

Guest Editorial

**The Reality of Pharmacogenomics: Optimizing Therapeutic Decision Making**

It is now well established that significant interindividual variability exists in the disposition and pharmacologic effects of certain medications. Influences such as environmental exposures, nutritional status, co-morbidities, severity of disease, and concomitant medications have all been associated with heterogeneity in drug responses. In addition, the profound contribution of genetics has been appreciated for some time and is receiving greater emphasis in recent years.

Approximately 1.8 million single nucleotide polymorphisms (SNPs) in the human genome have been identified by The SNP Consortium (<http://snp.cshl.org>), a collaboration of several companies and institutions. Numerous SNPs in genes encoding various drug-metabolizing enzymes, drug transporters, and drug targets (e.g., receptors, enzymes involved in metabolism of endogenous substrates, etc.) have been shown to be associated with interindividual differences in the pharmacokinetics and pharmacodynamics of certain medications (Evans and McLeod 2003). Many *in vitro* and *in vivo* “pharmacogenetic” studies performed to date have evaluated the association between SNPs in a single gene and a specific drug’s pharmacologic properties. Preclinical and clinical investigations have evaluated genetic determinants of drug metabolism and demonstrated that polymorphisms in genes encoding drug-metabolizing enzymes can markedly influence a drug’s pharmacokinetics, change its efficacy and/or toxicity profile, and necessitate dosing changes in certain individuals. More recent studies have begun to evaluate the association between drug target polymorphisms and pharmacodynamic effects. Three well-documented “pharmacogenetic” examples are outlined in Table 1.

Because of the complex interplay between the pharmacologic effects of drugs and disease pathophysiology, inherited differences in drug responses are most likely polygenic rather than monogenic in nature (Evans and McLeod 2003). Hence, “pharmacogenomics” has emerged as a new field of study that attempts to identify and elucidate the contribution of multiple interrelated genes to the efficacy and toxicity of certain medications. Ultimately, the goal of pharmacogenomics is to account for and minimize interindividual variability in drug response, thus allowing clinicians to enhance the efficacy and minimize the toxicities associated with drug therapy. By considering the role of multiple genes, the field of pharmacogenomics



seeks to divide a given patient population into smaller, less variable, more predictable subgroups, which enables clinicians to individualize drug therapy (i.e., to

administer the right drug, at the right dose, to the right patient) (Roses 2000).

For example, it is now recognized that SNPs can affect the activity of drug transporters and drug-metabolizing enzymes and can substantially influence an individual’s systemic exposure to certain agents. Genetic variation in the target of a given drug can also contribute to its pharmacologic effect. Moreover, variation in a disease-modifying gene can affect the rate and/or extent of disease progression, ultimately influencing the therapeutic effect of a drug. Therefore, simultaneously characterizing genetic determinants of drug exposure, drug effect, and disease progression will likely improve our ability to predict the overall effect of a drug in an individual patient. In other words, genomic data will divide a given patient population into subpopulations of “responders” and “non-responders,” allowing prescribers to better predict the potential therapeutic effect of a drug. Pharmacogenomic testing may also lead to more predictable toxicity profiling for individual patients, thus prospectively identifying and eventually minimizing idiosyncratic or unexpected drug reactions. Such testing might also offer new insight into the mechanisms of such toxicities. Overall, this approach has the potential to account for variability in drug response, maximize beneficial and minimize untoward drug effects, optimize therapeutic decision making, and ultimately improve clinical outcomes.

To facilitate utilization of pharmacogenomic-guided therapy, genomic diagnostics are also being developed at a rapid rate. Microarray and “chip” technologies have enabled the simultaneous evaluation of multiple SNPs in multiple genes. We envision that a variety of diagnostic pharmacogenomic “packages” will be developed for certain patient populations at risk for or recently diagnosed with specific diseases (e.g. breast cancer, cardiovascular disease, asthma). These packages will provide critical genomic information that will help clinicians predict disease susceptibility, the likelihood of disease progression, drug efficacy, and drug toxicity. Together with other clinical information (e.g. breast cancer stage, lipid profile, lung function studies), the genomic data will

**Table 1.** Examples of genetic predictors of drug response.

Gene target	SNP	Affected drug	Clinical implication
Thiopurine methyltransferase (Krynetski et al. 1996)	TPMT*2, *3A, *3C	Mercaptopurine/azathioprine	Increased toxicity (hematopoietic)
CYP2C19 (Furuta et al. 1998)	CYP2C19*2, *3	Omeprazole	Enhanced efficacy (ulcer cure rates)
β <sub>2</sub> -Adrenergic receptor (Lima et al. 1999)	Arg16Gly	Albuterol	Increased tolerance (receptor desensitization and reduced bronchodilation)

substantially improve a clinician's ability to identify subpopulations of patients most likely to respond to specific preventive or therapeutic strategies, as well as the ability to identify specific drugs and dosing regimens that can be used in individual patients to optimize outcomes. In addition, pharmacogenomic concepts will be applied to the development of novel therapeutic agents by the pharmaceutical industry, which has already reported substantial increases in the use of pharmacogenomic testing in clinical trials (Roses 2000). This approach will eventually yield medicines that will directly modify genetically validated targets.

The future of pharmacogenomics is quickly becoming a reality. Indeed, preclinical and clinical investigations are already evaluating the contribution of multiple genes to the observed variability in drug response. However, unraveling the full potential of pharmacogenomics will require the translation of discoveries from basic to clinical science, and eventually the application of these findings to patient care (i.e. from bench to bedside). Current approaches to pharmacogenomic research involve SNP discovery, *in vitro* studies that characterize the functional and mechanistic significance of known SNPs, and *in vivo* studies that investigate the clinical relevance of known SNPs in healthy volunteers or patients. Clinical evaluations have included prospective clinical pharmacology studies with pharmacokinetic and pharmacodynamic end points and retrospective outcome analyses of genetic subgroups from randomized controlled clinical trials. Prospective clinical trials that evaluate the safety and efficacy of pharmacogenomic-guided drug therapy will be necessary to determine if these strategies can improve patient outcomes. Furthermore, detailed economic analyses that evaluate the cost-effectiveness of such approaches will be crucial before widespread implementation into clinical practice can occur.

Understanding the relevance of genomic information will be crucial to close the gap between basic science and patient care. Moreover, open dialog regarding the numerous ethical issues surrounding genomic testing, such as the protection of privacy as it relates to insurance and employment, will be needed as this field moves towards clinical application. Ultimately, the factors essential to the appropriate utilization of pharmacogenomic data include collaboration between basic researchers and clinicians, development of a multidisciplinary approach to patient care, and education of clinician-scientists in pharmacogenomic medicine. Perhaps the biggest challenge to the effective use of pharmacogenomic strategies in clinical practice involves educating the public on its availability, uses, and limitations.

The recent sequencing of the human genome has facilitated identification of polymorphic variants in genes involved in the disposition and pharmacologic action of numerous drugs. The rapidly growing field of pharmacogenomics offers enormous potential for improving how clinicians use medications. Pharmacogenomics will ultimately minimize variability in how patients respond to medications, thereby enabling clinicians to individualize therapy and improve overall clinical outcome.

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