

PHARMACOGENOMICS: ARE PHARMACISTS READY FOR GENOTYPED PRESCRIBING?

By Sagbir Akhtar, PhD, MRPharmS



The complete sequencing of the human genome will result in improved understanding of the role of genes in disease and drug response. A spin-off from the Human Genome Project is the rapidly emerging field of pharmacogenomics, which aims to correlate genetic variations (polymorphisms) of patients with variations in their response to drugs. As this field develops, genetic profiling will become an integral part of the prescription process whereby drugs will be prescribed based on a patient's genotype. Pharmacists will need to understand the concepts and promise of pharmacogenomics in order to adapt to the demands of genotype-based prescribing. This article provides an overview of how pharmacogenomics might influence pharmaceutical health care in the future

A major landmark in medical science was reached early last year with the reporting of the first draft of the human genome sequence.^{1,2} Essentially we now have the complete anatomy of the human genome before us and work has already begun on the complex task of annotating genes with their function and role in human development and disease. This will ultimately lead to the so-called "Periodic Table of Life" containing a complete list of genes, their structure and their function in a given organ, tissue or cell type. The complete mapping of the human genome provides a starting point for a thorough understanding of our basic genetic make-up and how variations in our genetic instructions results in disease or a particular therapeutic outcome. Pharmacogenomics is the study of how an individual's genetic inheritance affects the body's response to drugs. It has been the subject of several recent reviews.³⁻⁵ The term is derived from the words pharmacology and genomics and is thus the intersection of pharmaceuticals

and genetics. It holds the promise that drugs might one day be tailor-made for individuals and adapted to each person's own genetic make-up. Environment, diet, age, lifestyle, and state of health all can influence a person's response to medicines, but understanding an individual's genetic make-up is thought to be the key to creating personalised drugs with greater efficacy and safety. Panel 1 highlights the potential benefits of pharmacogenomics to pharmaceutical health care in the future. However, the scenario in Panel 2 may provide a better flavour of the promise of pharmacogenomics in pharmacy.

This scenario is pharmacogenomic prescribing of the future. It implies that optimisation of drug therapy based on each patient's genetic code may be within our grasp and the above scenario highlights several advantages of genotyped prescribing. In conventional health care, the patient's resistance to therapy with drug C, would only be realised after trial and error (iteration). The unnecessary prescribing of drug C and the potential adverse reactions (with the associated costs) would thus be avoided. Furthermore, optimising of dose (as in the case for drug B) is classically performed by iteration following repeat visits by the practitioner. This is time consuming and may even prove fatal in life-threaten-

ing diseases, like brain cancer, where time is of the essence.

Pharmacogenomics aims to provide the right prescription immediately for the maximum benefit of the patient. Pharmacists are likely to be key players in the dispensing of drugs based on an individual's gene profile.

A GIVEN DRUG DOES NOT WORK FOR ALL PATIENTS

It is well known that a given drug does not work for all patients and certainly not at the same dose.⁴ Individual variability in both the response to therapeutic agents and drug toxicity is common in the clinical setting. For example, 30 per cent of patients with schizophrenia do not respond to treatment with antipsychotics, up to 35 per cent of patients receiving beta-blockers do not respond, and only one in three sufferers of multiple sclerosis respond favourably to interferon beta therapy.⁶ Furthermore, the daily dose of warfarin, for example, may have to be altered considerably to achieve the same pharmacological response in different patients. This can lead to adverse drug reactions. A therapeutic dose of a drug, especially if it has a narrow therapeutic index, in one patient may represent a toxic dose in another. Although

Professor Akhtar is chairman of the Department of Pharmaceutics, Faculty of Pharmacy, Kuwait University, PO Box 24923, Safat 13110, Kuwait. E-mail: s.akhtar@bsc.knuv.edu.kw

Panel 1: The potential benefits of pharmacogenomics to pharmaceutical health care

1 More powerful medicines

Pharmaceutical companies will be able to create drugs based on the proteins, enzymes, and RNA molecules associated with genes and diseases. This will facilitate drug discovery and allow drug makers to produce a therapy more targeted to specific diseases. This accuracy not only will maximise therapeutic effects but also decrease damage to nearby healthy cells.

1 Better, safer drugs the first time

Instead of the standard trial-and-error method of matching patients with the right drugs, doctors and pharmacists will be able to analyse a patient's genetic profile and prescribe the best available drug therapy from the outset. Not only will this take the guesswork out of finding the right drug, it will speed recovery time and increase safety as the likelihood of adverse reactions is eliminated.

1 More accurate methods of determining appropriate drug dosages

Current methods of basing dosages on weight and age will be replaced with dosages based on a person's genetics — how well the body processes the medicine and the time it takes to metabolise it. This will maximise the therapy's effectiveness and decrease the likelihood of adverse reactions.

1 Advanced screening for disease

Knowing one's genetic code will allow a person to make adequate lifestyle and environmental changes at an early age so as to avoid or lessen the severity of a genetic disease. Likewise, advance knowledge of a particular disease susceptibility will allow careful monitoring, and treatments can be introduced at the most appropriate stage to maximise their therapy.

1 Improvements in the drug discovery and approval process

Pharmaceutical companies will be able to discover potential therapies more easily using genome targets. Previously failed drug candidates may be revived as they are matched with the niche population they serve. The drug approval process should be facilitated as trials are targeted for specific genetic population groups — providing greater degrees of success. Targeting only those persons capable of responding to a drug will reduce the cost and risk of clinical trials.

1 Decrease in the overall cost of health care

Decreases in the number of adverse drug reactions, the number of failed drug trials, the time it takes to get a drug approved, the length of time patients are on medication, the number of medicines patients must take to find an effective therapy, the effects of a disease on the body (through early detection), and an increase in the range of possible drug targets will promote a net decrease in the cost of health care.

This panel is adapted from information provided by the human genome project and the department of energy's office of science, United States Government

diet, lifestyle, age and environmental factors can all influence drug response and toxicity, an emerging concept is that genetic variation (polymorphisms) is a key factor. Maximising drug response while minimising adverse effects for individuals through the study of gene variations is the goal of current pharmacogenomics.

GENETIC VARIATION AND SINGLE NUCLEOTIDE POLYMORPHISMS

Genetic variation or polymorphisms are generally defined as variations in DNA sequences that occur in at least 1 per cent of the population. Most genetic variations between individuals are due to single base differences in the DNA sequence. These are termed "single nucleotide polymorphisms", or SNPs (pronounced "snips"). SNPs occur with an average frequency of one per 1,000 base pairs and approximately two of every three SNPs involve the replacement of cytosine with thymine. Since the human genome contains three billion nucleotides, approximately three to 10 million SNPs are expected to exist between any two genomes.

However, it is expected that the majority will probably not be clinically relevant and only a fraction of these SNPs are likely to influence drug response.⁷

The first stage, though, is to discover these SNPs and catalogue them within the

human genome to produce a so-called "SNP map". This discovery stage is already well under way with, among others, the formation of SNP consortium in 1999, a joint venture between the Wellcome Trust, major pharmaceutical companies, eg, AstraZeneca, Pfizer and leading academic DNA sequencing centres, which aims to create a database of up to 300,000 SNPs in the next year or so.³⁻⁶

The goal then is to correlate the presence of SNPs with disease aetiology and drug response, the so called "SNP scoring". This promises to highlight how a given SNP pattern in a patient will determine therapeutic outcomes and the likelihood of acquiring a particular disease.

GENETIC TESTS AND GENOTYPE PROFILES

The potential correlation of patterns of SNP expression (genotype) with varying pharmacological actions (clinical phenotype) will ultimately lead to diagnostic gene tests or genetic profiling that will form the basis of prescribing in the future. Initially, genetic testing is likely to be specific for a given disease or drug response but ultimately, when sufficient information from SNP scoring is available, a single gene expression profile may be all that is needed for prescribing purposes. Of course, it may need to be updated regularly as a function of age or disease progression, but the smart card scenario may not be unrealistic. The storage, processing and accessing of test results has legal and ethical implications but such information could be retained by patients on smart cards. Alternatively, it may be held by health care professionals, for example, as part of pharmacy patient records or even as a central computer bank of patient information accessible only by authorised health care providers.

Genetic tests, especially those that require regular updating, may be performed in pharmacies. Pharmacists already play an important role in point-of-care testing of patients with asthma, the diagnosis of *Helicobacter pylori* infections and monitoring of anticoagulant therapy.⁸ So, genetic testing for pharmacogenomics based prescribing is a logical progression of

Panel 2: A future scenario?

Imagine you are the clinical oncology pharmacist on duty at a modern hospital. A patient presents with a suspected brain tumour and his referred to you for the correct treatment regimen. The first thing you do is ask for the patient's credit card, not because you want advance payment for the health care you are offering but, rather, because on this "smart"card is the complete individualised gene profile for this patient. You insert the credit card into your "super-computer", which has programs that can match drug treatments to known patterns of gene expression, and up comes on the screen, in a matter of moments, a list of three drugs (A, B, and D) which are specifically prescribed for this patient. Drug C, another common drug given to patients with the same type of brain tumours, was not indicated because this patient's credit card information revealed high expression of gene X. It just so happens that gene X is a drug resistance gene that neutralises the activity of drug C. Furthermore, the computer recommends a higher than conventional dose of drug B. You discover that this is due to expression of gene Y, an enzyme that partially metabolises drug B. You discuss the information with the medical practitioners on duty and dispense the computer-specified medication. You then counsel the patient on the personalised drugs dispensed.

the ever-expanding role of pharmacists in providing point-of-care services. This would make particular sense should pharmacist prescribing become a reality in the future. At the very least, pharmacists should be able to perform the genetic test, consult the health practitioner in charge (eg, a general practitioner) to "co-prescribe" the right dose and drug to the patient. This is in keeping with the Government's plan to allow repeat prescribing by pharmacists by the year 2004 and with the view that pharmacists could potentially act as supplementary prescribers whereby they can alter the dose of prescribed drugs as necessary.⁹ There is nothing in the plan to suggest that dose adjustments could not be based on information from genetic testing. Thus, genetic testing by pharmacists is a real probability rather than a mere possibility.

PHARMACOGENOMIC PRESCRIPTIONS

The scenario presented at the outset of this article suggests that pharmacogenomics is purely futuristic. In fact, pharmacogenomics is already being used for customised prescribing of several drugs both old and new.

Let us consider the case of metastatic breast cancer patients receiving the new drug trastuzumab (Herceptin), which has been available in the United States since 1998.¹⁰ This drug is the first humanised monoclonal antibody for the treatment of breast cancer. It is specifically designed to be effective in only about 30 per cent of breast cancer patients whose tumours overexpress the human epidermal growth factor receptor 2 (HER2) protein. Herceptin is one of the first drugs whose development and prescribing is based on testing of patients for the drug target (the HER2 protein) in order to predict drug efficacy. Since the drug can have unpleasant side effects including ventricular dysfunction and congestive heart failure, it is vitally important to limit its use to only those patients likely to respond. Testing for HER2 status thus avoids administration to non-responders and prevents their exposure to life-threatening side effects. In this case pharmacogenomics offers cost-savings on two fronts. By targeting responders only, it limits the number of patients receiving this effective but expensive therapy and by avoiding non-responders, it avoids costs that would otherwise be incurred in managing adverse effects. Indeed, recent data from the US estimated that adverse drug reactions accounted for more than two million hospital admissions and more than 100,000 deaths in 1994, making them a leading cause of mortality.¹¹

Cancer patients who are treated with the more established drug, 5-fluorouracil, sometimes develop severe neurotoxicity because of a reduced activity of dihydropyrimidine dehydrogenase, the enzyme responsible for metabolising 90 per cent of this drug. A single nucleotide polymorphism in the enzyme gene is thought to be responsible for its toxic build up in some patients causing severe pyrimidinemia and

pyridinuria. It is likely that a test for this deficiency may be the next standard clinical test.¹²

Furthermore, it is already well known that prescribing of many of the current drugs is based on hepatic and renal function tests. This includes knowledge of the patient's enzyme levels especially those influencing the drug's pharmacokinetic or pharmacodynamic properties, such as drug metabolising enzymes. It is now known that almost all of the hepatic cytochrome P450 group of enzymes (CYPs) exhibit genetic polymorphisms that influence a patient's ability to metabolise drugs. Such variations, which are also linked with ethnicity and gender, are largely due to genetic polymorphisms in four of the functionally most important isoenzymes: CYP2A6, CYP2C9, CYP2C19 and CYP2D6, and which account for about 40 per cent of all drug metabolism mediated by CYPs.⁵ Genetic variation in these enzymes results in patient populations that, in the extremes, are either "extensive metabolisers" or "poor metabolisers" of drugs. Hence, the same dose of drug could yield poor or no effect in extensive metabolisers or a toxic response in poor metabolisers.

CYP2D6 plays an important role in the metabolism of many drugs including tricyclic antidepressants, and beta-blockers whose dose has to be adjusted in patients with a polymorphism that essentially inactivates or reduces its activity (Table 1). In asthma patients, the contribution of polymorphism in CYPs may be complicated by additional polymorphism in the beta-adrenergic receptor that produces variable response with beta-agonists at the drug receptor level.¹³ If a patient is an extensive metaboliser of beta-agonists and has receptors insensitive to the drug, then it is likely that the patient will not respond at all to this therapeutic option. On the contrary, if high doses of drugs are

administered to overcome these problems, the risk of adverse reactions in these patients becomes significant. Thus, the interplay between different SNPs in different genes in the same disease can be complex. However, the level of complexity increases significantly in the case of pharmacogenomics of a patient with multiple conditions who is receiving many drugs. No wonder pharmacists will need to be equipped with "super-computers" to get the prescription right, as suggested in the scenario in Panel 2.

Adding yet another level of complexity is the use of pro-drugs that require activation by enzymes before they can exert therapeutic effects. The CYP group of isoenzymes, in addition to metabolism, are also responsible for activating some pro-drugs. For example, many narcotic analgesics are activated by CYP2D6. Thus patients with varying activity of this enzyme will produce variable levels of the active metabolite and hence acquire varying degrees of pain relief from a given dose of a narcotic analgesic such as codeine.³

In addition to drug metabolising enzymes and drug receptors, genetic polymorphisms that underlie disease pathogenesis can also be major determinants of drug efficacy. For example, mutations in apolipoprotein E not only predict onset of the disease but also determine the responsiveness of Alzheimer's patients to tacrine therapy.¹⁴ Hypertensive patients' response to angiotensin-converting-enzyme (ACE) inhibitors is determined by a genetic polymorphism in the DCP1 gene encoding the enzyme. This polymorphism is thought to account for almost half the statistical variance in serum ACE levels among individuals.¹⁵ Table 1 provides examples of known genetic polymorphisms in drug metabolising enzymes and other drug targets and their clinical significance upon treatment with candidate drugs.

TABLE 1: SELECTED EXAMPLES OF GENETIC POLYMORPHISMS INFLUENCING DRUG RESPONSE

Polymorphic gene	Example of drug(s) affected	Pharmaceutical consequences of polymorphisms
<i>Metabolising enzymes</i>		
CYP2D6	Beta-blockers Antipsychotics Narcotics eg, codeine Imipramine	Altered beta-blocker effect Tardive dyskinesia Narcotic side effects Adjustment of imipramine dose
CYP2C9	Warfarin	Adjustment of warfarin dose
CYP2C19	Omeprazole	Variable response in peptic ulcers
Dihydropyrimidine dehydrogenase	5-Fluorouracil	5-FU-induced neurotoxicity
<i>Functional enzymes</i>		
Angiotensin converting enzyme (ACE)	ACE inhibitors eg, enalapril, captopril	Variable response in hypertension
<i>Protein targets</i>		
Apolipoprotein E4	Tacrine	Variable Response to Alzheimer's disease
5-Hydroxytryptamine transporter	Fluvoxamine	Variable response in delusional depression
<i>Receptor protein targets</i>		
Beta,-adrenoreceptor	Beta-blockers	Variable response in asthma
Glucocorticoid receptor	Dexamethasone	Variable response to cortisol and insulin

Adapted from Evans and Relling³ 1999.³ For a more comprehensive list see website:
<http://www.sciencemag.org/feature/data/1044449.sh1>

THE IMPACT ON DRUG DEVELOPMENT

Pharmacogenomics has obvious benefits for patients, but it will also benefit the pharmaceutical industry (see also Panel 1). The formation of the SNP consortium, which includes many major pharmaceutical companies, indicates the excitement and expectation of the industry towards developing drug products that use genetic susceptibility as part of the rationale for selecting new medicines. Information derived from pharmacogenomic studies could have an impact on drug development at several stages in the process.

It can help identify specific targets for drug action (eg, a particular genetic variant of a receptor), better identify the target patient population (eg, those patients with the targeted receptor variant) and similarly, improve the design of clinical trials (eg, limit trials to patients most likely to show a response). The ability to predict adverse outcomes in some patients (and possibly explain unexpected results in clinical studies) gives the study sponsors the opportunity to manage clinical trials and the drug approval process itself better. There are clear cost-benefits associated with this approach. However, a potential drawback is that if a different drug has to be developed for every polymorphism, then the cost of developing drugs, and thus health care costs, might become excessive. Also, if the patient population with a particular polymorphism is too small then pharmaceutical companies may be unwilling to develop a drug based on poor returns relative to the cost of bringing the drug to market.¹² The latter is an issue of supply and demand, something that the pharmaceutical industry is well aware of, and already addresses.

The drug approval and regulatory authorities (eg, Food and Drug Administration in the US) are supportive of pharmaceutical companies using pharmacogenomics testing throughout drug development.¹² They realise that understanding how to adjust dose to avoid toxicity may allow the marketing of a drug that would have an unacceptable risk of adverse effects if its toxicity were unpredictable and not preventable. Information on genetic polymorphisms affecting important biopharmaceutical pathways (eg, absorption-distribution-metabolism-elimination), will allow for dosing adjustments to achieve the safe and effective use of a new drug. The industry could use this information to improve dosing recommendations in patient information leaflets and product labelling, thereby increasing the effectiveness of prescribed drugs.

ETHICAL AND LEGAL ISSUES

There are considerable social, legal, ethical and moral issues that arise regarding the possible use of genetic tests assessing a patient's predisposition to a particular disease or drug response. These include issues of privacy and confidentiality, risk-benefit

analysis, DNA and data storage and pharmacoeconomics.¹⁶ In addition, the issue of gender and ethnic differences in drug response could lead to additional concerns. For example, the case of potential variations in drug response by individuals from different ethnic communities has led to a recent argument that a new principle for research ethics, "the principle of respect for communities", should be added to currently accepted working principles of bioethics.¹⁷

It is envisaged that such legal and moral concerns will be greatest when gene expression profiles are presented in a "widely accessible" credit card scenario. Issues of data accessibility and confidentiality become paramount. However, there may be differences between the ethical implications of testing for disease predisposition such as confidentiality, the patient's right to know, availability of treatment options, refusal of employment and life insurance, and those concerning tests designed simply to predict the effectiveness of therapies for existing conditions. The latter may be more acceptable to the general public, though it is hard to predict the social, legal and ethical consequences of pharmacogenomics. The lessons learned from the public's outcry to genetically modified foods may help refine strategies (of scientists, legislators and Government) that are used to educate both the public and health care professionals alike.

CONCLUSIONS

The promise of pharmacogenomics is immense. Pharmacogenomics offers powerful new opportunities not only to identify, at an early stage, those individuals likely to develop a given disease but also to improve their therapy by increasing efficacy and specificity of treatment. The future impact of pharmacogenomics is likely to be in improved point-of-care health services (ie, customised and rational prescribing based on genotype) and in improvements in new drug development. Pharmacists and pharmaceutical scientists will likely be involved in both instances. As encompassed in the earlier "future scenario", the immediate impact of pharmacogenomics will be to allow medical practitioners and pharmacists to avoid the prescription of drugs to non-responders (eg, due to the presence of a drug resistance gene or lack of target gene) or those patients who are predisposed to adverse reactions. Also it will allow practitioners to prescribe the most effective drug dose at the outset (eg, through knowledge of the levels of metabolising enzymes) rather than rely on iterative methods of dose adjustment. Pharmacists have an essential role to play in providing this health care, and therefore, need to be aware of the new opportunities that pharmacogenomics will present.

REFERENCES

1. International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. *Nature* 2001;409:860-921.
2. Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG et al. The sequence of the human genome. *Science* 2001;291:1304-1351.
3. Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. *Science* 1999;286:487-91.
4. Sadee W. Finding the right drug for the right patient. *Pharm Res* 1998;15:959-63.
5. Vessel ES. Advances in pharmacogenetics and pharmacogenomics. *J Clin Pharmacol* 2000;40:930-8.
6. Destenaves B, Thomas F. New advances in pharmacogenomics. *Current Opin Chem Biol* 2000;4:440-4.
7. McCarthy JJ, Hilfiker R. The use of single-nucleotide polymorphism maps in pharmacogenomics. *Nature Biotechnol* 2000;18:505-8.
8. Moffat T. Point-of-care testing in the community pharmacy. *Pharm J* 2001;267:267-8.
9. Bellingham, C. Point-of-care testing in the community: a new role for pharmacists. *Pharm J* 2001;267:256-7.
10. Stebbing J, Copson E, O'Reilly S. Herceptin (trastuzumab) in advanced breast cancer. *Cancer Treat Rev* 2000;26:287-90.
11. Lazarou J, Pomernaz BH, Corey PN. Incidence of adverse reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998;279:1200-5.
12. Rioux PP. Clinical trials in pharmacogenetics and pharmacogenomics: methods and applications. *Am J Health-Syst Pharm* 2000;57:887-901.
13. Kotani Y, Nishimura Y, Maeda H, Yokoyama M. Beta₂-adrenergic receptor polymorphisms affect airway responsiveness to salbutamol in asthmatics. *J Asthma* 1999;36:583-90.
14. Poirier J. Apolipoprotein E: a pharmacogenetic target for the treatment of Alzheimer's disease. *Mol Diagn* 1999;4:4335-41.
15. Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. *J Clin Invest* 1990;86:1343-6.
16. Issa AM. Ethical considerations in clinical pharmacogenomics research. *Trends Pharmacol Sci* 2000;21:247-9.
17. Weijer CW. Protecting communities in research: philosophical and pragmatic challenges. *Camb Q Health Ethics* 1999;8:501-13.