including new biotechnologies of the future) through the development of a group of scalable standards for genomic information. Given the very recent advances in human genomic knowledge and biotechnology methods, it is not feasible to assume that physicians, pharmacists, nurses, and other professionals within the health care industry have sufficient knowledge to translate raw genomic data into information relevant to health outcomes. Therefore, essentially all genomic data will be “automatically” filtered into categorical definitions by the data management system, and the
known (or potential) impact of a given SNP will then be presented to the health care professional. For example, if a patient is prescribed a drug in which an adverse response has been associated with 1 or more specific genotypes, then the patient’s electronic health record will indicate that the patient is “at risk for an adverse response due to genomic information” and make a recommendation to choose an alternate drug (including a specific drug recommendation if one is available) and/or reduce the dose of the drug.

Given patient privacy concerns, data standards for sharing genomic data must precede the practical use of genotyping in the medical clinic. Thus, with respect to system-wide adoption of a clinical genotyping system, it will be advantageous to categorically separate SNP data relevant to drug safety from SNP data relevant to general health outcomes. In other words, the utilization of pharmacogenomics will be more easily facilitated if the system is limited initially to the prediction of adverse drug reactions. This approach is not hindered by the limited knowledge of genomics in the health care community and overcomes patient privacy concerns as a fundamental adoption barrier. By categorically separating SNPs relevant to drug safety from SNPs linked to other health outcomes as well as SNPs with no known linkages (it is recognized that some small overlap in this distinction exists), consumers can (1) understand how their own genomic data are being used and gain trust in these systems, (2) indicate how their own genomic data are managed and who can gain access to these categorical data sets, and (3) provide a rationale for data security that is dependent on the category of the data. For example, data from an individual whose specific genomic profile is clearly associated with severe drug safety issues may be more easily accessed by worldwide health care institutions and pharmacies because these data would be needed in an emergency for an injured traveler. In contrast, other SNP categories associated with the propensity to develop chronic disease may not be shared across institutions. This concept assumes that (1) consumers will be able to control access to their genotypic information and (2) SNPs inherent to drug safety are far less likely to serve (or be abused) as indicators of general health for an individual.

This approach to facilitating the early adoption of pharmacogenomics in the medical clinic is consistent with the perceived value and use of pharmacogenomic data from the health care professional perspective. The integration of SNPs would be linked to drug safety outcomes within an information-based guidance system for ensuring drug safety (i.e., decision support for both the physician and pharmacist) for patients harboring potentially harmful SNPs. Early utilization of this genomic information will likely involve screening for drug safety at the pharmacy because a prescription/dispensing system exists that is already linked to an information system capable of providing guidance for patients and pharmacists. This type of system has the potential to impact nearly all health care consumers because it is not limited to a particular disease domain. Ultimately, the linkage of SNPs to the prediction of drug response within specific disease domains will be implemented on the heels of a pharmacogenomic drug safety system as the entire health care community becomes accustomed to working with information in the human genome.

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REFERENCES