It appears that the 21st century may mark the merging of two inter-related fields: biology and medicine. Today, physicians in all medical practices (including psychiatric and neurodegenerative disorders, oncology, as well as metabolic and cardiovascular diseases), have to guess which medication will work best for a given patient via trial and error method. This approach is often inefficient, costly, and sometimes becomes unacceptable when life-threatening conditions occur. However, because of the new spectrum of knowledge generated by the human genome project, this type of guessing-game practice may no longer be needed for drug selection in the future. If the concept of pharmacogenomics is credible, then the genetic make-up of an individual patient can be checked prior to drug treatment. By doing so, physicians may have the opportunity to treat not only the disease, but also individual patients more efficiently and safely using appropriate drugs.

Development of the Concept of Genotype-based Medicine

Any medical drug treatment initiation will raise questions about its efficacy and safety. This is because of individual variations in drug response and adverse drug reactions, which pose a major public health problem. At present physicians cannot predict which groups of patients respond positively, which ones are non-responders, and which ones experience adverse reactions for the same medication and dose. In each and every case, it becomes a challenge for clinicians to work out a dosage regimen for an individual patient. For instance, a subset of patients with cardiovascular disease did not respond to cholesterol–lowering drugs; in fact and a minority of them exhibited severe adverse effects. Similarly, a significant portion of epileptic patients, when treated with anti-epileptic drugs, exhibited a high rate of adverse drug reactions. In the United States alone, over two million cases of adverse drug reactions (including 100000 deaths) are reported each year. Moreover, according to a German study, about 69% of adverse drug reactions are attributable to new hospital admissions. Therapeutic responses of drugs vary over time and are influenced by age, sex, environmental and genetic factors, and even pathology itself. These
factors affect drug absorption, distribution, metabolism and excretion. The inter-individual variation (20% – 95%) in drug response could be partly due to genetic polymorphisms in drug-metabolizing enzymes and drug transporters. For instance, in surgical anesthesia and in chronic pain management, fentanyl is used as an adjunct. However, it has recently been shown that its toxicity could be partially due to cytochrome P450 (CYP) 3A4*1B and 3A5*3 variant alleles, which cause variable metabolism. Moreover, homozygosity in the CYP3A5*3 allele has also been found to impair the metabolism of fentanyl. Similarly, the best way to avoid the side effects of warfarin treatment is to determine the genotype of the CYP2C9 locus given that the CYP2C9*2 and CYP2C9*3 alleles reduce the clearance of warfarin and increase the risk of bleeding. In another study, poor response in the treatment of depression is shown to be due to gene duplication of CYP2D6 that metabolizes many anti-depressants. Additionally, azathioprine and its metabolite 6-mercaptopurine have been extensively used in the treatment of acute lymphoblastic leukemia, rheumatoid arthritis and a range of other conditions. However, when some patients were treated with standard doses of mercaptopurine and azathioprine, approximately 3% experienced severe and life-threatening hematopoietic toxicity. This adverse effect was shown to be caused by the loss of the function of thiopurine S-methyltransferase (TPMT). There is also a growing list of genetic polymorphisms in drug targets that have been shown to influence drug response. For example, genetic variation in the ABCB1/MDR1 gene and its product P-glycoprotein-170 increases the risk of ulcerative colitis. Its intrinsic and acquired over-expression also results in chemoresistance.

In short, the available literature suggests that there is strong evidence that genetic polymorphisms of drug-metabolizing enzymes affect about 30% of all drugs. Therefore, it is possible to improve the quality of life for some patients just by designing the drug according to the genotype of an individual.

**Progress in Genotype-based Drugs**

Recent important advancements in the human genome project, the availability of a large collection of single nucleotide polymorphisms (SNPs), the haplotype map (HapMap), and many other techniques such as microarray have opened the way to develop new strategies for improving drug efficacy and safety. It is now possible to analyze many drug-metabolizing and drug-transporting genes for inherited variations, and to address how the genetic make-up of an individual may be associated with individual variability in response to drug treatment. As a result of this advancement as well as to understand drug deposition and its clinical consequences, two rapidly developing fields—pharmacogenetics (where the focus is on single genes) and pharmacogenomics (where the focus is on many genes) — has undertaken studies on the genetic personalization of drug response. In individualized medicine, drugs and doses are selected using the genetic background of an individual. Such personalized drugs are expected to enable physicians to optimize the dosage of drugs with the highest therapeutic efficacy while minimizing adverse effects. Thus, pharmacogenetic testing prior to drug treatment offers powerful tools for the development of personalized medicine for those patients who exhibit other adverse effects.
or no benefit. This may also have a profound impact on the treatment of complex psychiatric disorders such as schizophrenia. However, progress in this field is slower than expected.

**Potential Difficulties and Pitfalls**

Much has been published in the literature in recent years about the potential of pharmacogenetic testing and individualized medicine. It is possible that a greater understanding of the workings of the human genome may change the way we understand modern medicine. Results from genetic polymorphism studies illustrate how pharmacogenomic testing may contribute to the goal of individualized medicine. However, whether it will lead to improved and economically feasible therapy remains to be seen. Its impact on medicine at present is minimal. In designing any such drugs, one should not forget the complexity of multi-gene diseases such as heart disease, diabetes, and psychiatric disorders. They remind us that a combined analysis of multiple genetic variants in several genes may be necessary rather than information on a single gene. In addition, there are many negative results regarding the association of gene polymorphism and drug efficacy and toxicity. For instance, the previously reported relationship between the CETP Taq-1 variant and the response to statins have now been disproved. Similarly, in the multi-drug resistant gene (MDR1), certain polymorphisms may not have any effect on drug response. Although CYP3A is expressed in the kidney and extensively metabolizes cyclosporine, CYP3A5*1 allele expression is not involved in cyclosporine dosing and blood pressure regulation in the Caucasian population. Additionally, several polymorphisms in the human carboxylesterase 2 gene are not found to be associated with protein activity. Conversely, some genetic variants in the non-target gene may also be involved in producing adverse effects of drug treatment. This is because multiple genes and factors control most drug responses. In addition, variable gene expression and patient population heterogeneity may also contribute to new problems. Therefore, to promote this personalized medicine, information on pharmacogenetics that is clinically convenient is necessary.

To date, studies that unambiguously prove the clinical value of pharmacogenetic testing are lacking. When such testing does become available in the future, it may prevent some but certainly not all adverse drug reactions. This is because of our lack of knowledge of mechanisms of the action of drugs on genes or their off-target effects. Therefore, personalized medicine developed by genotype screening of an individual may not become an error-free treatment, and there will always be false positive and negative results similar to other screening procedures. However, it has the potential to do good and as suggested by other investigators, it can be regarded as an add-on technology in addition to established methods. Most importantly, the translation of personalized medicine into clinical practice requires public education, confidentiality, physician training, novel clinical trial design, new statistical methods, and validation of the data. In addition, social, ethical, and economical consensus on issues such as genetic discrimination needs to be addressed by regulatory agencies. In spite of these limitations, however, the pharmacogenomics approach offers optimism, powerful tools, and challenges for the future to optimize drug therapy that is suitable for individual patients.
References


