**INTRODUCTION**

As molecular and biochemical sciences unveil the molecular etiology of disease, the focus of drug development shifts from global treatment modalities to more individualized therapeutics based on genomic data. To health care providers, this represents a paradigm shift in patient care. Are health care providers equipped to apply the knowledge provided by pharmacogenomics in clinical practice? Are they prepared to explain pharmacogenomic data and its implications to their patients?

**GENETICS**

Genetic data are not new to clinical practice. For years, clinicians have used pharmacogenetics, the precursor to pharmacogenomics, in patient care; trisomy 21 Down’s syndrome, sex-linked disorders, and autosomal dominant or recessive disorders have been identified and treated based on genetic data. Patients with these disorders display gross chromosomal changes or single nucleotide alterations that confer disease.

**SCOPE AND DEFINITION**

How does pharmacogenomics differ from pharmacogenetics?

Pharmacogenomics reveals the heritable differences in multiple genes that influence an individual’s response to medication. Pharmacogenomics encompasses pharmacogenetics and expands the concept further by evaluating not just one genetic change but many genetic changes. Whereas a drug target might not change as a result of genetic differences, people’s responses to a medication might vary and often present as adverse drug events (ADEs). This is evidenced by the fact that patients experience diseases and ADEs despite preventive measures and treatment.

For example, statin-induced myopathy, myocardial infarctions (MIs) that occur in aspirin-treated patients, uncontrolled high blood pressure that does not improve despite antihypertensive therapy, and blood clots in patients receiving anticoagulation therapy represent untoward medical events that are harmful to patients and costly to all involved—and that exemplify the predictive power of pharmacogenomics. One cannot ignore the impact of environmental factors in drug response; however, pharmacogenomics represents the application of a patient’s genetic data in the selection of drug therapy to improve the efficacy and safety of treatment.

Pharmacogenomics encompasses a variety of molecular biology tools. Single nucleotide polymorphisms (SNPs) occur in approximately every 1,000 to 3,000 bases in DNA, whether in a gene’s coding, noncoding, or regulatory regions. SNPs do not always change the actual phenotype, but they can alter the response of the end product (protein) to the environment; hence, SNP genotyping is one of several molecular biology tools available for use in clinical medicine.

**LIMITATIONS AND STRENGTHS**

Currently, the clinical application of SNP genotyping is limited for several reasons. Only approximately 5% of human DNA has a known function; thus, 95% of DNA remains to be deciphered. Knowing that pharmacogenomics attempts to explain the complexity of multiple genetic changes and its influence in drug response, we can ascertain that SNP descriptions of unknown regions are of minimal clinical utility. As molecular biology continues to unravel the transcript–structure–function relationship of the human genome, SNP genotyping may help to enhance the therapeutic decision-making process.

Although pharmacogenomics is in its infancy, it equips health care providers with the power to use genetic information in an effort to improve patient care. It is not just a scientific application for the future; pharmacogenomics is a tool that can be used now to improve patient outcomes.

In late December 2004, for example, the U.S. Food and Drug Administration (FDA) approved the first pharmacogenic assay for identifying SNPs related to drug metabolism. The AmpliChip™ CYP450 (Roche Molecular Systems) is about the size of a credit card, with thousands of DNA molecules representing small variations in selected isoforms of the cytochrome P-450 (CYP450 2D6 and 2C19) enzyme system. Used in conjunction with current clinical evaluation tools, this chip provides genetic information about how a person metabolizes various medications, including antidepressants, antipsychotics, beta blockers, some chemotherapeutics, analgesics, and so on. The chip is based on 30 years of genetic research, but it represents an initial step into the realm of pharmacogenomic medicine.

It is worth noting that CYP450 2D6 and 2C19 have a strong genetic correlation and a minimal environmental correlation to polymorphic states, thereby representing the exception, as opposed to the norm, for polymorphisms. Future pharmacogenomic assays must consider stronger environmental influences for clinical utility to materialize.

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Commentary: Pharmacogenomics

CLINICAL TRIALS

A recent English-language Medline search for the phrase “pharmacogenomics and clinical use” from 2003 to the present revealed 369 articles from every specialty of health care, disease identification, patient monitoring, and therapeutics. At present, large clinical trials are under way to establish the correlation between genomic information and therapeutic response.

A study called GenHAT (Genetics of Hypertension-Associated Treatment), an ancillary to ALLHAT (Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial) and GENECARD (A Genome-wide Scan for Early-Onset Coronary Artery Disease) are just two examples. Upon its completion, GenHAT will be able to characterize genetic variations in hypertension and establish correlation to therapeutic response. GENECARD aims to identify chromosomal regions as well as specific SNPs related to the early onset of coronary artery disease.

Numerous smaller clinical trials are elucidating the impact of genomic variability in drug response and applying this information to an array of medications. Researchers at the University of Kentucky have published a small study on the metabolism of risperidone (Risperdal®, Janssen), ADEs, and drug discontinuation. Using inpatient samples from 325 patients who experienced ADEs and 212 patients who discontinued risperidone, genomic assay techniques, including the AmpliChip™ CYP450, have been used in conjunction with logistic regression to determine the association of genomic enzyme data and response. Researchers have determined that when the CYP450 2D6 poor metabolizer phenotype was associated with both ADEs and response. GENECARD aims to identify chromosomal regions as well as specific SNPs related to the early onset of coronary artery disease.

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Jefferson et al. have investigated aspirin resistance and polymorphic differences in four candidate genes known for their role in platelet aggregation. Blood samples of 330 Caucasian men from the Cleveland Clinic with a medical history that includes a percutaneous coronary intervention (PCI), MI, and a daily dose of aspirin (81–325 mg) have been screened for aspirin resistance. After correcting for confounders, researchers found that one polymorphic change in the P2RY1 gene was associated with a 2.7-fold increase (95% CI: 1.12–6.57; P = .03) in aspirin resistance. Again, this was a small trial in a limited population but a harbinger of what is to come.

Both of the aforementioned trials, while interesting, provide little information to clinicians. The small sample sizes and limited populations diminish external validity. Moreover, validation of study results from either trial in a large clinical setting is lacking at this time. Until the results can be reproduced, pharmacogenomic testing will remain experimental and nonessential in clinical medicine.

The number of trials using genomic data could double within a year—this is exciting but daunting news to health care professionals. Armed with genetic information, a clinician has the power to evaluate a patient for drug dosing and response before initiating therapy, further reducing the possibility of serious ADEs and negative clinical outcomes. The clinical impact of pharmacogenomics is potentially tremendous. For example, genomic data will assist in identifying aspirin-resistant patients at the time therapeutic decisions are made, thus helping clinicians in selecting pharmacotherapy and possibly preventing the devastating consequences of a stroke.

COST

The predictive power of pharmacogenomics is not without a substantial initial investment. The cost of the AmpliChip™ CYP450 assay is $500 to the patient, but specialized equipment and laboratory personnel are required. Although the fee is nominal in relation to other health care procedures, the information derived is basic phenotypic data; third-party payers do not routinely cover the assay because it is considered nonessential. Future pharmacogenic studies will evaluate more complex interactions and probably at a higher cost, as foreshadowed by receptor-based therapeutics such as epidermal growth factor (EGF) inhibitors; however, the economic impact of pharmacogenomics remains to be determined.

Knowing that ADEs are prevalent and costly to the health care system, the pharmacoeconomic implications of genomic monitoring are conceivably extensive and favorable when the long-term savings of better clinical outcomes and improved quality of life are considered. Cost–benefit analyses that encompass total costs and long-term benefits will advance the acceptance of pharmacogenomics in clinical medicine; in the near future, pharmacogenomics will be synonymous with standard of care.

QUESTIONS TO BE ANSWERED

With the gross influx of information and the jargon of molecular biology infiltrating health care at an accelerated pace, several questions arise:

- How will health care teams handle genomic data in a patient’s profile?
- Is it the physician’s responsibility to order and interpret genomic data before giving treatment?
- Is it the pharmacist who will effectively evaluate genomic data and provide not only therapeutic recommendations but also patient counseling?
- Is it the nurse who must understand and add genomic profiles to a long list of monitoring parameters?
- Does everyone in the multidisciplinary approach to patient care share in the responsibility of pharmacogenomics?
- Will adding another professional (a molecular biologist or geneticist) to the patient-care team potentially thwart cost-reduction efforts?

Such questions must be answered as we move into the genomic era of medicine.

CONCLUSION

Where does pharmacogenomics stand in the field of clinical medicine? Just as Alice (in Wonderland) fell for a seemingly long time to the bottom of the rabbit hole with one key and numerous doors surrounding her, clinical medicine has embarked on the initial phases of pharmacogenomic medicine with the completion of the sequence identification of the human genome as the key in hand. Unlike the vivid dream in
the beloved children’s tale, however, pharmacogenomics is a very real scientific endeavor into the complexity of drug response.

Currently, the primary key—the complete human genome sequence—has unlocked only a few doors in drug–response pathways. Many doors remain locked, and there are more questions than answers. Nonetheless, with the accelerated pace of molecular biology research, clinicians can be assured that the discovery of additional keys in the structure–function relationship of the human genome will revolutionize patient care and improve outcomes.

REFERENCES