

Editorial

Personalised Medicine: Fantasy or a Realistic Goal?

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Hardly a week goes by without mention in the medical literature, and even the lay press^[1,2], of gene expression data obtained from DNA microarrays and the potential of individualising patients' diseases and treatments. Personalised medicine is based on the concept that diseases are heterogeneous, from their causes to rates of progression to their response to drugs. Each person's disease might be unique and therefore that person needs to be treated as an individual. Most people would agree with this in principle, but how realistic is it in practice? This article focuses on the current status in cancer.

Genetic understanding of common disorders is still in its infancy^[3] and although classical genetics has been a powerful tool for dissecting molecular diseases that are affected by the gain or loss of function of a protein encoded by a single gene, it has proved to be less useful for understanding diseases such as cancer that are controlled by many genes (polygenic). The analysis of differential gene expression - expression genetics or functional genomics - has become one of the most widely used strategies for discovering and understanding the molecular basis of cancer^[4]. The expression of almost all human genes is being examined in human malignancies by using DNA microarrays. Results to date have demonstrated that patterns of gene expression can distinguish between tumours of different anatomical origin, as well as define new subgroups of cancer with similar histological appearance but distinct molecular profiles. Advances in the classification of cancer are illustrated by: the ability to distinguish accurately between acute lymphocytic leukaemia and acute myeloid leukaemia by examining the expression of 50 genes^[5]; the conclusion that gene expression profiling can be a more powerful predictor of the outcome of disease in young patients with breast cancer than standard systems based on clinical and histological criteria^[6,7]; as few as 6 genes being sufficient to predict overall survival in diffuse large

B-cell malignancies^[8]; the use of aggregate patterns of gene expression (metagenes) that correlate with lymph node status and recurrence and which are capable of predicting outcomes with 90% accuracy in breast cancer^[9].

While being impressive, these results have had only a limited impact in the clinic. Why is this? The main barrier impeding the routine clinical implementation of DNA-microarray based diagnosis of cancer is not just the cost but rather the time required to perform the necessary carefully controlled, large-scale studies to confirm these findings.

The 'common disease, common variant' hypothesis predicts that most of the variation in susceptibility to highly prevalent diseases is caused by variants that occur at high frequency in human populations^[3]. Any two unrelated individuals differ by approximately one base pair (bp) change in every 1,000 bp and this frequency equates to 3×10^6 differences between any two unrelated individuals. Many of these single-nucleotide polymorphisms (SNPs) affect health and clinical outcome and they have the potential to identify the genetic factors contributing to complex diseases such as cancer, and to medically complex phenotypes such as drug sensitivity and drug resistance^[10,11]. The use of SNP markers has made it possible to search for variants systematically.

A disappointing feature of modern medicines is how often they fail to work. Even when they do work, they are often associated with serious adverse reactions and these are one of the leading causes of death and illness in the developed world^[12]. Pharmacogenomics/pharmacogenetics (PG), is the study of genetic polymorphisms in relation to drug response. Variability in response to drugs can lead to therapeutic failure or adverse drug reactions in individuals or sub-populations of patients. By predicting the drug response of an individual, it should be possible to increase the success of therapies, reduce the incidence of side effects and to create a SNP profile for patients who

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experience adverse events or those that respond clinically to the medicine^[13].

This may seem simple, but in practice, for any gene there may be multiple alleles that give rise to the condition, most or all of which will need to be detected. There may be multiple genes that contribute independently to a particular drug-related response, leading to a low positive predictive value for any one of these. Also, variations in drug response are not just related to genetic background - age, health, diet, and other drugs - many different factors must be considered.

Nonetheless, PG has the potential to provide patient-specific diagnostics to optimise drug treatment. Using DNA that can be isolated from a few milliliters of blood it is possible to determine thousands of genotypes and it will soon be possible to screen for thousands of SNPs in one test. This will be necessary due to the polygenic nature of most drug effects, so treatment decisions will be based on a panel of SNPs. These will provide additional tools for individualising and optimising drug therapy. This approach is already being applied clinically in, for example, the case of Iressa (gefitinib, ZD-1839), which is a tyrosine kinase inhibitor that targets the intracellular domain of the epidermal growth factor receptor (EGFR). The drug works best in those patients with EGFR-dependent tumours and Iressa responders have mutations in a specific stretch of the EGFR gene. Identifying these mutations, and hence those patients with EGFR-dependent tumours that will respond to therapy, is the basis of a recent genetic test to guide physicians treating patients with non-small cell lung cancer. Enthusiasm for the application of PG has to be tempered by, however, the example of 5-Fluorouracil (5-FU) where there are over 29 genes involved in the 5-FU pathway. Genetic variations in any or all can contribute to systemic toxicity or anti-tumour response.

There are many other reasons why PG is rarely used in clinical practice at present. The sensitivity and accuracy of the analytical methods must improve dramatically when searching for candidate genes and must be standardised to permit comparisons across studies. Relationships established through correlation analysis between drug response phenotype and genetic variations are correlative, not causal. Methods of candidate gene validation must be improved, with particular attention paid to the microenvironment of the cancer tissue *in vivo*. Genes and proteins do not work in isolation but function within integrated systems that are responsible for the biological properties of the cancer cell and determine chemosensitivity. This is why steps are being taken to integrate drug pathway analysis, rather than

single gene studies, into clinical trials to assess the predictive power of chemotherapy (CT) activity and response^[14]. Resolving the intricate interactions among proteins in these systems will require the development of novel analytical models^[11]. Another critical issue is that functionally important polymorphisms can reside outside the coding or regulatory regions of genes^[15].

For a test to be clinically valid it must also adequately predict the association of the test result with a clinical outcome. Primarily this is a function of the relationship of a gene, and sequence variants of that gene, with an expected outcome. This relationship can be difficult to establish. It is difficult to conduct definitive clinical trials to prove that individualisation of drug therapy on the basis of genetics improves clinical outcomes as well as to control for non-genetic confounders e.g. drug interactions, diet and smoking. It is essential, therefore, that clinical trials include correlative science components in order to define clearly the relative contribution of PG to optimisation of CT^[14]. If the use of medication is to evolve to individualised therapy using genetics at least two aspects of health care will have to change: (1) protection against the misuse of genetic information has to be introduced (2) the additional costs for this has to be accepted with the realisation that that in the long run, decreasing the frequency of adverse drug effects and increasing the probability of successful therapy will probably lower the cost of health care^[16]. However, whether taxpayers and patients will be prepared to pay more for individualised treatment is uncertain at present^[11]. In addition, for decades clinicians have been advised to start treatment with the default 'average dose'. Individualising dosages, even based on easily assessed patient characteristics (such as age or renal function) has not been widely accepted by the medical or pharmaceutical professions. There is resistance to relying on tests for every medical decision, and a 'trial and error' approach to drug dosing has become widely accepted. Not only does PG require a laboratory test, it also requires an interpretation of genotypes, which will require clinicians to receive further training in molecular biology or genetics.

Genetic variation defines us as individuals and also defines populations. Due to population heterogeneity a specific genotype may be important in determining the effects of medication for one population or disease but not for another; therefore, PG relations must be validated for each therapeutic indication and in different racial and ethnic groups. Remembering this will help ensure accurate elucidation of genetic determinants of drug response and facilitate the translation of PG

into wide-spread clinical practice^[17]. Even if 'the right drug for the right patient' may still be some years away, the right drug for the right population may be a more achievable goal in the future^[10]. DNA microarrays and PG deserve the excitement that they have generated, but this should not lead to unrealistic expectations about the rate at which medicines can be personalised according to genotype^[12]. Gene-based diagnosis makes the education of patients and clinicians imperative. The successful implementation of personalised gene-based medicine will require informed physicians who can critically evaluate the new type of clinical trial and who are prepared to counsel their patients when these methods become routinely available^[18]. Changing clinical practice is always difficult as has been seen with the major difficulties of introducing evidence based medicine and clinical guidelines into routine daily practice^[19]. However, despite the numerous challenges that will need to be met to make personalised medicine a reality, it seems likely that with time, this approach will replace the traditional 'trial-and-error' practice of medicine and one of the first diseases to benefit from this will be cancer^[1,2,11].

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