

Pharmacogenomics: today, tomorrow and beyond

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Introduction

Pharmacogenomics is today's hot topic in biotechnology. In 1996 the word did not even exist; now international pharmacogenomics meetings are held monthly, and articles appear weekly in scientific journals and the popular press. In this Viewpoint article, we will discuss what pharmacogenomics is and elaborate on what the impact of pharmacogenomics will be on medical practice in the next few years and further in the future.

Pharmacogenomics is the merging of the small but well established field of pharmacogenetics with the new technologies of genomics. The focus of pharmacogenomics is on the variability of patient responses to drugs due to people's inherent genetic differences. The variability among humans that is so apparent in such features as height, skin and hair colour, temperament, and disease susceptibility also exists in drug metabolism and response. Many of these

differences are due to genetics. By understanding which genetic factors are responsible for whether a patient will benefit from a drug or be at risk for a particular side effect, it is possible to develop tests to predict these responses before exposure to the drug.

The benefits of such tests are clear. First, the patient can get well sooner because he or she can be prescribed the optimal drug at the outset of therapy without having to go

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through a series of 'the usual-drug-routine' to find the best treatment. Second, early selection of optimal therapy will reduce medical costs, reduce the incidence of polypharmacy and increase patient satisfaction and therapy compliance. Third, identification of genetic causes of patient variability can deepen understanding of the nature of important diseases, leading to new cures. From the viewpoint of a large, diversified health care company with core businesses in pharmaceuticals and medical testing, Abbott Laboratories is excited about the potential for developing improved therapies through pharmacogenomics.

Currently, there are several genes known to influence a patient's response to specific drugs. These genes generally are ones that specify enzymes responsible for drug metabolism in the liver, intestine, and other drug metabolising organs. (The alternative sequences within a gene carried by different people are called alleles.) Information concerning the genes that are now known, and about their principal alleles, is all derived from knowledge of drug metabolism, and as such is limited by our knowledge of biochemistry. Consequently, the number of known drug-metabolising enzyme genes is small. Nevertheless, some of these genes are quite important. For instance, with the cytochrome P450 (CYP) genes, the allele variant CYP2D6 is responsible for the metabolism of many drugs, including tricyclic antidepressants and a number of antiarrhythmics, beta-blockers, and neuroleptics. Certain alleles of the CYP2D6 gene are the cause of slow metabolism of the drugs and have been found to be responsible for some of the characteristic side effects of these drugs (proarrhythmias in the case of the antidepressants and malignant hyperthermia in the case of some neuroleptics).

Variability in the metabolism of azathioprine, a treatment for leukaemia and auto-immune disorders, provides an excellent example of the clinical relevance of pharmacogenetics. The major route of metabolism of azathioprine is by the enzyme thiopurine S-methyltransferase (TPMT). About 10% of Caucasians carry an allele of the TPMT gene that encodes an inactive protein. Since these individuals also carry a normal allele on the other chromosome set, they produce normal enzyme and can metabolise azathioprine normally. However, a small fraction of individuals, less than 1%, have the inactive allele on both chromosome sets (ie they are homozygous) and so cannot metabolise azathioprine (or do so very slowly). When such individuals are treated, the blood levels of azathioprine become very high, leading to acute bone marrow failure. A genetic test is available to identify patients with the TPMT deficiency, and a determination that a patient is homozygous for the inactive allele is used to direct alternative therapy or to reduce the azathioprine dose. This pharmacogenetic test has clear value to potential azathioprine users. The number of patients who can benefit from such a test, however, remains low.

Gene Identification.

We should soon see a major change in the field of pharmacogenetics. The new technologies created in the

Human Genome Project have changed the face of genetics, creating genomics and pharmacogenomics, the blending of high technology and pharmacogenetics. Whereas pharmacogenetics was based on biochemistry, the new pharmacogenomics takes advantage of high throughput DNA sequencing, gene mapping, and bioinformatics. The result is a quantum leap in the ability to discover genes, which are associated with physical attributes, disease susceptibility, or the response to drugs.

A leading example is the technology at the Paris based genomics company, Genset. Under the direction of Professor Daniel Cohen, the Genset group has developed a high resolution map of the human genome that enables them to compare DNA sequences between individuals who differ in a particular characteristic, such as a specific drug response. A comparison of sequences of a group of responding individuals to a group of nonresponders can identify the gene and which allele of that gene is responsible for the characteristic. Thus, genes can be found without any knowledge of the biochemistry of the response.

This technology can be applied to a wide variety of drug responses. Adverse side effects such as agranulocytosis from clozapine, heart valve abnormalities from diet drugs, muscle damage from statins, and cholinergic effects of tricyclic antidepressants might all have significant genetic components that can be found through genetic-association studies. The pharmacogenomic approach can apply to variability in therapeutic response as well as to drug toxicity. We suspect that the occasional-to-frequent failure of such drugs as interferon-alpha for hepatitis C infection, antihypertensives, and selective serotonin reuptake inhibitor antidepressants is related to the genetics of the patient and that tests can be designed to determine whether a patient is likely to respond or not.

The technology of pharmacogenomics is much more likely to make an impact in the field of cancer chemotherapy. In this area there appears to be a significant association between carcinogenicity and genetic makeup.

Developing Tests.

What are these pharmacogenomic tests likely to be? There has been much discussion about "genetic bar codes" and "genetic profiles," suggesting that it will be possible to include all gene sequence information relevant to an individual within a single test. At this point, we have neither the knowledge nor the technology to develop such a test. For the foreseeable future, tests based on pharmacogenomics will be directed towards single responses. The tests will currently focus on three key attributes: therapeutic need, clinical utility, and ease of use.

Therapeutic need is a combination of the number of patients likely to be tested for a particular drug response, the consequence of that response, and the alternate means of obtaining an equivalent answer. For instance, a drug used by many people but which is frequently ineffective and has a high incidence of therapeutic failure would have a high medical need for a test to predict efficacy in individual patients.

Clinical utility is a measure of the degree to which the test answer (and its applicability) will be relied upon to direct a physician's treatment of a patient. A test that can predict a particular response in only one quarter of the patients is unlikely to be used widely, and it would have a low clinical utility. Similarly, a test that has a high rate of false positives, that is, one that misidentifies a large number of individuals, would also have low clinical utility. Assessment of clinical utility will vary depending on the disease, the drug choices, and the consequence of the response being predicted.

Finally, a test must be usable in a conventional, automated clinical laboratory and not require special equipment or expertise. Intricate, labour intensive tests are likely to be slow, unreliable, and unreasonably expensive.

Development of an automated genetic test will involve a process much like that of any other conventional diagnostic assay. Once a gene sequence that influences a particular drug response of significant medical importance is identified, a clinical trial will be carried out in a representative population to determine how well the presence of the sequence will predict the response. If the response rate is adequate to meet the clinical-utility goals, then an assay will be developed for a clinical laboratory analyser. Data for the performance of the assay will then be submitted to regulatory agencies for approval of the test for a specified use. Even though this is a long and expensive process, it ensures a reliable and high quality product.

As more and more genes that influence drug response become known, we can expect to see not just an increase in the number of tests but also a difference in the way tests will be used. The first advance will be panels of tests that might cover a variety of different drugs all related to a single disease. With such a panel, it should be possible not

just to rule in or rule out a specific treatment but to select from among all therapies the one with the greatest potential benefit. Given the need to demonstrate the clinical utility of each component of such a panel, the development of such assays will require considerable gene discovery and clinical trial evaluation.

Further in the future might be the gene chips, in which many gene sequences relating to a variety of conditions, traits, and characteristics could be stored for every one of us, providing a universal testing platform. Before we reach that point, however, we will first have to answer many questions in science, information technology, and bioethics.

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