

# My Very Own Medicine: What Must I Know?

Information Policy for Pharmacogenetics



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David Melzer

Ann Raven

Don E Detmer

Tom Ling

Ron L Zimmern

Funded by



The Wellcome Trust



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## Research Team

David Melzer, MB, BCh, MSc, FFPHM (Principal Investigator)  
Director, Epidemiology for Policy Unit  
Department of Public Health and Primary Care  
University of Cambridge

Ann Raven, BSc, MSc (Lead Researcher)  
Senior Research Associate  
Department of Public Health and Primary Care  
University of Cambridge

Don E Detmer, MD, MA  
Gillings Professor of Health Management  
Judge Institute of Management Sciences  
University of Cambridge

Tom Ling, MA, MA, PhD  
Professor of Public Policy  
Anglia Polytechnic University, Cambridge

Ron L Zimmern, MA, MB, FRCP, FFPHM  
Director, Public Health Genetics Unit  
University of Cambridge

Denise Jillions, MA (Project Coordinator)  
Department of Public Health and Primary Care  
University of Cambridge

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For additional copies, please contact the Department of Public Health and Primary Care, University of Cambridge Institute of Public Health, University Forvie Site, Robinson Way, Cambridge CB2 2SR.  
Tel: +44 (0) 1223 330326 Fax: +44 (0) 1223 330330 Email: bcm10@medschl.cam.ac.uk

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## Summary of policy points

- A policy framework for pharmacogenetics is needed, but it is currently premature to lay down detailed rules or regulations, as the science is still unclear.
- The establishment of a clinically relevant evidence base for pharmacogenetic tests and test-drug combinations is a key priority.
- A balanced public policy framework for 'orphan' tests and drugs will have to be developed as the scientific and economic issues become clearer.
- Public sector expertise in pharmacogenetics needs strengthening, with investment in clinical pharmacology and other relevant disciplines.
- Current uncertainty about privacy and confidentiality safeguards for DNA samples could stifle pharmacogenetic trials. Balanced guidance to ethics committees/IRBs is needed on pharmacogenetic studies, covering areas such as consent, identification and sample storage.
- Pharmacogenetic tests offered by laboratory services should be subject to formal clinical appraisal in order to confirm the clinical validity of test results for the patient population served.
- Pharmacogenetics is likely to add substantially to the growing complexity of prescribing: computerised 'expert' systems will be needed to aid the safe and effective use of pharmacogenetic tests and drugs.
- Post marketing surveillance of pharmacogenetic tests needs to be strengthened, covering not only the manufacturing quality of test kits, but also clinical performance. Surveillance should cover the range of clinical settings and genetically diverse populations that are routinely tested.
- Post marketing surveillance systems need further development in the light of pharmacogenetics. Systems should investigate genetic factors in adverse events, especially the severe events.

# Executive Summary

## Introduction

In the second half of the 20th century, enormous strides were made in the development of effective pharmaceuticals, resulting in many lives being saved. On the whole, this progress has been achieved by focusing on large groups of patients with precisely defined diseases. This strategy ensured that drugs were relatively safe for the group, even if they were not always effective in every patient. It is clear that large individual differences exist in response to drugs, due to a variety of factors.

The term 'pharmacogenetics' ('PGx') is used in this report to cover the study of genetically-determined variability in response to drugs. The report also discusses the resulting clinical applications or 'products', all of which involve genetic testing of individual patients. Genetic tests may be used to help:

- Choose the most appropriate drug for each individual
- Select an optimal dose for each individual
- Identify those at risk from atypical adverse drug reactions

Recent advances in molecular genetics and the falling costs of genetic testing have lent momentum to this field of research.

In theory, genetic testing can have several advantages over more traditional therapeutic drug monitoring, because it can be undertaken before treatment begins; may be easily and inexpensively performed (with, for example, buccal swab samples); can be predictive for multiple drugs substrates rather than a single drug; and the relevant genetic markers are constant over an individual's lifetime.

In the optimistic days of the race to map the human genome, a number of influential proponents argued that pharmacogenetics would revolutionise drug marketing and prescribing. Instead of hoping for the best, a simple and decisive gene test would indicate to the doctor which drug would be optimal for the specific patient sitting in front of her. Large pharmaceutical companies could also exploit pharmacogenetics as a tool to accelerate drug development, because patients who could not benefit or might be at risk could be removed from trials, and clearer results could be obtained.

## The uncertainties of pharmacogenetics

Much of the policy debate on pharmacogenetics appeared to assume that the new products (i.e. genetic tests and test-drug combinations) would have high levels of precision, both for predicting safety and efficacy. This view, however, can be seriously questioned in the light of increasing evidence that genetic

tests for complex traits often do not perform well in practice. This may be partly because many genes can be involved in drug responses, but also because of other factors, including liver and kidney function, ageing and the taking of other drugs. Medical errors and poor quality of care are also thought to be responsible for many adverse events and lack of response.

## Assessing the 'quality' of a genetic test

Ensuring the degree of precision and usefulness of a genetic test involves two distinct steps:

- Agreeing the academic concepts and standards for good evaluation of a test
- Establishing a practical and efficient evaluative system that balances costs and benefits and produces an adequate level of information on tests

Within the context of solving a specific clinical problem, four conceptual aspects of test validity can be defined:

- **Analytic validity** refers to the accuracy with which a particular genetic characteristic (for example, a DNA sequence variant) can be identified in a given laboratory test
- **Clinical validity** describes the accuracy with which a test predicts a particular clinical outcome (for example, are patients with the tested DNA sequence actually 'slow metabolisers', and are there 'slow metabolisers' who don't have the sequence?)
- **Clinical utility** is the likelihood that using the test result will lead to improved care and an improved health outcome
- **Ethical, legal, and social implications** of having the test, which may sometimes outweigh the benefits

Currently, clinical tests are often not thoroughly evaluated, and there are some examples of patient harm from inaccurate testing. Recent controversy over cervical cancer screening, for example, has produced evidence that the new test may be less accurate and more expensive than the older test, with the result that more cancers are missed and more women without cancer wrongly told that they may have the disease. Misleading test results linked to drug selection, dosing or avoidance of adverse events can clearly be severely harmful.

## Aims of the study

In the light of claims about the future role of pharmacogenetics, the study reported here was set up to explore:

- The nature of the evidence and knowledge that will be needed to allow the regulatory authorities, clinicians, and patients to decide on the appropriate use of new pharmacogenetic tests and pharmaceutical agents
- The policy options for ensuring that such balanced, timely and relevant information is produced and made available, especially to clinicians and patients

## Research methods

The research involved a literature review and consultations with European and American experts via semi-structured interviews and focus groups. It included many of the leading experts from key fields, including drug and device regulation, government policy makers, reimbursement and public health agencies, representatives from pharmaceutical and biotechnology companies, clinical researchers, prescribers – in pharmacy, primary and hospital care settings, patient representatives, economists, geneticists, ethicists and bio-informatics specialists.

## Results

In the sections below, we summarise the main issues raised by those consulted. Inevitably opinions differed, and conflicting views were put forward. Participants identified a number of potential action points, and these are also presented in summary form.

### Pharmacogenetics – the science

The basic science of pharmacogenetics was seen as still being substantially uncertain but both the technology and knowledge base are evolving fast. Most researchers in the field believed that pharmacogenetic tests will often not be deterministic, since many external factors influence responses to drugs. Personalised medicine is not seen as imminent and as yet there are very few commercial products on the market or in clinical trials. Introduction of pharmacogenetic 'products' is likely to be gradual, but a majority believed that pharmacogenetics could have an impact on the care of more than 15% of patients within 15 years.

Establishing a good evidence base on pharmacogenetic tests was universally seen as a high priority. Much of the debate on pharmacogenetics has focused on tests linked to new drugs, but pharmacogenetics has important potential applications for the many generic drugs that are used clinically. A programme of targeted public investment in pharmacogenetics was seen as required by many of those consulted. There was concern that pharmacogenetics is evolving at a time when public sector clinical pharmacology is in decline and is perceived as under-funded.

Significant genetic variation exists between populations, and ethnicity is known to affect the frequency of certain variant alleles. Concern was expressed that certain ethnic minorities may be excluded from both research and treatment in a socially unacceptable manner. An alternative view is that pharmacogenetics may provide a more satisfactory and accurate predictor of response to treatment than apparent racial phenotype.

## Commercial development

Most major pharmaceutical companies are investing in pharmacogenetics, mainly for pre-clinical trial research on drug candidates. Other companies are forming strategic alliances with diagnostics groups. Specialist contract research organisations are emerging to undertake both testing and storage of samples. Some report that candidate drugs showing evidence of 'PGx problems' are often dropped from current development programmes.

Those involved in pharmacogenetics in the commercial sector find resistance to clinical PGx projects from commercial colleagues who are fearful of segmenting markets. Tensions also exist among those involved with clinical trials, who fear that consent, ethics committee and logistic delays of DNA sampling will delay trials. Commercial experts feel that current uncertainty about regulatory requirements for pharmacogenetic evidence could stifle investment and innovation. Current uncertainty about privacy and confidentiality requirements for DNA samples is also seen as a barrier to exploratory trials. Ethics committees/Institutional Review Boards need guidance to generate a standardised approach to pharmacogenetics studies (in respect of consent, identification and sample storage, etc).

There is widespread concern that pharmacogenetics knowledge is being restricted to industry 'silos', with a dearth of public sector and regulatory expertise and limited access to commercial research findings. Mechanisms are needed to ensure that non-proprietary information reaches the public domain for scientific debate. The US Food and Drug Administration (FDA) is proposing that a 'safe harbour' system is created wherein sponsors could share preliminary data with regulators. This should engender a more iterative approach to design and development decisions, and build greater certainty into the regulatory approach.

## Regulation of pharmacogenetics

The great majority of those consulted believed that the clinical quality of pharmacogenetic tests should be evaluated in some way. The key questions are to what extent and how. The consultation made limited progress in answering these questions. Patient representatives generally assumed that tests were already being evaluated with the same rigour as drugs.

The regulation of tests and devices by the FDA has always been closely aligned to the regulation of drugs, with an explicit requirement for clinical evidence to support manufacturers' claims, covering analytic accuracy, safety and clinical relevance. Test and device regulation in Europe and Japan has evolved from consumer protection legislation and has been a 'kite-marking' system for the test apparatus, based primarily on manufacturing quality and analytic validity but not clinical appraisal. However, the European system may become more clinically relevant with the implementation of the new In-Vitro Diagnostic Devices directive (IVDD). These may, in practice, require performance data on each test apparatus 'in its intended use in patients'. Some experts believed that this will become equivalent to a requirement for evidence of clinical validity; others were less clear that this is how the phrase would be interpreted.

In most countries, laboratories offering clinical testing services are subject to quality assurance and accreditation systems, but these generally relate to laboratory procedures rather than the clinical validity or utility of the tests offered. Clinical tests themselves, provided via laboratory services or a single laboratory (so-called 'home-brew' in the US), are not currently licensed or appraised in the same way as test kits, although in the US this is under review. In Europe if a laboratory service test is commercialised, it will come under the new In-Vitro Diagnostic Devices directive, and work is ongoing to clarify how regulation will work. Many of those consulted believed that laboratory services offering pharmacogenetic tests should not only have formal accreditation but also the test itself, at least in certain circumstances, should be subject to appraisal by an appropriate regulatory 'mechanism' to confirm its clinical validity.

Direct marketing of unregulated pharmacogenetic tests is a concern for both regulators and health service providers. Marketing via the Internet was seen to be particularly difficult to control with existing national regulation. There may well be a need for public protection, given the potential hazards of misleading pharmacogenetic test results linked to drug choice. Action could be taken in a number of ways, including the use of existing consumer legislation and advertising standards.

There were divergent views as to whether pharmacogenetic products applying to small populations should qualify for 'orphan' drug or device status, with the accompanying tax and patent benefits to companies.

## Health Technology Assessment (HTA)

There was a general consensus that there were few entirely novel technical issues in the assessment of pharmacogenetics, other than the prospect of very large numbers of genetic tests becoming available, for example on silicon chip devices. It is debatable whether existing health service HTA organisations are capable of contributing to the clinical assessment of pharmacogenetic tests and drugs. Typically HTA groups rely heavily on the research produced for licensing regulators. Licensing requirements are seen as focused on safety and evidence supporting manufacturers' claims that specified clinical benefits can be achieved in selected patients. Licensing information is thus seen as falling short of that needed by clinicians when deciding on the best package of treatments for the wide range of clinical problems they face. Pharmacogenetics is likely to highlight this information gap between current licensing requirements and the needs of patients and prescribers.

Patients are very concerned about adverse events and lack of efficacy of their medicines. They are generally supportive of both PGx sample collection and testing in a research setting, since pharmacogenetics is perceived as potentially beneficial, but patients expect their legal and ethical interests to be protected.

The potential for financial savings from pharmacogenetics has been much heralded, but there have been few reports of formal economic evaluation. Some participants see a need to build capacity in public sector health economics, particularly in Europe, to expedite economic appraisal of pharmacogenetics.

## Barriers to implementing pharmacogenetics in the clinic

Application of pharmacogenetics in routine care was seen as generally needing to be integrated into the professional consultation, as an adjunct to good prescribing, rather than directly marketed to consumers.

Pharmacogenetics will increase the complexity of prescribing and change accepted minimum standards of care. There are dangers that this could result in additional legal liability if healthcare professionals lack adequate knowledge. Given the complexity of the therapeutic choices likely to be involved, computerised expert systems will be needed to aid clinicians. Computerised health records will need to accommodate pharmacogenetic information.

There were concerns that doctors may use PGx drugs outside licensed indications – so-called ‘off-label use’: this was seen as a potential barrier to the safe diffusion of the technology, especially by regulators. There were also concerns about unequal provision of PGx tests – perhaps geographical or through different health plans. This could put some patients at increased risk if doctors prescribed a PGx drug without the necessary testing.

Pharmacogenetics will need to be integrated into undergraduate and postgraduate medical and pharmacist training.

## Post Marketing Surveillance (PMS)

Many of the adverse events associated with new drugs only become apparent after marketing, through post marketing surveillance systems under which clinicians formally report events. With pharmacogenetics, if clinical trial sample sizes are reduced, then the ability to identify adverse events and establish safety at trial stage will be even weaker.

Most participants saw a current need to strengthen PMS systems with pharmacogenetic analysis of serious adverse events. Public funding may be needed for national PMS systems incorporating genetic samples. However, experts in the field believed that there were serious technical difficulties in obtaining good quality data on adverse events from routine clinical settings under current arrangements, which contain few incentives for clinicians.

Current confidentiality and data protection concerns are beginning to limit the use of secondary sources for safety research. If data and samples are anonymised they are of little value for PMS research: the use of trusted third parties could provide a way forward for post marketing drug safety studies.

Post marketing monitoring systems also operate for tests and devices, but these are generally considered to be weak and under-resourced. One of the strengths of the new European medical device directive is the emphasis on PMS, a process of continually reviewing the behaviour of devices or tests. Irrespective of this, PMS of tests and devices needs to be strengthened, preferably via existing regulatory agencies rather than companies. PMS should produce the information needed for informed use of pharmacogenetic tests in routine clinical settings.

## Stakeholder perspectives

Unsurprisingly, there was not full agreement on all points of interest and there were considerable variations in practice and perspective between the UK, Europe and the US. The key issues of debate included:

- The status of the science
- The impact of consent and confidentiality arrangements
- Regulatory and licensing systems

In the US there is a more overt expectation that pharmacogenetics will deliver prescribing benefits in the near future. There is a sense of urgency and imminence which is less apparent in Europe, where there is far more scepticism – particularly amongst the clinical pharmacologists consulted. There was also greater fear in the US that confidentiality arrangements would stifle PGx research.

Most US regulators were confident that the existing licensing system was both robust and sufficiently flexible to accommodate pharmacogenetic product applications as they appear. There has been much dialogue about pharmacogenetics between manufacturers and regulators in the past three years, resulting in a common terminology and approach. In Europe there appears to be a less iterative system of drug and device regulation and a mismatch of perspectives. Senior industry pharmacogenetics experts profess themselves unsure about routes for regulatory submissions and more importantly, the level and nature of evidence required. Regulators in the UK and Europe have been addressing the perceived shortcomings – notably of test evaluation – and profess themselves satisfied that the European systems will be appropriate and adequate.

## Conclusions

Pharmacogenetics is a potentially exciting aid to accurate and efficient prescribing, but personalised medicine, with access to 'my very own medicine', faces several hurdles. While there are few qualitatively new issues in the evaluation of PGx tests and drugs, the potential hazards of misleading tests for drug use, and the large numbers of tests in prospect are likely to add to pressures for better clinical evaluation. The predominant view was that such evaluation should be made obligatory, through regulation or health services technology assessment arrangements, but good clinical evaluation could not be left to the market. Whether current regulatory and health technology assessment arrangements will produce good information for prescriber and patient decision making is still unclear, with the area of greatest uncertainty being test regulation, especially in Europe. Finally, pharmacogenetics will need to be integrated into educational programmes and knowledge management systems in order to achieve the aim of safer and more effective use of medicines.



# Introduction

In the second half of the 20th century, enormous strides were made in the development of effective drugs for a wide range of conditions. These drugs have undoubtedly made major contributions to saving lives and reducing the burden of disease. On the whole, however, this progress has been achieved by focusing on large groups of patients with precisely defined disease entities. The strategy ensured that drugs were safe relative to the expected benefits for the group, even if they were not always effective in every patient. The public policy implications of this were relatively clear: identical products were to be delivered to large sections of the population following a long period of testing. This required large-scale trials providing information to large sections of the population where the emphasis was on a safe regime rather than an individualised regime.

This strategy of 'one size fits all' in drug development was challenged, however, almost from the beginning, by accumulating evidence of individual differences in response to drugs. In several cases such differences were traced to individual differences in enzyme structure and function, which had dramatic effects on the safety and effectiveness of specific compounds in certain individuals (Motulsky, 1957). Public policy had to be adapted incrementally to manage these exceptions. Many of these differences were soon recognised to be genetically driven.

In the last decade, new techniques in genetics have provided powerful and potentially inexpensive tools for studying the genetic basis of such differences in drug response on a large scale. The mapping of the human genome and the technology that made it possible opened up a new vision, in which individual patients could be tested for a host of relevant genetic differences, and the results could be used to choose the safest and most effective compound for each patient – finding each person's 'very own medicine'. This poses new challenges for public policy makers, challenges which are explored in this report.

## Uses of genetic testing for drug choice

Genetic testing of individual patients to guide drug treatment choices in clinical settings is referred to as pharmacogenetics. There are three main potential uses of genetic tests in guiding individualised drug treatment:

- To adjust doses
- To choose the most effective drug for a particular individual
- To avoid serious adverse events due to individual metabolic idiosyncrasies

In the first category of application, tests would identify individual differences in absorption, metabolism, transportation or elimination of a drug. If doses of drugs were individually tailored, those who were previously inadvertently 'overdosed' would be at lower risk of adverse events, while those who previously received too small a dose could instead be given a sufficient amount to ensure greater effectiveness of treatment. Secondly, testing could identify those who would respond particularly well to a specific compound. For example, there is some suggestion that polymorphisms play a role in the response to  $\beta_2$  adrenergic agonists (Martinez et al, 2001), and could be used in choice of asthma medication. A third type of genetic testing would identify those at risk from unusual adverse events due to relatively rare metabolic idiosyncrasies. For example, most drugs implicated in QT interval abnormalities are affected by 'pharmacogenetic' enzymes and genes (Caldwell, 2001).

In theory, genetic testing could have several advantages over more traditional therapeutic drug monitoring (Ensom, Chang & Patel, 2001), because pharmacogenetic testing could be undertaken before treatment begins; would not require the assumption of steady-state conditions (or patient compliance) for the interpretation of results; could be performed less invasively (with, for example, buccal swab samples); should be predictive for multiple drugs substrates rather than a single drug; and should be constant over an individual's lifetime.

### Pharmacogenetics and the optimism of the nineties

In the optimistic days of the race to map the human genome, a number of influential proponents argued that pharmacogenetics would revolutionise drug marketing and prescribing (Ginsburg & McCarthy, 2001; Roses, 2001). In papers in the leading medical journals, the prospect of developing medicines and medical practice tailored to individual patient differences was vaunted as the way of the future. Instead of hoping for the best, a simple and decisive gene test would indicate to the doctor which drug would be best for the specific patient sitting in front of her. Patients taking the right drug at the right dose would have fewer adverse events, and treatments would be more effective.

For the companies, effective drugs that had been withdrawn from development or marketing due to side-effects could be remarketed with a test, ensuring that they would be taken only by those for whom they were safe. Large pharmaceutical companies could also exploit the pharmacogenetic paradigm as a tool to accelerate drug development, because patients who could not benefit or might be at risk could be removed from trials, and clearer results could be obtained.

The vision of the impact of individual medicine also stretched to the level of health systems, suggesting that socialised medical systems would be fatally undermined by pharmacogenetics and the wider genetics revolution (Sykes, 2000). In this atmosphere of excited anticipation, policy makers were warned to prepare for a tidal wave that would sweep away the old patterns of health service delivery.

## The uncertainties of pharmacogenetics

Much of the policy debate on pharmacogenetics appeared to assume that the new products (i.e. genetic tests and test-drug combinations) would have very high levels of precision, both for predicting safety and efficacy. It was implied that there would be little uncertainty over the interpretation of test results or the choice of the right drugs in routine clinical practice, and that genetic factors were of overwhelming importance. This view, however, can be seriously questioned on the basis of increasing evidence that genetic tests do not always offer high precision (Holtzman & Shapiro, 1998). It can also be questioned because of experience with existing drugs and tests, which are often marketed with uncertain benefits over alternatives, and an incomplete evidence base on which to make informed clinical decisions. This uncertainty poses additional problems when making policy recommendations; it suggests the need for approaches that are adaptive, responsive and able to respond quickly to new developments.

Genetic testing for disease can be broadly divided into testing for the relatively rare single gene disorders, and testing related to common diseases influenced by multiple genes (Holtzman & Shapiro, 1998). For single gene (Mendelian) diseases, the finding that a healthy person possesses a disease-causing genotype will be highly predictive that future disease will occur, although expression can be very variable. For instance, the severity of the lung disease in cystic fibrosis cannot be predicted well by the genotype. Also, not all disease-causing genotypes will be detected by many routine tests.

For common disorders, genetic tests are likely to give even less precise information. Inheritance of a mutation may alter the risk but does not always result in the disease. Common disorders are generally influenced by many genes of low penetrance, plus environmental factors. Genetic polymorphisms may contribute to the appearance of disease, but most people with the risk-increasing form of the polymorphism will never develop the disease. For instance, fewer than 30% of people with the apolipoprotein E4 polymorphism develop Alzheimer's disease (Seshadri, Drachman & Lippa, 1995). Alleles of single genes play a significant role in only a small proportion (usually less than 5%) of all people with common diseases, including breast and colon cancer and Alzheimer's disease.

The extent to which individual pharmacogenetic tests will target relatively simple Mendelian rather than more complex traits will be crucial to their precision. Ingleman-Sundberg (2001) has speculated that 10-15% of today's drugs are affected by a limited number of high penetrance genes and perhaps 35-40% of drug therapy is affected by polygenic factors.

Genetic determination of differences in structure and function of drug metabolising enzymes or targets should also be seen as just the first step in influencing what actually happens in routine clinical settings. Numerous other factors alter drug response, including other drugs, environmental and physiological factors such as nutrition, ageing, liver and kidney function. It is also clear that poor quality of clinical care and medication errors are important in adverse events and failed treatments (Bates & Gawande, 2000). In addition,

many patients do not take the drugs prescribed for them in the ways intended, sometimes not taking them at all, sometimes taking too much in order to control troublesome symptoms.

## Assessing the 'quality' of a genetic test

Ensuring the degree of precision and usefulness of a genetic test involves two distinct steps:

- Agreeing the academic concepts and standards for good evaluation
- Establishing a practical and efficient evaluative system that balances costs and benefits and produces an adequate level of information

In terms of defining the academic concepts in assessing genetic tests, much recent progress has been made. A US workshop convened by the Center for Disease Control (CDC) has set out the current consensus on the ideal academic standards for evaluation of genetic tests (Burke et al, 2002). Their report makes a series of critical distinctions, identifying the elements involved in the validity of a test.

Firstly, they argue that the benefit of a genetic test can only be evaluated in the context of specific health outcomes. Thus, the starting point for considering the use of a genetic test is a well-defined clinical problem of the types outlined in the applications of pharmacogenetic testing.

Four aspects of validity of a test are then defined:

- **Analytic validity** refers to the accuracy with which a particular genetic characteristic (for example, a DNA sequence variant) can be identified in a given laboratory test
- **Clinical validity** describes the accuracy with which a test predicts a particular clinical outcome; when a test is used diagnostically, clinical validity measures the association of the test with the disorder; when used predictively it measures the probability that a positive test will result in the appearance of the disorder within a stated time period
- **Clinical utility** is the likelihood that using the test result will lead to an improved health outcome; to evaluate this, the important information is about the effectiveness of the interventions available for people who test positive and the consequences for people with false positive or false negative results
- **Ethical, legal, and social implications:** evaluation of these is essential in establishing the full impact of testing

Currently, clinical tests in general are often not thoroughly evaluated, and there are some examples of patient harm from inaccurate testing. Recent controversy over cervical cancer screening, for example, has produced evidence that the new test is less accurate and more expensive than the older test, with

the result that more cancers are missed and more women without cancer wrongly told that they may have the disease (Coste et al, 2003). Similar concerns over the accuracy of genetic tests have been voiced (Holtzman & Shapiro, 1998). Misleading test results linked to drug selection, dosing or avoidance of adverse events can clearly be severely harmful.

The academic framework for the evaluation of tests set out above clarifies the issues involved in getting good evaluative data on tests. The critical policy issue is how governments, regulatory and health systems will react to ensure that such information is available in practice. The complex nature of the information required and the lack of a 'fixed link' between the analytic quality and clinical usefulness of a test raises complex problems for regulating tests.

## Aims of the study

In the light of claims about the future role of pharmacogenetics, this study was set up to explore:

- The nature of the evidence and knowledge that will be needed to allow the regulatory authorities, clinicians, and patients to decide on the appropriate use of new genetic tests and pharmaceutical agents
- The policy options for ensuring that such balanced, timely and relevant information is produced and made available, especially to clinicians and patients

Good evaluative information was seen as providing the basis for dealing with subsequent implementation issues, including deciding on clinical appropriateness, funding, delivery logistics and information management. The investigators believe that improving existing evaluative mechanisms for the challenges posed by pharmacogenetics will benefit society through the development of a more informed ethics debate and by providing a firmer basis for clinical decision making and healthcare priority setting.

# Methods

## Introduction

The project sought to elicit expert practitioner and academic views of the policy issues raised by meeting information needs for pharmacogenetics. It was important, therefore, not only to review the literature on the subject but also to interview key people involved in the area in order to capture insights about a rapidly evolving area of activity. Furthermore, because of the uncertainty surrounding these developments, it was important to provide a selection of experts with the opportunity to debate and argue before arriving at a judgement. Those involved in the study are listed in the Appendix.

Data for this project were generated by:

- A literature search
- Interviews with experts
- Focus groups with stakeholders

These data were then critically evaluated and the findings tested at an analysis workshop.

## Literature search

The literature review was limited to the last 20 years and restricted to English language publications. Literature was identified through on-line literature searches employing Embase, Medline and Social Science citations. Search strategies were developed in concert with the Cambridge Medical School information specialists. Also identified were many non-indexed publications from industry and academia (part of the so-called 'grey' literature). Those searches were repeated later to pick up new literature, and key journals were regularly scanned. Following review of abstracts, key papers considered most relevant were obtained and the references also reviewed. Throughout the project, members of the project team and interviewees were also asked for relevant papers and regulatory documents.

## Interviews

At the start of the project scoping interviews were conducted with ten US experts and eight UK experts to discuss the scope and focus of the project. The purposes of this were to ensure that the topic was approached appropriately as well as to identify the key players in the field on both sides of the Atlantic. These interviews followed a set framework in the US and were more discursive in the UK. They were mostly tape-recorded, and reported in summary.

We chose semi-structured interviews with experts as a good way to understand current developments in a rapidly changing area. Closed interviews might have

failed to identify important developments that had not been previously identified. Conversely, open-ended interviews might have provided a more anecdotal set of accounts that would have been difficult to organise. A limitation of this approach was the linear nature of the enquiry, but that was partly redressed by the subsequent focus groups. A few general questions were asked to focus their thinking on the concerns of the project, followed by seven or eight key questions that sought their particular perspective and expertise. Finally, some open-ended questions were posed to explore completeness and omissions.

A list of potential interviewees was compiled by the project team from published sources and recommendations from those working in the field. The list included the following categories:

- Policy makers (government and institutional)
- Regulatory experts and those involved in medicine and test evaluation
- Clinical pharmacologists/specialists involved in PGx research in the clinic
- Industry pharmacogenetics specialists
- Pharmacovigilance experts
- Geneticists
- Ethicists and social scientists
- General practitioners and pharmacists
- Patient representatives
- Bio-informatics specialists

From each category, two to three key individuals were selected for interview, and the remainder were invited to participate in focus groups. Each interviewee was sent a formal letter containing information about the project and the focus of the interview, and, if necessary, a topic guide. The interviews lasted approximately one hour and were tape-recorded, but the researcher (AR) also took extensive notes. These and the tapes were transcribed promptly and a summary report with quotes was produced.

## Focus groups

We adopted the focus group method because in a highly uncertain area the experts are able to reflect on the uncertainties with other experts and arrive at measured conclusions. Also, we wanted to engender debate from various perspectives and increase the possibility of creative solutions.

Advantages of the focus group method for this project:

- Participants were able to bring to the fore issues that they deemed important and significant (instead of being as controlled as in a group or individual interview)
- Participants could be challenged by their colleagues if they were inconsistent (or incorrect); this process of arguing meant the researcher ended up with more realistic views as individuals were obliged to think about/revise their views

- Developing policy is interactive and the process of test/drug evaluation and information needs are inherently complex and involve trade-offs; the focus group can be regarded as both more focused and constructive than the group interview in this context

Limitations of the focus group method:

- The researchers had less control and there were limits on how much a facilitator could direct the group – this is a potential problem in funded research where an explicit set of questions are to be answered
- The data were difficult to analyse fully – to address both what people said and the way they interacted
- Because of the relatively loose control there may have been a group effect – that is, dominant or reticent group members or even a perfectly legitimate individual view being suppressed to produce a group opinion

Each group was planned three months in advance with invited delegates receiving a detailed programme and a pre-meeting questionnaire (comprising a number of policy statements linked to a Likert scale). A professional facilitator (TL) ran the group with support from other members of the project team.

The six focus groups were constituted to accommodate the perspectives of the various constituencies affected by pharmacogenetics policy as follows:

**UK:** International pharmacogenetics working party chairs with policy makers  
Government regulators with industry researchers  
Clinical and academic researchers with prescribers  
Ethicists and social scientists with bio-informatics, economists and patient groups

**US:** Government regulators with industry researchers  
Clinical and academic researchers with prescribing doctors and patient groups

Each focus group comprised three sessions: first, we introduced the focus of the project, followed by a fairly unstructured discussion of the key issues arising; second, we examined the information needs relating to tests, drugs (old and new) and combination products, post marketing surveillance and the associated evaluation methodology; third, this information was collated onto hexagons and the final session aimed to group the issues into policy themes and prioritise them.

Professional recording using table-top microphones was employed for each group. In addition, the project co-ordinator attended the groups and noted the topic and speakers serially to aid voice recognition and correct attribution at the transcription stage. The recordings were transcribed and then edited by the researcher for coherence, themes, etc. Deriving from each focus group was a brief report capturing the key issues, agreements and uncertainties expressed, including illustrative quotes (anonymised).

## Analysis

All issues arising from focus group meetings were listed, collated and reported back by the researcher and reviewed by a second member of the team. The project team then met to map all the project intelligence. Through a careful analysis of the data we arrived at the following headings:

- What is distinctive about pharmacogenetics?
- Regulatory systems and uncertainties
- Information needs
- Evaluation methods
- Knowledge management
- PMS/Safety
- Patient perspectives/ethics
- Medical practice/education
- Key policy responses

Information needs were initially considered at three levels of efficiency: doctor-patient encounter; health commissioners/HMOs; and, national government/regulatory level. It was later decided that to communicate our findings in a better way, the analysis would be more usefully divided according to a temporal relationship, as follows:

- The basic science
- Early and clinical development
- Formal regulation/licensing
- Post licensing evaluation
- Clinical practice issues
- Economic and infrastructure/systems issues

The relevant policy response ideas were then applied to each group of issues, leaving a number of overriding policy issues to be resolved at a later time. This method was repeated separately with the semi-structured interview data. Discreet issues or those not specifically debated by focus groups were also identified. Finally, the literature review was mapped onto the temporal analysis.

## Analysis workshop

Following the completion of the main research process but prior to writing the final report, the key findings and analysis were tested with a small group of policy makers from each sector, many of whom had been included in the main research. A summary report was circulated and a short residential workshop organised. This workshop addressed all the key issues and proposed policy solutions derived from the project research. The participants were invited to discuss and give their perspectives on prioritising. It was professionally facilitated and detailed minutes taken. This formed the basis of the final report. Areas of dissent and areas requiring new systems, policies and leadership were also identified for future study.

## Some comments on the methodology

It is widely agreed among social scientists engaged in qualitative research that the entire research process from the research agenda and design to data collection and interpretation is affected by, among other things, the personal characteristics and experience of the research team. Rather than trying to disguise this bias and promote the fiction of 'objectivity' by introducing quantitative measures or standardised methods of collection and interpretation that might eliminate subjective influences, the results of this study were enhanced by engaging with the process in an interactional and reflexive way.

The aim of the project was to investigate the many issues and perspectives intrinsic to the evolving science of using genetic information and technology to develop and prescribe drugs in a new way. Different points of view were represented by the choice of participant, but beyond that, triangulation was used to minimise the bias that might arise from use of a single methodology. For example, scoping interviews at the outset established the research issues, which were then confirmed (or disputed) in the course of more in-depth interviews and focus groups. A questionnaire was used in advance of focus groups to suggest the diversity of opinions that might be challenged in the course of group discussion. Each focus group had a different 'theme' based on the sectors represented by participants in order to allow a particular aspect of the problem to be considered in depth. Summary reports of each focus group were disseminated to participants to check the validity of initial findings and recommendations. A final analysis workshop representing the key sector viewpoints confirmed and prioritised these recommendations. So there were not only multiple sources of data, but also various stages to the project where different methods were employed to serve the final aim of identifying viable policy actions.

The project employed an inductionist approach, considering the hypotheses arising from the data on an ongoing basis. This approach, often referred to as grounded theory, is based on allowing analytical insights to emerge from the qualitative evidence (as opposed to testing pre-given hypotheses against the data). In a rapidly evolving area such as pharmacogenetics, this is more appropriate and helps to capture the uncertainties and complexities. Without the use of a guiding theory established from the outset, the challenge of combining data to produce a coherent analysis, let alone recommendations, relied on methodological triangulation. It has been suggested that this is a complex process that relies on playing each method off against the other so as to maximise the validity of field efforts. It was our experience that use of triangulation unearthed the complex issues underlying the main research topic, and that while final policy pointers and priorities may be disputed, the scope of issues that must be addressed by further work is clear.

# Results

In the chapters that follow we summarise the main issues raised by those consulted. The policy issues in pharmacogenetics are highly interlinked, but we have tried to impose order on the collected material by summarising it under the following chapter headings:

**Pharmacogenetics – the Science** – policy implications of the basic science

**Commercial and Clinical Development** – covering pre-licensing research

**Regulatory Framework** – including drug and device licensing arrangements

**Health Technology Assessment** – covering post-licensing evaluation

**Economics of Pharmacogenetics** in the development and marketing of linked tests and drugs

**Clinical and Public Health Perspectives** – covering implications for routine health service use

**Post Marketing Surveillance** – covering monitoring of device and drug safety and effectiveness in routine practice

Inevitably opinions differed and in some areas conflicting views were put forward. We have tried to report the main areas of consensus and also identify the important areas of disagreement. Throughout the text we have included a number of direct quotes from those interviewed to illustrate key points (printed in colour). Also, three 'case studies' are included: 'P450 Polymorphisms', 'Pharmacogenetics and Warfarin' and 'PMS Opportunity: the DARE project'.

After reviewing the interview and focus group material, the authors believe that there is widespread support for policy initiatives in a number of specific areas. Each section ends with these policy points or recommendations.

## Pharmacogenetics – the Science

Pharmacogenetics is the study of the genetically determined variability in responses to drugs, including efficacy and adverse reactions. Individual variation in response to drugs is frequently unpredictable and constitutes a substantial clinical problem (McCarthy et al, 2002).

A clear distinction needs to be drawn between **pharmacogenetics** and **pharmacogenomics**. These terms are still sometimes used interchangeably and when not, are often given different meanings by different authors.

Pharmacogenetics is here defined as the study of genetically-determined variability in response to drugs. The report also discusses the resulting clinical applications or 'products', all of which involve genetic testing of individual patients. For practical purposes, all applications of pharmacogenetics will be characterised by the testing of individual patients in order to guide therapeutic choices. Pharmacogenomics, by contrast, is concerned with the discovery of new drug response genes and the development of novel molecules to target these genes (Dayan, 2001). The former relates mainly to selecting appropriate patient therapy and the latter to drug discovery. The focus of this research project is pharmacogenetics.

### What is the nature of pharmacogenetics, what does it promise, and how is it distinctive?

Recent advances in molecular genetics and related laboratory technology have lent considerable momentum to pharmacogenetics research. Applications will include choosing an appropriate drug, selecting a suitable (starting) dose and identifying those at risk from atypical adverse drug reactions. There is consensus that the earliest applications will be in enhancing safety.

*'It is perhaps premature to think about policy **decisions** although appropriate now to develop a policy framework'*

Pharmacogenetics will not impact on all drugs – perhaps 15-20% of currently available drugs could be potentially involved. A continuing theme throughout the consultation was the uncertainty concerning the imminence of pharmacogenetic products, their clinical application and the degree to which pharmacogenetics as a technology is novel and distinctive.

Personalised medicine on a large scale is not imminent and as yet there are few real commercial products on or near the market – although some argue that the linked test-drug products Herceptin and Glivec (also known as

## P450 Polymorphisms

The main causes of variation in drug metabolism are genetic polymorphisms, induction or inhibition due to concomitant drug therapies or environmental factors, physiological status and disease state. Of these, the first two appear in many cases to be of major importance for the occurrence of adverse effects or lack of therapeutic efficacy. The drug industry has tended to drop drug candidates that are primarily selective substrates for the polymorphic enzymes. An alternative would be to individualise the drug dose based on the genotype of the specific patient and take both pharmacokinetic and pharmacodynamic aspects into consideration. This method could be more advantageous and avoid the elimination of drugs that would otherwise be suitable.

A significant proportion of drugs are cleared through the action of cytochrome P450 enzymes. CYP3A4 is by far the most important, affecting 50% of such drugs, followed by CYP2D6 (20%) and CYP2C9 and CYP2C19 (15%). The genes encoding CYP2C9, 2C19 and 2D6 are functionally polymorphic and the variant alleles causing defective, altered, diminished or enhanced rates of drug metabolism have now been identified for many of the P450 enzymes. The distribution of the variant alleles for P450s differs markedly between ethnic groups, reflecting global variations in treatment responses to many drugs.

The impact of P450 polymorphisms for poor metabolisers would result in reduced drug effectiveness. For example, poor metabolisers given the prodrug codeine will not metabolise it to morphine and hence no analgesic effect is seen in these individuals. The impact on some other affected drugs is summarised in the table below. Rapid metabolisers tend not to achieve therapeutic plasma levels at ordinary doses.

### Impact of human P450 polymorphisms on drug treatment in poor metabolisers

Polymorphic enzyme	Decreased clearance	Adverse effects	Reduced prodrug activation
CYP2C9	S-Warfarin Phenytoin Losartan Tolbutamide NSAIDs	Bleeding Ataxia	Losartan
CYP2C19	Omeprazole Diazepam	Hypoglycaemia GI-bleeding (?)	Proguanil
CYP2D6	Tricyclic antidepressants  Haloperidol Anti-arrhythmic drugs Perphenazine Perhexiline SSRIs Zuclopenthixol S-Mianserin Tolterodine	Sedation Cardiotoxicity  Parkinsonism (?) Arrhythmias  Neuropathy Nausea	Tramadol Codeine Ethyl morphine

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors. (Source: Ingelman-Sundberg et al, 1999)

The most significant polymorphisms causing genetic differences in phase one drug metabolism are now known and therapeutic failures or adverse drug reactions caused by polymorphic genes can, to a great extent, be foreseen. The drug industry is already taking advantage of this knowledge in both drugs selection and development. However, owing to the rapid development of efficient and inexpensive methods of genotyping, plus the need to genotype patients only once in a lifetime, it may be advisable to include the genotypes in the patient's medical record. This would provide the doctor with valuable information in order to individualise treatment and improve the likelihood of successful drug therapy.

Gleevec) provide useful models for pharmacogenetics. It is anticipated that the introduction of pharmacogenetics products will be incremental, with only a handful of test-drug combinations being licensed in the next five to ten years. There is widespread recognition that pharmacogenetics may have been oversold, particularly with respect to timelines. Media excitement about genetic applications may be exaggerating investment and research activity.

The basic science is still substantially uncertain and both the technology and our understanding are evolving very fast. Genetic variation is only one factor influencing drug response and many other external factors are involved, so many pharmacogenetic tests are unlikely to be deterministic.

A view that any application involving DNA is somehow special and requires a different ethical, legal and regulatory framework is prominent in some quarters. Most participants felt that this perspective needed to be challenged. Pharmacogenetics should be seen as a prescribing tool and the intended consequences of the test results seen as little different from, for example, using drug levels in the blood as a guide to dosage. These uses are entirely different from using a test to diagnose or predict a serious inherited disease, and have different ethical implications.

*'If pharmacogenetics is to be a success we need to get away from the perception that genetic data is special'*

It is, therefore, important that these perceptions do not mitigate against the many positive aspects of pharmacogenetics – particularly the prospect of prescribing drugs with more confidence in their effectiveness and safety. It may lead to more rational drug design and testing with drugs targeted more precisely and evaluated more efficiently in trials of selected individuals.

On the other hand, some participants did believe that predictors of drug response may sometimes also be markers of disease susceptibility, thus raising issues about the social, ethical and legal consequences.

There was lively debate over whether pharmacogenetics was distinctive from other areas of medical testing and therapy. Policy makers will need to understand both the distinctive features of pharmacogenetic tests and the similarities between them and other diagnostic tests, in order to put the technology into context. In terms of application of the test or the combination of test and drug, the issues are not unique to pharmacogenetics. Many clinical diagnostic tests can yield unwanted or unintended information, while certain tests that yield genetic information, for example those that determine blood groups, are already well accepted in clinical practice. However, pharmacogenetics is likely to result in many thousands of different tests. The complexity is beyond the scope of a regional genetic laboratory or hospital laboratory service to evaluate, and certainly beyond the ability of any physician to use effectively without the results of formal evaluations and expert systems to aid decision making.

It was apparent that pharmacogenetic information would need to be sensitively handled. Unintended consequences of pharmacogenetic testing, beyond prescribing, should be considered. For example, test results may have implications for family members.

Concern was expressed that pharmacogenetics is evolving at a time when clinical pharmacology is in decline and under-funded. It is important to reverse this trend and to build capacity and expertise in pharmacogenetics and related fields, such as clinical epidemiology and health economics, in order to have sufficient public sector capacity to evaluate products.

Patients and members of the public were felt to have an excessive confidence in the precision of genetic tests and to assume all are highly predictive. Whatever the reality of pharmacogenetic tests, these tests will be seen by the public as different, and needing safeguards.

The context in which pharmacogenetic tests are used is important (disease population, treatment group, direct to consumer, etc) and makes it difficult to generalise, both in terms of development methods and appropriate service delivery policy.

### Policy points

- A policy framework for pharmacogenetics is needed, but it is considered currently premature to lay down detailed rules or regulations, as the science is still unclear.
- The establishment of a clinically relevant evidence base for pharmacogenetics tests and test-drug combinations is a key priority.
- Publicly funded programmes of research are needed to develop pharmacogenetic tests relevant to the safety and effectiveness of existing (generic) drugs.
- Public sector expertise in pharmacogenetics needs strengthening, with investment in clinical pharmacology departments and other relevant disciplines.

# Commercial and Clinical Development

Commercial companies develop the great majority of new drugs and tests, partly due to the high cost and large scale of the clinical research required by regulatory agencies. It might therefore be anticipated that pharmacogenetics would increasingly be driven by industry (McCarthy, 2001). To date, however, most published studies on the genetic basis of drug response have been produced by academic groups. In the future it will be important for the two sectors to collaborate to expedite new therapies.

*'The type of tests that are likely to come out of the pharmaceutical industry ... are likely to protect the market share of drugs, or create new markets for drugs that otherwise wouldn't get to market. Where are the type of tests that Health Services would want to see ... to improve the cost-effectiveness of medicines?'*

## Commercial incentives and challenges

There is considerable excitement in the commercial sector about the potential of pharmacogenetics, both in terms of discovery and, more relevant here, in the development and marketing of more targeted drugs. Commercial commentators claimed that their aim has always been to create and promote safer, more effective medicines, with pharmacogenetics but one tool in the quest. Pharmacogenetics also gives them the opportunity to differentiate products in crowded markets. The traditional objective of pharmaceutical companies to achieve blockbusters – new chemical entities satisfying unmet medical need in a substantial (and preferably chronic) patient population – may alter. Pharmacogenetics is more likely to produce a number of 'mini-busters' – products with a relatively high cost for low volumes that are tailored to the needs of well-defined, relatively small groups. The commercial implications of this scenario are likely to be significant but precise effects on the industry are as yet unclear.

Within individual companies, there are very mixed views about the balance of commercial risk and benefit from pharmacogenetics. Those involved in pharmacogenetics – as internal consultants or service groups to R&D – often find the main obstacles to further clinical research are presented by their own commercial colleagues fearful of segmenting their market, rather than the challenges of science or technology.

Most major companies are investing in pharmacogenetics, mainly in infrastructure and laboratory capabilities, in particular for high throughput

genotyping. Other companies are forming strategic alliances with diagnostic groups, and specialist contract research organisations are emerging to undertake both pharmacogenetic testing and storage of samples. Some marketing divisions are anxious not only about the perception of market segmentation but also about the disincentive to clinicians of making a prescribing decision dependent on a test procedure. Others recognise that pharmacogenetics could be a strategic tool for companies that expect to be third or fourth onto the market - where segmenting becomes an advantage. Clearly pharmacogenetics will not be relevant or useful for all pharmaceuticals, and companies will be selective in their application of the science.

Tensions also exist with clinical trial divisions who fear the consent procedures required by ethics committees and logistic delays of DNA sampling will compromise their trial schedules. As a result, most pharmacogenetics work in the clinic exists primarily as a protocol addendum and optional to both trial subjects and investigators. Inconsistencies about rules for collecting DNA samples between different national regulatory agencies and also between ethics committees continue to hamper prospective studies in this area (Theilade, Knudsen & Renneberg, 2001).

Commercial participants identified uncertainty about regulation in respect of evidence requirements and submission processes. They felt that it could stifle investment in innovation and result in high risk for the first commercial entries. It is therefore likely that one of the larger pharmaceutical companies will be the first to register a truly pharmacogenetic product. Regulators, in contrast, largely felt that there was no such uncertainty and that having an appropriate framework in place would not be a problem.

*'There is nothing more guaranteed to stifle investment in innovation in pharmaceutical industries than lack of clarity from regulatory authorities'*

The drug development process may need redefining to integrate pharmacogenetics fully. It has been suggested that pharmacogenetics could also be employed in the 'rescue' of drugs that would otherwise be withdrawn from development in Phase III, once it was established that toxicity or adverse events were confined to a subgroup definable by reference to genetic variation or there was too much variation in response rates.

Whilst better definition of disease and more targeted medicines may lead to net patient benefit, it is also likely to render more visible groups of non-responders or those susceptible to risk of specific toxicity. These so-called 'orphan groups' and 'orphan indications' may not be sufficiently numerous to justify the development costs of appropriate treatments.

Pharmacogenetics clearly brings important economic considerations for both the commercial sector and health service providers and a requirement to align their respective interests with appropriate incentives. For example, whether the test is very cheap in relation to an expensive drug or very expensive in relation to a cheap drug will be a key determinant of its attractiveness in clinical practice.

Another disincentive for adoption of this technology would be if exclusive intellectual property rights or patents were granted on gene sequences implicated with drug metabolism. This was largely viewed as potentially limiting progress in pharmacogenetics. Commercial incentives to develop products for a restricted market are needed, particularly for certain sectors of the independent biotechnology industry whose main focus is on diagnostic tests rather than on drug development.

There is a belief amongst academic scientists that pharmacogenetics has been oversold. This overselling may have led to inappropriately large investments in pharmacogenetics. With escalating R&D costs and an overall reduction in the number of pharmaceutical products reaching the market (Taylor, 2003), commercial interests may be under pressure to market test-drug combinations as quickly as possible, to the detriment of good clinical evaluation of products.

*'Who is ensuring that time lines are known and flow of evidence is ongoing and appropriate? Otherwise marketing may be premature and proceed in the absence of adequate evidence'*

Good intelligence on when pharmacogenetics products will arrive is important for policy makers so that they have the information required for decision making before products reach the market. Policy researchers wishing to identify the scope of existing, specifically pharmacogenetically-derived products may experience difficulties because some companies may not wish to stress their 'specialness' lest they attract unwanted regulatory questions. This has caused some commentators to underestimate the amount of work ongoing in the private sector. The public sector work is more likely to be discussed openly – notably in schizophrenia, asthma, anti-coagulation and hypertension – but certainly there are still very few publications of clinical trials that demonstrate pharmacogenetic drugs or tests near to the market.

Certain stakeholders believed that there is a potential conflict of interest if the same company markets both the pharmacogenetic test and drug, as the price could then be manipulated to optimise the market. Some postulate that if a pharmaceutical company found its market share under threat from a diagnostics company marketing a pharmacogenetic test, it would move to purchase or control the diagnostics company. However, biotechnology or diagnostics companies may be more likely to develop tests relevant to the safer or more efficient prescribing of widely used generic drugs, where the economic arguments could be compelling. For example, warfarin starting dose is notoriously unpredictable and greater accuracy may be attained by the use of testing via the CYP2C9 alleles to improve the anticoagulant control and reduce the risk of major haemorrhage (Meyer, 2000). Other experts have disputed whether this could work reliably in practice.

Some analysts believe that pharmacogenetics could transform prescribing practice, with the result that drug choice and dose are not ultimately influenced by the medical sales representative, but rather the genetic profile of the individual. This would also revolutionise the marketing of prescription drugs. However, this scenario was viewed as probably decades away.

## Impact on trial design and conduct

The premise behind pharmacogenetic research at the clinical stage of drug development is that a more discrete and suitable patient population can be selected. Few examples are yet published, although GlaxoSmithKline has recently demonstrated promising early association studies with two compounds in trials (Roses, 2002). An early impact is likely to be on patient selection and recruitment processes. At present, commercial studies include genetic testing as a protocol addendum and collect additional samples from existing trial subjects in the hope of correlating treatment response (including adverse events) with genotype. In many cases these experiments have been described as 'fishing trips', but are often part of a strategic approach, starting with genotyping in Phase I, selecting subgroups by genotype in Phase II and conducting prospective confirmatory trials by Phase III (Rioux, 2000). This approach can have important strategic consequences because the population studied in the pivotal trials will be the one to which claims (and hence a license) will relate. Therefore a sponsor needs to be confident in the discriminatory performance of the pharmacogenetic test, and the cost-effectiveness of such an approach.

*'The impact of genetics in terms of the early development is that it offers us the opportunity to stratify and study smaller numbers in select genotypes'*

## Methodological uncertainties

Currently, most of the candidate pharmacogenetic markers relate to drug metabolising enzymes (Jazwinska, 2001). Once the metabolic pathways of a new drug are known, a test can often be developed to discriminate between poor and extensive metabolisers. More than one metabolic pathway may be implicated so tests may have to be complex or might lack sensitivity.

Generally, tests will be evaluated in healthy volunteers and patients within a specific population. A key question is how the sensitivity and specificity of the test might decline as a more heterogeneous general hospital or community-based population is involved, which might include individuals showing a wide range of disease manifestation, co-morbidity, other drug use and other factors that may influence rates of metabolism in 'real life'.

The generalisability of the pre-licensing drug trials, already a major concern for those espousing evidence-based medicine, might be further compromised by pharmacogenetic selection. There are already suggestions that the small size of pharmacogenetics studies renders them unconvincing.

Rioux (2000) has argued that pharmacogenetic clinical trials will not use any special methods. A drug development programme should include a strategy for evaluating the potential value of pharmacogenetics by determining the maximum possible gain in response rate for the highest responding genotypic subgroup. Sample size could be reduced if a more homogeneous sample could be selected, with less inter-individual variation, resulting in an anticipated larger effect size. Researchers have explored the impact of different allele

frequencies, gene action and gene effect size on clinical trial sample sizes (Fijal, Hall & Witte, 2000). Unless the susceptible allele is relatively common (>30%), and the effect of the gene on response is relatively large, the sampling requirements may be extremely large and not feasible in early phase trials. If, however, the gene action is dominant, it may be that less than 50% of the traditional sample size would suffice. It is therefore crucial that prior genetic information be available to ensure appropriate study design (Cardon et al, 2000). Reduced sample sizes could bring economies in the R&D process to balance the potentially smaller target population. But it might also reduce the ability of the trial to detect rare adverse events and limit the quality of the safety data.

Some statistical and methodological questions remain. There are a number of advanced statistical methods that offer promise for application in pharmacogenetics, although none are established. For dosing studies, one expert suggested Bayesian techniques may provide the next step, but guidelines on what standards will be required in submissions to the regulators are still awaited. Studying subgroup differences in response within trials can be made more efficient by using so-called 'adaptive' trial designs. These designs allow a trial to start with a number of aims, and then drop inappropriate ones as the statistical evidence accumulates. These designs are still seen as being at a theoretical stage, and consensus is not quite established.

Clinical trials are frequently of short duration relative to the time-course of the disease, and sometimes employ surrogate endpoints. Selecting meaningful clinical and patient outcomes will be critical to establishing the clinical utility of pharmacogenetic test-drug combinations.

There is public sensitivity about the collection of biological samples for genetic studies, including pharmacogenetic studies. As DNA samples tend to be perceived as qualitatively different by patients and ethics committees, separate and additional review and informed consent procedures are often demanded. This causes both scientific and logistic problems, particularly in association studies where a sponsor may be genuinely unable to state in advance exactly which tests will be performed on stored samples. Although the former Advisory Committee on Genetic Testing (ACGT, 2001) and, more recently, US policy groups have considered research involving genetics (National Human Genome Research Institute, 2003), pharmacogenetic testing was not explicitly addressed. Some argued that pharmacogenetic testing did not pose the same issues as testing for disease inheritance or susceptibility and should not be burdened with the same ethical requirements as may apply to genetic disease testing.

## Policy points

- There is uncertainty about the requirements of regulatory agencies for evaluative evidence on pharmacogenetic products, especially in relation to tests.
- The potential hazards of non-evidence-based use of pharmacogenetic tests and drugs should trigger greater regulatory efforts to require information relevant to prescribers and patients in routine practice.
- Current uncertainty about privacy and confidentiality safeguards for DNA samples could stifle pharmacogenetic trials. Balanced guidance to ethics committees/IRBs is needed on pharmacogenetic studies, covering areas such as consent, identification and sample storage.
- Pharmacogenetic tests and drug development will inevitably be uneconomic for many small 'genetic minorities'. A balanced public policy framework for 'orphan' tests and drugs will have to be developed as the scientific and economic issues become clearer.

## Regulatory Framework

For the purposes of this project, the term 'regulation' is used in the broadest sense and is not restricted to the work of government regulatory agencies. The regulation of pharmacogenetics extends beyond the licensing of new drugs and test kits to include the overview of laboratories offering pharmacogenetic test services, the infrastructure for health technology assessment and post marketing surveillance. An important part of the overall appraisal of pharmacogenetic drugs and tests is fulfilled by the various pre-licensing approval systems, and these are being considered here.

Tests are already available that have dubious utility. It is widely agreed that the quality and clinical utility of pharmacogenetic tests should be subject to some form of evaluation. The key question is to what extent and how. The consultation failed to achieve consensus on this matter. Consumers assume that pharmacogenetic tests are evaluated with the same rigour as drugs and are not aware that medical tests often undergo no or minimal evaluation, at least with regard to their clinical efficiency and utility. A concern of this project was to explore whether prescribers and patients are well served by current licensing processes.

### Current regulatory framework for tests

**US:** The regulation of medical devices, which includes tests, has only a 25-year history. The first regulation to be introduced was the US Medical Device Amendments Act in 1976, which derived from the Food, Drug and Cosmetic Act. As a result, the regulation of tests and devices in the FDA has always been closely aligned to the regulation of drugs, with an explicit requirement for safety and effectiveness evidence. This was further reinforced by the *Temple Report* (CDRH Committee of Clinical Review, 1993) which identified several deficiencies in applications for pre-marketing approval (PMA), highlighting 'an important lack of information for the physician and patient who must decide whether to choose a new device over available alternatives'.

There is therefore a concern that, although the existing US regulatory framework is impressive, there remains a regulatory gap. If a company chooses to market via the FDA, the information needed for submission is still insufficient for the needs of patients or prescribers. Nor is it regarded as adequate to inform the 'payer' whether to approve reimbursement. Clinical utility may never have been addressed within the regulatory process.

**Europe:** Test and device regulation in Europe has evolved from consumer protection legislation and is a 'kite-marking' system based primarily on technical appraisal. Also, in 1993, the EC Medical Devices Directive (MDD) broke away from the pharmaceutical approach and introduced several features more appropriate to engineering products (Higson, 2002). Under this directive,

medical devices are classified in a uniform manner and have to provide information on performance and safety in accordance with 'Essential Requirements'. Conformity Assessment procedures for a harmonised compliance to standards are carried out by relevant Notified Bodies designated by each member state. If a product complies with this it can be issued with a CE Mark.

It is currently unclear which devices require clinical data to be approved or if some discretion is permitted. A variation to the MDD for in-vitro diagnostic medical devices (Directive 98/97/EC) was agreed in 1998 and will become mandatory in the EU in December 2003. This legislation specifically addresses the requirements for diagnostic tests, but no specific mention of pharmacogenetic tests is made. Under the IVDD directive, the requirements for licensing test equipment will be more rigorous. Some experts believe that the requirement for performance data 'in its intended use in patients' might become equivalent to asking for evidence of clinical validity, but this interpretation is not universal.

The complexity of pharmacogenetic prescribing may require additional resources for regulatory agencies to build expertise not only in clarifying the regulatory requirements but also in harmonising them worldwide. Currently there is an initiative to harmonise worldwide device regulation, called the Global Harmonisation Task Force (GHTF), encompassing US, EU, Australia, Canada and Japan ([www.ghtf.org](http://www.ghtf.org)). On the pharmaceutical side internationally there is a CIOMS working party (Council for International Organizations of Medical Sciences, part of WHO) on pharmacogenetics. In May 2002, the FDA and representatives of the pharmaceutical industry met to debate a wide range of regulatory issues pertaining to pharmacogenetics, and their deliberations have been published (Lesko et al, 2003).

Regulatory perspectives included:

- Anonymised data and samples without a link to the patient record cannot be used to validate and support new results and hypotheses discovered during later stage development of a drug, for example in validating the test against clinical response observed in subsequent trials
- Until there is greater experience with pharmacogenetics, specific requirements for the use of pharmacogenetic data in exploratory drug development or in registration trials should be defined on a case-by-case basis
- The confirmation of identified genetic associations is mandatory if pharmacogenetic biomarkers are to be included in drug labelling
- The FDA expressed a willingness to explore the feasibility of a 'safe harbour' for genome-based data on both local and non-lead compounds; this is a process in which exploratory genome-based data submitted under an active IND (investigational new drug) application would not undergo formal regulatory review until more is known about the validity of the technology used and appropriate interpretation of the data

The European Agency for the Evaluation of Medicinal Products (EMA) too has formed an expert group through the Committee for Proprietary Medicinal Products (CPMP) to clarify terminology and make recommendations for pharmacogenetic sample collection in clinical trials (EMA, 2002). Both EMA and the FDA are also setting up iterative processes for less formal sharing of early development data. All this activity may go some way to clarify the most likely future routes and requirements for pharmacogenetics drug and test products.

Notwithstanding these initiatives there appears to be some residual uncertainty – both amongst regulatory staff and industry researchers – about the roles and responsibilities for evaluating pharmacogenetic tests in Europe and the US. Opinions were divided as to whether pharmacogenetic tests could or should be evaluated and regulated in the same way as other clinical diagnostic tests, or whether (together with other types of genetic tests) they require more stringent regimes. In the US it appears that companies are waiting for the FDA to tell them the minimum standard for producing genetic testing products.

Pharmacogenetic test kits could include sophisticated software to aid complex prescribing decisions for individual cases. In the past there have been considerable problems where embedded errors with the software were uncovered, which compromised the safe and effective use of the test. The FDA regulates the software too and issues software standards guidance. It has been decided recently that the new EU Medical Devices Directive will also address this area.

## Direct marketing

Direct marketing of diagnostic tests (not just pharmacogenetics) is already occurring. In the US, Centers for Medicare and Medicaid Services (CMS) Clinical Laboratory Improvement Amendments office and the FDA have undertaken review at the pre-marketing stage. The US Secretary's Advisory Committee on Genetic Testing (SACGT) and CDC have also been involved at a high level. Direct marketing of unregulated pharmacogenetic tests is a concern for both regulators and the health service. Particularly with marketing via the Internet, this is difficult to control with existing national drug and devices statutes. There may well be a need for public protection, most suitably through existing consumer legislation and advertising standards. Attempts have been made – notably in New York State – to control the claims made by those who market tests directly to consumers. Recently, the FDA published advice to consumers suggesting they ensured laboratory services were on the FDA-approved list before making a purchase.

This topic has recently been considered by the UK Human Genetics Commission (HGC) ([www.hgc.gov.uk/genesdirect/](http://www.hgc.gov.uk/genesdirect/)) who are recommending stricter controls on certain categories of direct genetic testing rather than a statutory ban. They suggest differentiating between predictive tests for serious conditions that should be available only with medical consultation and other tests, for example, diet-related, that may be suitable for wider access. They also recommended improved health service funding to enable better access to predictive genetic tests (Human Genetics Commission, 2003).

## Laboratory services

Tests provided via laboratory services or a single laboratory (so-called 'home-brew' in the US) are not currently licensed and appraised in the same way as a test kit, although in the US this is under review as a result of the recent Secretary's Advisory Committee on Genetic Testing recommendations (SACGT, 2000). In Europe a commercial laboratory service would be covered by the In-Vitro Diagnostic Devices directive. Work is ongoing to clarify how this would be regulated in practice. The laboratory itself is subject to quality assurance authorisation and accreditation via inspections systems such as CLIA (US) and NEQAS (EU), but this does not infer any appraisal of the clinical validity or clinical utility of individual tests.

Controlling variability between laboratories for evaluating test results is critical to the reliability of tests. An example was cited where the same patient sample was reported to a regulator as that of a slow metaboliser by one laboratory and an extensive metaboliser by another. Test provision is sometimes by a commercial testing laboratory, a hospital laboratory service or by in-house pharmaceutical/diagnostic company partnerships. A third possible regulatory mechanism related to testing is the use of reference laboratories in quality assurance schemes to ensure that laboratory procedures are adequate. Such schemes are currently being developed in the UK and Europe for genetic testing. Laboratory quality assurance schemes generally oversee laboratory procedures only and as a rule do not monitor the clinical validity or utility of the tests being offered.

It may be that test development will be incremental, in parallel with drug development. Initially, during pre-licensing drug trials, a test may be provided by a single laboratory, with simple quality assurance. A suitable diagnostic device or test kit could then also be marketed after marketing of the drug, with a more comprehensive evaluation. Regulators are currently considering the scientific and safety implications of this approach. It has been suggested that the appropriate level of regulation should depend on the seriousness of the consequences of the test outcome. For instance, if it were decided that prescribing a drug was 100% dependent on the result of a pharmacogenetic test, that test would have to receive formal appraisal and approval – at least in the US.

It may be possible to learn from the Herceptin example. The ER2 test is available as at least two kits or as a laboratory service. The testing capability had to be developed alongside the drug because the accuracy and reliability of the test was critical to the benefit of the drug – so standards of test performance/laboratory capability were established.

## Current regulations for combined (test-drug) products

The most striking finding of the project questionnaire was the split in opinion about the adequacy of current regulatory arrangements for each application of pharmacogenetics. Regulators are well informed about the genetic basis of drug response and several ICH and national guidelines already exist, particularly with reference to Phase I and drug interaction studies (Shah, 2001).

Where tests and drugs are intimately linked, as in the case of new pharmacogenetic products, their evaluation needs to be co-ordinated and any licensing approval issued in concert. It is evident – at least from the industry perspective – that there remains some uncertainty about both requirements and process for combined test and drug pharmacogenetic products. One explanation for the expressed uncertainty may be that ‘big pharma’ research directors are unfamiliar with both the evaluation and regulatory processes for devices and tests – usually the domain of diagnostic companies. Pharmaceutical industry representatives have been asking for more clarity from the regulators, but regulators prefer to be reactive rather than proactive and will adapt existing systems as necessary once sponsors begin to present data. In the absence of actual product examples there is a resistance to making premature decisions about requirements lest they stifle innovation. New processes may be required where drug and test are very closely linked.

*'My hope is that the science will drive the regulation rather than the regulation drive the science'*

In the US, following recommendations from an internal working party, the FDA framework is now more explicit, and administrative processes exist for combined products. Also, Herceptin and other recent linked products provide good models for product evaluations that require co-ordinated review and approval.

The new European Medical Devices Directive includes specific guidance on the evaluation responsibilities for combined medicinal devices that would apply to tests also. For pharmacogenetic tests it appears that the legislation requires the combined product to be licensed via the medicines evaluation system, but in addition the device or test must also satisfy the essential requirements of the In-Vitro Diagnostic Devices Directive. In the UK the situation is more informal, but this should be resolved with the merging of the MDA and MCA in 2003.

Some genetic polymorphisms relevant to drug metabolism vary in their frequency in different ethnic subgroups (Foster, Sharp & Mulvihill, 2001; Wood, 2001). The generalisability of evidence generated within a traditional drug development programme to these groups may be problematic. It has been suggested that the needs of such groups will be appropriately addressed via so-called ‘bridging trials’. The International Conference on Harmonisation has published guidance (ICH, 1998) on the requirements for the acceptability of data generated in different populations, including those differentiated pharmacogenetically. Development of those drugs where this is likely to be relevant will require a bridging studies strategy to address major ethnic subgroups in their own populations and for other markets, but the extent of their use in different geographic populations is still a matter of uncertainty. There are also a number of ethical issues surrounding pharmacogenetic testing in ethnic minorities, which are addressed later in this report.

Treatments which have only a small potential market/low patient prevalence but where an unmet medical need exists may be granted ‘orphan’ status by regulatory authorities in the US and Europe. This encourages the development

of products that would not otherwise be commercially viable. Orphan status carries considerable tax incentives for R&D investment in the US and also patent protection. It has been anticipated by industry that subgroups of patients, defined by genotype, would qualify for orphan status. There are differing opinions about the appropriateness of this route for regulation and licensing pharmacogenetic derived drugs, particularly where the target population is only a subgroup of the disease indication. Unexpectedly, Herceptin, often quoted as a rational model for pharmacogenetics, was refused orphan status by the FDA.

A substantial proportion of prescribing errors occur when label warnings and instructions are overlooked (Dean, 2002; Gurwitz et al, 2003). Regulators in both Europe and the US have considerable concerns about 'off-label' use of combined test-drug products – particularly when the clinicians fail to carry out the pharmacogenetic test but prescribe the linked drug. This concern may translate into a requirement for a wider safety dossier than the genotypic subgroup, and also for increased audit of prescribing. Some commentators believe that applying the precautionary principle may mean that some pharmacogenetic drugs will not be granted a license simply because of the risks if doctors do not perform the test. It may be that a more flexible approach offering 'conditional' approvals could be appropriate here.

### Policy points

- An explicit framework for the regulatory review of combined (test-drug) pharmacogenetic products is required. The framework should address the information needs of clinicians, patients and health systems.
- Pharmacogenetic tests offered by laboratory services should be subject to formal clinical appraisal in order to confirm the clinical validity of test results for the patient population served.

# Health Technology Assessment (HTA)

Following the licensing of a new test or drug, all health systems have to decide whether and how to use these new 'technologies'. While individual doctors often made these decisions in the past, increasingly these decisions are made formally by healthcare funding or reimbursement systems, or health service provider organisations. The process of approval or recommendation is generally based on a review of the available evidence, which often consists mainly of the results of licensing trials. Pharmacogenetics may serve to highlight the disparity between the information needs of patients and prescribers compared with current licensing requirements. Many of those consulted believed that the relationship between health technology assessment (HTA) and licensing needs strengthening.

Several study participants believed that tensions exist between health technology assessment with a public health focus and the paradigm of individual or personalised medicine.

Many of those interviewed felt that the public perception that genetic medicine was different and required special consideration and consent will be an obstacle to acquiring evidence on new products, and may impede the adoption of this technology in the clinic.

The last ten years have seen a steady increase in efforts to secure public involvement in science and technology policy making. The issue of how best to include the public in the debate over pharmacogenetics has not been addressed directly here. The development of pharmacogenetics policy will have to combine attempts to improve the public understanding of the science with strategies for increased public involvement. With a radically new technology, which may bring with it a new form of service delivery, the public may tend to frame their responses in terms of what they know about health services or about pharmaceuticals. Given the uncertainty that surrounds developments in this field, public engagement activities will often be unable to provide the public with certainties. Under these circumstances, a process of continuing dialogue and deliberation will be needed rather than one-off snapshots or short-term processes.

## Information needs of prescribers and patients

Prescribing decisions require quite pragmatic information about the clinical usefulness of the pharmacogenetics test, such as:

- How well does it identify those who will benefit (or not) from treatment, or those who might suffer adverse events, in the relevant hospital or primary care setting?

- If a patient has a 'positive' test related to drug absorption or metabolism, for example, is it clear what action the doctor and patient should take? By how much should doses be altered in individual patients?
- How does the test-drug combination perform compared to the alternative approaches to dealing with the same clinical problem?

Many current genetic tests measure only common genetic variants of target genes, and are thus insensitive to clinically important polymorphisms. Information about the variants that are tested will be important to clinical decision making. The severity of clinical problems and of interacting factors (including drugs, liver or kidney disease) tends to be more variable in routine practice than in research settings.

Different ethnic groups can have markedly different prevalence rates of specific mutations. The performance of a test can therefore be different in different populations, and information on performance in relevant settings will be needed. Clinical validity is likely to be uncertain for new genetic tests, partly because of the limitations of study designs (Burke et al, 2002).

Although tests are likely to accurately identify most target genetic variants, the value of the test results for predicting drug response may often be limited. For several drug metabolising enzymes there is a good existing laboratory science knowledge base, but for other pharmacogenetic markers the underlying science is still uncertain. For safety and efficacy prediction, evaluative information will be needed on a drug-by-drug basis.

*'We need to have the same level of evidence required for a test as for a drug'*

Many of those consulted supported the need to demonstrate clinical utility of pharmacogenetic tests at the licensing stage. In addition, many felt that guidance for healthcare professionals on the use of tests would be needed. Mechanisms will need to be established for evaluating tests and issuing guidance for health service use, both for new drugs and well-used generics. Recent research has revealed that general practitioners have only limited understanding of the terms 'sensitivity' and 'positive predictive value' in relation to diagnostic tests (Steurer et al, 2002) and therefore education of professionals will be important.

Some pharmacogenetic tests may be made available over the counter or direct to consumers. Efforts to regulate such tests are needed, and might include use of consumer legislation as well as licensing.

Pharmacogenetic test results for an individual drug may have implications for other drugs, disease susceptibility and even prognosis. Since the science is evolving there may be unintended consequences of being tested that will not emerge until a later date. Furthermore, the results may have implications for other family members. The prescriber will have to be aware of the uncertainties inherent in the state of knowledge and be equipped to communicate this appropriately to patients.

The public are likely to be aware of pharmacogenetics because of media interest in genetically-derived products and research. Patients and members of the public will need to be well informed and understand that while 'genetic' test results will be both exact and unchanging over time, the interpretation of clinical implications are likely to be complex and uncertain. Public involvement at an early stage could ensure that educational and ethical concerns are addressed and debated in a timely manner.

## Societal barriers to pharmacogenetics

Whilst most patients would like better data sharing and co-ordination of their health information among those caring for them, they also have genuine concerns about confidentiality, notably disclosure to third parties such as insurance companies, employers or even partners. The majority of US respondents believe that data privacy rules are a serious barrier to pharmacogenetic testing, but this view tended to be less strongly held by Europeans. The evidence base needed to evaluate pharmacogenetics and provide the information will not become available to researchers unless both the logistics and ethical framework of recording and linking genetic information are addressed in a timely manner.

In the UK, the Human Genetics Commission reported on balancing interests in the use of personal and genetic data (Human Genetics Commission, 2000). It concluded that more consideration needs to be given to pharmacogenetic testing due to the increasing use in prescribing and 'the wider social and ethical implications'. They also intend to 'monitor any future schemes for the ready storage and accessing of genetic information for prescribing purposes'.

In the US, the NIGMS Population Advisory Group has an ongoing brief to consider their pharmacogenetics research portfolio with particular reference to privacy issues (NIGMS, 2000). Initiatives such as Decode in Iceland and the UK BioBank have also stimulated widespread debate about the ethics (and legal framework) of collection and storage of genetic material for research (Kaye & Martin, 2000).

It is clear that the potential individual benefits to be derived from pharmacogenetic testing must be balanced against the risks – as it may reveal information that has broader medical, personal, social and family consequences (Robertson, 2001). Some believe that research clinicians must inform the patient as completely as possible, to enable proper consent and protect their privacy and rights of confidentiality (March, Cheeseman & Doherty, 2001; Issa, 2003). Others believe that feedback is necessary only when discovered information is clinically relevant, but that it would be harmful to feed back results of unclear significance.

Significant genetic variation which exists between populations and ethnicity are known to affect the frequency of certain variant alleles (Foster, Sharp & Mulvihill, 2001; Bradford, 2002). This information can be harnessed to help streamline global drug development and improve international access to medicines (McCarthy, Davies & Campbell, 2002). Already with the ICH E5 agreement, bridging trials are obligatory when marketing new pharmaceuticals to 'foreign' populations (ICH, 1998).

Concern has been expressed that certain ethnic minorities may be excluded from both research and treatment in a socially unacceptable manner. An alternative view is that pharmacogenetics may provide a more satisfactory and accurate predictor of response to treatment that will not be simply based on racial phenotype (Schwartz, 2001). Notwithstanding, sensitivity will be needed in this area to avoid apparent or real discrimination in research and prescribing practice.

The information about pharmacogenetics available to the public is predominantly commercial and this raises concerns about quality and possible bias. In a time of increasingly informed patients, not least through the Internet and direct marketing, there is likely to be a patient demand for 'tailored medicines'. But in the context of incomplete information, and where treatment choices are limited, this may result in drugs being prescribed even if the test results suggest they are less likely to have certain benefit.

### Policy points

- Resources for health technology assessment of pharmacogenetics will be needed, especially to support evaluation of tests and for research on generic drugs.
- Fears concerning the confidentiality of genetic information for both research subjects and in the routine medical context need to be addressed, but crucial clinical pharmacogenetic research should be safeguarded from stifling and unnecessary confidentiality rules.

## Economics of Pharmacogenetics

The potential for financial savings from pharmacogenetics has been much heralded, but there have been few reports of formal cost-benefit analysis to date. It is thought by some that cost savings from avoided adverse reactions and ineffective treatments will offset the additional cost of testing.

Adverse drug reactions cost health services substantial sums each year and emergency admissions occupy scarce resources (Lazarou, Pomeranz & Corey, 1998; Gautier et al, 2003). However adverse drug reactions are notoriously difficult to cost accurately, and most studies include heroic assumptions. Attribution of adverse drug reactions and their cost is not an exact science. Adverse events are usually multi-factorial, but there is some evidence that a proportion of these could be avoided by better selection of drugs based on pharmacogenetic testing. Although data are substantially lacking, there is potential for saving healthcare resources if patients do not need to be seen so frequently to try different drugs or to adjust doses. There is also a considerable but intangible cost to the patient of receiving ineffective or poorly-tolerated drugs.

*'Who is doing the cost-benefit analysis of these new tests?'*

The application of pharmacogenetics in clinical settings will be driven by pragmatic considerations. There is insufficient empirical evidence, as yet, of the cost-effectiveness of pharmacogenetic testing. One rare but now dated example is a study exploring the impact of cost and reliability on the utility of CYP2D6 testing in psychiatry (Chen et al, 1996). The rapid development of high throughput detection methods is likely to bring down the costs of testing by an order of magnitude within the next few years.

In the context of drug development, it has been suggested that pharmacogenetics will enable compounds to be developed more efficiently and within a short time frame – due to smaller trial samples, more homogeneity in treatment response and overall a more predictable outcome. For some drugs, pharmacogenetic considerations may result in drug 'rescue', wherein a drug destined for withdrawal can be licensed successfully, albeit for a more limited market. Balancing these financial advantages for the manufacturer is the expected reduced size of the target patient group and hence reduced market potential. This could lead to either a company ignoring the pharmacogenetic approach or increasing the unit price (Danzon & Towse, 2002). Pharmaceutical companies may also feel justified in setting a high price for a drug that has evidence of a high level of efficacy. Similarly, a test that successfully discriminated those at risk of catastrophic adverse events could attract a premium.

Inevitably, several factors will impact on the potential of a pharmacogenetic test to be cost-effective: firstly, the seriousness (and costs) of the clinical consequences to be avoided by use of the pharmacogenetic test; secondly, the strength of the association between the genotype and clinical phenotype; and thirdly, the frequency of the variant allele and the lack of simple alternative methods of monitoring drug response (Veenstra, Higashi & Phillips, 2000).

If the introduction of pharmacogenetics into drug development will produce a large number of products that would theoretically qualify for orphan drug status, policy makers will then need to consider how the resources available for orphan drug research should be allocated. Economic analysis could make a useful contribution to this debate (Rai, 2002).

The financial attractiveness of pharmacogenetic treatments to individual prescribers or healthcare commissioners may depend on the relative cost of drugs and tests – a cheap test for an expensive drug would have obvious appeal. Pharmacogenetics could have a negative effect on the healthcare budget if it proliferates in an uncontrolled fashion. It could yield health gain and cost-savings but should not be considered a homogeneous technology, so policy responses need to be proportional to the relative impact in different contexts.

### Policy points

- Greater capacity in academic health economics will be needed to enable economic research on pharmacogenetics, particularly in Europe.
- A balanced public policy framework for 'orphan' tests and drugs will have to be developed, as the scientific and economic issues become clearer.

# Clinical and Public Health Perspectives

The principal benefit of pharmacogenetics should be the better targeting of medicines. A key issue is service delivery and application in the clinical context. There are a variety of health service infrastructure, educational and ethical considerations to be addressed for it to be introduced successfully.

*'It is imperative for governments to consider the process for implementing pharmacogenetics in the clinic'*

## Obstacles to implementing pharmacogenetics in the clinic

The ethical, legal and social implications of pharmacogenetics have been reviewed by several authors (Clarke et al, 2001; Moldrup, 2001; Rothstein & Epps, 2001; Thomas, 2001; Buchanan et al, 2002) and the UK Nuffield Council has conducted an extensive consultation (Nuffield Council on Bioethics, 2003).

Issues of concern are in general comparable with those relating to other genetic developments, but society and industry have very different views of pharmacogenetics. Similarly, group versus individual perspectives and needs are at variance (Moldrup, 2001). Ethical issues may influence the social acceptance of pharmacogenetics.

There are six broad ethical issues:

**Regulatory oversight:** Will there be optimal evaluation and assessment for these new products? Will the information collected for licensing inform and protect the individual and the healthcare decision makers? Is there a regulatory gap in single laboratory ('home-brew') testing?

**Confidentiality and privacy:** These concerns are not unique to pharmacogenetics, and whilst suitability testing for a particular drug treatment may not be sensitive, the revelation of possible secondary information about disease predisposition or progression may have adverse employment or insurance effects, and also implications for relatives (Buchanan et al, 2002).

**Informed consent:** Although also not unique to genetics, there is little consensus on what should be told to subjects; what should be recorded in medical notes; what we can say about the quality/reliability of the test; what counselling/resources (if any) are appropriate and at what stage of development is formal research consent for the test obviated? The ethical

and legal implications for passing that information on to other family members are also not inconsiderable.

**Availability of tests:** There are concerns about unequal provision of the test – perhaps geographical or through different health plans. This could put some patients at increased risk if doctors prescribed a drug intended only for a selected group. This already happens but may become more explicit.

**Access:** People receiving a ‘negative’ test result will be denied a (more remote) chance of the drug working for them. Where there are no alternatives this may cause conflict.

**Clinicians' changing responsibilities:** There is inevitably a medico-legal dimension to pharmacogenetics. It will increase the complexity of prescribing and hence impacts on the accepted standard of care. There are dangers that this could result in additional liability if healthcare professionals lack adequate knowledge. Will the doctor and pharmacist have an obligation to be educated in pharmacogenetics? In what circumstances must they offer a pharmacogenetic test? When must the results be followed – and when can they be ignored?

Application of pharmacogenetics should ideally be in the context of a professional consultation, as an adjunct to good prescribing, rather than direct to consumers. In many circumstances alternatives to pharmacogenetic testing for tailored drugs and doses already exist (for example, therapeutic drug level monitoring), so pharmacogenetics may not be the first option.

Physician behaviour may be a limiting factor. Many doctors do not use currently available (and simple) clinical and diagnostic tests even when appropriate.

*‘The link between discovery of the drug and the benefit to the patients is only as strong as the weakest point – and that is the person writing the prescription’*

Primary care is particularly vulnerable to overload. Pharmacogenetics may be used only if the information can be available in a suitable form and at the point of prescribing. However, it may be cost-effective to identify the correct starting dose, particularly for a disease-modifying drug. A focus on the clinical utility and a way to link testing with outcomes, by way of reinforcing best practice, would be advantageous.

It is also important to bear in mind the 7 to 20 minute consultation time for primary care doctors in Europe, for whom it is very difficult to manage, understand and communicate a large body of new (genetic) information. The complexity of pharmacogenetics means that computerised ‘expert’ systems will be needed to support clinical decision making. PRODIGY and similar expert systems (for example, in Boots pharmacy) should improve the quality (and safety) of prescribing. However, there are already suggestions from the US that physicians do not always use these even when available. The quality of the information employed in these expert systems will need specialist overview

and regular updating. Drug metabolising enzyme information could usefully be included in some labels now. In our questionnaire, the majority of respondents disagreed that current systems of information and dissemination will be sufficient to equip healthcare professionals to employ pharmacogenetics appropriately.

In addition to expert systems to guide complex prescribing decisions, the information infrastructure for patient records needs to support and integrate the new genetic information.

### Pharmacogenetics and warfarin: a prospect for the clinic

Although opinions about utility vary at present, some experts believe that the pharmacogenetics of warfarin may provide the first clinically useful application of this new technology in general practice. As a generic drug this poses an interesting question to policy makers: if there is limited commercial interest in this application, but undoubted potential public benefit – who would provide the funding for test development?

Warfarin is one of the world's most widely prescribed oral anti-coagulants. However, optimal use is hampered by its more than ten-fold inter-patient variability in the doses required to attain therapeutic responses and subsequent frequent bleeding complications.

Pharmacogenetic polymorphism of CYP2C9 may be associated with impaired elimination of warfarin and hence an exaggerated anti-coagulation in some patients. A recent study has shown not only *in vitro* but *in vivo* evidence (Takahashi & Echizen, 2001). Several human allelic variants of CYP2C9 have been cloned and designated CYP2C9\*1, CYP2C9\*2, CYP2C9\*3, and CYP2C9\*4. The allelic frequencies for these variants differ considerably among different ethnic populations – Caucasians appear to carry the CYP2C9\*2 (8-20%) and CYP2C9\*3 (6-10%) more frequently than Asians (0% and 2-5% respectively).

The relationship between *in vitro* enzyme activity of CYP2C9 variants and the *in vivo* disposition of warfarin has been studied extensively. The CYP2C9\*3 mutation consistently confers a substantial reduction in clearance. It has now also been demonstrated, in both British and Japanese patients, that this allele and CYP2C9\*2 may be associated with increased risks of bleeding complications and excessive anti-coagulant responses with initial treatment.

Although further studies are needed to replicate and confirm these findings, this application of pharmacogenetics appears to be promising and potentially near to the clinic.

The challenge will be the public sector commitment to funding the development of a test that could be conducted conveniently and inexpensively, either by providing commercial incentives for a private test kit or by funding public sector research and development.

Pharmacogenetics may be consistent with existing policy initiatives to extend prescribing to nurses and pharmacists. It may even serve to redefine the role of pharmacists where they have the specialist knowledge of which class of drug and dose will be suitable, based on stored genotype test results for each individual.

There are very limited controls on individual prescribers' compliance with drug labels advising restricted use of compounds. Much anxiety has been expressed by regulators that doctors do not prescribe carefully and can fail to keep to essential conditions of the drug label. There are several recent examples of a

drug being withdrawn even though it caused adverse drug reactions only when used 'off-label'.

*'The moral issue, too, is that we ensure 'off-label' prescribing doesn't happen'*

Concerns about prescribing errors and 'off-label' prescribing may lead to more controls of prescribing practice via audit and other monitoring activities. There is a tension between regulatory and ethical concerns for prescribing without a good evidence base, and clinical freedom and innovation.

The evidence from the clinical trials will need to be expressed in terms of a probabilistic benefit or risk, as it is clear that pharmacogenetic test results are unlikely to be predictive or deterministic. Too many external factors, such as co-morbidity, concomitant medications and compliance, will impact on individual drug response, so results will be probabilistic. Pharmacogenetics may also provide an indicator of prognosis, which would have a major impact on patient management. If so, this could also raise considerable ethical and economic issues.

Education is therefore vital – both to teach healthcare professionals to incorporate genetic information into their prescribing decisions and also to understand when to test and how to interpret and communicate the results. At the level of the doctor-patient encounter the clinical validity of tests will need to be well established and understood. Education should be multidisciplinary and timely.

Teaching healthcare professionals is challenging because changing behaviour and communicating new and complex information is very difficult. Doctors in particular do not want to know about the applications of pharmacogenetics in 10 to 15 years time, they want to know what impact it will have now in clinical practice: 'what the test means for my patient'. But it would be a mistake to only educate people about medicine now, so the needs of immediate knowledge and future developments must be balanced. Prescribers also need to know about evaluation processes, knowledge they can draw on as medicine evolves. The prescribers and academics consulted believed that pharmacogenetics education should be integrated into clinical pharmacology training.

*'Whilst some healthcare professionals want to know the underlying molecular science others only want to know the algorithm they can use'*

Education of patients will also be needed. The challenge will be to make the information timely – it is of only peripheral interest until a prescribing decision presents, and yet some background or framework for the decision would be helpful. Education aimed at the public about potential advantages and limitations of pharmacogenetics is urgently needed to counteract widespread misinformation and media hype. Responsibility for this education probably rightly resides with health ministries. There has been much excitement and over-reaction in the press. In the absence of progress in this area, there will be a reliance on industry and patient advocate groups to supply the information, with some inherent bias.

*'The baby boomer generation is going to get chronic disease. Information technology will raise awareness and these individuals will be very demanding'*

Public health experts need to determine which products/tests are priorities for each health service as pharmacogenetics will not provide equal utility for all classes of drugs. Some of the changes to prescribing practice produced by pharmacogenetics may be consumer-driven and may not echo the more 'rational' deliberations of evidence-based practice.

### Policy points

- Pharmacogenetics is likely to add substantially to the growing complexity of prescribing: computerised 'expert' systems will be needed to aid the safe and effective use of pharmacogenetic tests and drugs.
- The clinical application of pharmacogenetics needs to be integrated into undergraduate and postgraduate medical and pharmacist training.
- The possible roles of pharmacists in the implementation of pharmacogenetics in the clinic and community need to be further explored.

# Post Marketing Surveillance (PMS)

All companies marketing proprietary drugs develop and maintain global pharmacovigilance systems for all adverse drug event data generated during clinical trials. These data are shared with regulatory authorities, with clearly defined serious and unexpected adverse events being reported expeditiously, and less serious events at the end of each study. Once drugs are marketed, most licensing authorities have a system for clinicians and companies to report serious and unexpected events. There are also independent research units which monitor adverse events on new drugs, such as the Drug Safety Research Unit (DSRU) in the UK ([www.dsru.org.uk](http://www.dsru.org.uk)). The national systems vary in terms of uptake and also the route of reporting – in the US most reporting is initially to the manufacturer who later reports to the FDA, whilst in Europe clinicians usually report directly to the national agency. Current rates of reporting are both very variable and low (estimated at between 10 and 25% in the US), particularly in primary care, and clinicians lack incentives for reporting (Moride et al, 1997). This is particularly true for older or generic drugs.

*'There is a research infrastructure question as to who conducts continuing surveillance on side-effects for generic drugs'*

## **Can pharmacogenetics be used in post marketing surveillance to enhance safer prescribing?**

A primary benefit of pharmacogenetics is said to be the reduction of adverse drug reactions. Enhanced safety has been heralded as one of the earliest applications of the technology. Adverse drug reactions (ADR) are a major source of morbidity and mortality (Lazarou, Pomeranz & Corey, 1998). In a recent systematic review of the drugs most frequently cited in ADR studies, 59% are metabolised by at least one enzyme that has a variant allele known to cause poor metabolism. Pharmacogenetics may hold the key to identifying individuals who are at risk (Ensom, Chang & Patel, 2001; Phillips et al, 2001). The challenges, time and costs of prospective studies means that only limited numbers of subjects can be exposed to new products prior to licensing, so most significant evidence will be generated via pharmacovigilance and PMS schemes.

The reduction in trial sample size that is likely to accompany pharmacogenetic drug development will lead to a greater requirement for a comprehensive system of post marketing surveillance. One policy option is to mandate the collection of DNA samples as part of drug-related adverse event reporting and create a resource accessible to the academic community for analysis. The project questionnaire showed this had overwhelming support for life-threatening ADRs, but there was division about whether it was justified for less serious events. Most US respondents felt not, whilst Europeans were content to have more widespread testing. It could also be desirable to

integrate DNA sampling into national PMS systems - such as the UK yellow card. Examples of such activity, such as the project described below are already being reported.

### PMS opportunity: The DARE Project

Large-scale PMS provides an opportunity to identify a cohort of patients with a particular disease or complication and conduct pharmacogenetics association studies. The Drug Safety Research Unit (DSRU) in Southampton is an independent charity which undertakes Prescription Event Monitoring for new drugs ([www.dsru.org.uk](http://www.dsru.org.uk)).

The British Heart Foundation is funding a collaboration between St George's Hospital, London and the DSRU: The DARE Project. This aims to establish a national registry in England for patients with suspected drug-related Torsades de Pointes and ventricular arrhythmias and compare them with matched controls. [Torsades de Pointes and ventricular arrhythmias associated with non-cardiovascular and cardiovascular drugs can be life-threatening. These adverse events are usually related to prolongation of cardiac repolarisation. This has generated understandable public and medical concern due to the unpredictability of such events and the incomplete understanding of the epidemiological and clinical significance.]

In addition, the study will undertake a genetic analysis of blood samples from 500 cases and 2,000 controls for mutations and polymorphisms of the cardiac sodium and potassium ion channel genes implicated in the Long QT and Brugada syndromes.

Cases will be recruited over a five-year period from consultant cardiologists and electrophysiologists based in England. The results of the epidemiological study would be expected to improve the understanding and appreciation of proarrhythmia as a public health issue, to enable proarrhythmic events to be prevented and to avoid the exclusion of culpable drugs from general usage without sufficient justification.

The genetic project will examine the association between the risk of proarrhythmia and carrier status for cardiac ion channel mutations (including polymorphisms). These are of interest in that a subtle change in the function of part of the cardiac repolarisation current may only be exposed pathologically by drug interaction. This will statistically examine the hypothesis of the genetic predisposition to drug-induced sudden death in phenotypically apparently 'normal' individuals. The project could be an important step towards making proarrhythmia predictable and avoidable in the prescription of drugs for use in the general population.

The incompleteness of data collection in post marketing surveillance limits its usefulness. It is important to record good phenotypic information and improve patient tracking in order to generate a sound evidence base for the pharmacogenetic basis of (atypical) adverse events. Ideally, PMS systems could also be employed to monitor drug response, i.e. effectiveness, in addition to safety. There is no mechanism in the public PMS systems to identify the degree of response (or non-response) to a drug. Also the attribution of adverse events to genetic factors or other external factors is currently lacking once the drug is marketed.

Most insurance databases are not designed to collect PMS data although they could, but these data do not reach the public domain. The NHS, with its coverage of 59 million people, could provide a wonderful research resource for pharmacogenetics once the electronic record system is in place and functioning (Fears & Poste, 1999). Current data protection legislation is beginning to significantly limit the use of secondary sources for safety research purposes. There is concern about the sharing of information with commercial

players and government. But if samples are permanently anonymised they are of little value for PMS research. Alternatives, such as (reversibly) de-identifying samples, need further consideration. The use of trusted third parties could have a role in facilitating a better system. Computerisation of health records offers significant opportunities to link adverse drug reactions with pharmacogenetic information, so genetic information needs to be incorporated proactively.

Tests and devices also have systems for post marketing monitoring, but it is generally agreed that these are under-resourced and primarily the responsibility of manufacturers. One of the strengths of the new EC Medical Device Directive is the emphasis on PMS, a process of continually reviewing behaviour of devices or tests. The premise is that safety and effectiveness information is best gathered in normal clinical use. All member states must establish a central unit for recording and evaluating incidents and all manufacturers must institute a systematic procedure to review post marketing experience gained with new devices. For in-vitro diagnostic tests the requirement was extended to establish a European databank, which has recently been achieved by the EUDAMED database.

For tests and devices in the UK, MDA have a compliance programme and randomly select and audit data supporting the claims of selected products. There is also a PMS system of voluntary reporting in the event of death or risk of death. Devices which are CE marked (such as pharmacogenetic tests) should be systematically monitored after licensing within a defined legal framework.

In the US there has been mandatory reporting by manufacturers of adverse events relating to devices since 1984. However, the methodology of PMS for tests is not well understood and reporting rates tend to be very low. In the context of a pharmacogenetic test, the reporting of false positive and false negative results could be very burdensome for clinicians but may be valuable for the protection of public health.

A recent initiative in DNA collection collaboration, EUDRAGENE, part-funded by the EU 5th Framework, is the creation of a database linking pharmacovigilance information and DNA samples. The scheme, still in its infancy, currently involves a network of academic centres. The hope is that it can accumulate sufficient cases and controls to explore hypotheses concerning the genetic basis of significant adverse drug reactions (for example, hepatotoxicity, Torsades de pointes) and marketed drugs.

### Policy points

- Post marketing surveillance systems need further development in the light of pharmacogenetics. Systems should investigate genetic factors in adverse events, especially the more severe events.
- There should be a publicly accessible database of pharmacogenetics and adverse drug reactions. It may be necessary to provide industry with incentives to share relevant data.
- Post marketing surveillance of pharmacogenetic tests should be strengthened.

## Discussion

At the conclusion of this two-year consultation it is tempting to echo T.S. Eliot's lines from his poem *Little Gidding*:

*'and the end of all our exploring will be to arrive where we started...'*

as many of the questions the project has raised are still being voiced.

As with any emerging technology, there is evidence of some confusion about terminology and boundaries in the field of pharmacogenetics. Over the course of this project, 'pharmacogenetics' has increasingly been used to denote efforts to achieve safer and more effective prescribing through genetic testing of individual patients. At the same time the term is increasingly understood to cover the use of the new laboratory genetic technologies to identify novel drug targets.

The timing of the project was excellent for considering the potential information needs of clinicians and patients and the accompanying policy responses. However, it soon became evident that few if any valid examples of pharmacogenetic products are yet commercially available. During the project a couple of potential products emerged – in AIDS treatment and schizophrenia – but in each case implementation had been delayed because of inadequate sensitivity of the test in trials in the clinic.

Whereas there is genuine promise for more efficient use of some pharmaceuticals and the avoidance of some serious side-effects, it is clear that pharmacogenetics will neither be universally applicable or perfectly predictive. There is a recognised tension between the current information needs of regulators and the often more clinically practical evidence needed by patients and prescribers. Complex technical products, such as linked tests and drugs, highlight this. Pharmacogenetics may precipitate a re-examination of ways to produce more information relevant to clinical practice, including via regulatory requirements.

Since the focus of the technology is genetic, pharmacogenetics has suffered from media 'geno-hype'. However, it is difficult to find much justification for treating pharmacogenetic tests differently from other diagnostic or clinical tests used in patient management. The complexity of the science and the potentially large numbers of different tests that may emerge could nevertheless pose unusual challenges.

Regulators prefer to be reactive to new technologies or product types, but we have yet to see a 'clear cut' pharmacogenetic challenge to the existing processes. Thus far, only two new compounds linked to genetic tests have been

licensed, both for treating specific cancer cell subtypes. During the project there was an emerging acceptance that formal evaluation arrangements for pharmacogenetic products would benefit from some proactively implemented changes. Firstly, current device and test appraisal is focused on proof of analytical validity and claims of clinical relevance. Most of those interviewed believed that more thorough evaluation of pharmacogenetic tests would be needed, with formal evaluation of clinical validity and utility across the routine clinical populations for which the test was intended. Although there is academic agreement on the appropriate study designs, regulatory requirements for clinical test studies in this area are presently unclear. Many of those interviewed favoured an approach in which evidence requirements are adjusted according to the clinical importance of the test: where the consequence of an inaccurate test result would be severe, levels of clinical proof of test performance would have to be very high. Secondly, tests offered by laboratories, as services, were viewed as not currently subject to adequate clinical evaluation. Thirdly, it is widely recognised that post marketing surveillance systems for drugs need to investigate pharmacogenetic causes of adverse reactions, especially severe reactions. Similarly, PMS systems for test devices have been too focused on manufacturing issues, and healthcare professionals in Europe and the US have little incentive to contribute their experiences of the clinical performance of tests undertaken with marketed equipment. A number of timely initiatives both by industry and the regulators are already promoting these changes.

One of the strengths of this research project was the participation of a broad group of experts representing most of the stakeholder groups involved in pharmacogenetics. Unsurprisingly, there was not full agreement on all points of interest and there were considerable variations in practice and perspective between the UK, Europe and the US.

The key issues of debate included the status of the science, patients' expectations and regulatory and licensing systems. In the US, amongst clinical pharmacologists, industry representatives and patient groups, there is far more overt expectation of pharmacogenetics delivering prescribing benefits in the near future. There is a sense of urgency and imminence not so apparent in Europe. In Europe, we were met with far more scepticism, particularly amongst the clinical pharmacologists who emphasised that pharmacogenetic variants had been recognised for 20 or more years with very little evidence of utility in clinical practice. Even the industry representatives had a more measured and cautious approach and most felt it would be five or ten years before many pharmacogenetic products were licensed.

Academic clinical pharmacologists on both sides of the Atlantic had major concerns about the inequality of information, with real anxieties that the industry was not sharing data as they might. There are tensions between the need for market and patent protection and the understandable unwillingness to share incomplete data with the desire from the public sector for more openness – with some believing that this situation slows the implementation of pharmacogenetic technology. In the US, current confidentiality and consent rules were also seen as important threats to the development of pharmacogenetics.

The patient representatives in the US are enthusiastic about consumer-led healthcare in general and pharmacogenetics in particular and would wish to be both better informed and then at least a partner in decision making. There appears already to be a significant patient demand for pharmacogenetics, and direct marketing is more of a concern there. The climate is such that patients are more likely to press for rights of access to new technology.

By contrast, European patient groups, whilst wholly enthusiastic about the potential benefit of pharmacogenetics, appear to be willing to wait for it to be evaluated professionally. There appeared to be more limited concern about the privacy of patient records, as people expect data sharing – within the medical context – to be to their benefit. There is an assumption here that pharmacogenetics lies within the context of a treatment consultation. However, patients in Europe, too, want to understand the potential advantages and limitations of pharmacogenetics so they can be empowered in the treatment decision process. Ethicists, lawyers and sociologists were far more concerned about the data privacy and confidentiality issues than the patient representatives we met.

In the US, the approach to regulation of tests, including pharmacogenetic tests, is quite centralised and similar to the drug system. Most US regulators were confident that the existing system was both robust and sufficiently flexible to accommodate pharmacogenetics technology. In the past three years there has also been much dialogue about pharmacogenetics between manufacturers and regulators, with the result that concerns have been shared and a common terminology and approach derived. This is typified by the proposed 'safe harbour' system.

In Europe, there is a less iterative system of drug and device regulation, and an apparent mismatch of perspectives. Senior industry pharmacogenetics experts profess themselves confused about routes of regulatory submissions and, more importantly, the level and nature of evidence required. This may be explained in part by them being drawn from a pharmaceutical background with little experience or familiarity of device or test evaluation and regulation, traditionally the domain of the diagnostics companies. It is, in our view, still not entirely clear the extent to which the European directive on In-Vitro Diagnostic Devices will be able to require evidence of clinical validity or utility, or whether its provisions serve only to deal with claims of analytical validity. Regulators in the UK and Europe have been busy addressing some perceived shortcomings – notably of the test evaluation systems – and are satisfied that the European systems are now appropriate and adequate. It is likely that over the two years of this project the international harmonisation process and increased awareness of pharmacogenetics has improved mutual understanding in pre-licensing regulation.

All stakeholders shared a perception that health technology assessment was crucial, and additional capacity and expertise were needed to bridge any information gaps between licensing and prescribers. Similarly, there was a chorus of agreement that PMS systems both in the US and Europe were under-resourced and held the promise of yielding valuable evidence for using pharmacogenetics to improve safety.

Prescribers in primary care and hospital care and pharmacists all made a plea for more practical information about clinical usefulness, for education in using pharmacogenetics for prescribing, and for decision support systems where diagnostic and treatment algorithms are complex.

Policy responses to the uncertain and complex field of pharmacogenetics need to concentrate on enabling a sound evidence base to be built as soon as possible. At present, there is insufficient capacity to provide an evidence base and conduct appropriate evaluations of commercial tests or drugs, or undertake research on the many valuable generic drugs that could be improved with pharmacogenetics. There is a need to build public sector capacity and expertise in relevant disciplines, including clinical pharmacology, clinical epidemiology and health economics.

This expertise needs to be supported by creating the environment for acquiring the evidence. We need to actively encourage more transparency between industry and academic groups for the common good and further the education of ethics committees/IRBs to facilitate pharmacogenetics research. With respect to information management, we need to promote electronic patient records, record linkage and incorporate (pharmaco-) genetic information proactively. Finally, we need to resource a public sector system for post marketing surveillance of drugs and devices and integrate pharmacogenetics research into post marketing surveillance.

There are a number of regulatory initiatives under way which will add value to the appropriate evaluation of pharmacogenetics. It may be helpful to encourage a more flexible regulatory framework for conditional approval of products as information evolves. In addition, orphan product procedures need to be clarified in the light of pharmacogenetics, to facilitate targeted and efficient developments for smaller groups of patients.

Once products are licensed and available, the health technology assessment and the education of prescribers and patients becomes vital. We should, therefore, invest in health technology assessment capacity, notably for pharmacogenetic tests, and ensure education of healthcare professionals and the public in pharmacogenetics. It is important for public confidence that we provide more oversight of laboratory services to ensure tests are both analytically and clinically validated.

In conclusion, pharmacogenetics is a potentially exciting aid to accurate and efficient prescribing. The vision of largely personalised medicine, 'my very own medicine' for many conditions, is a distinct but still a distant prospect. Policy makers need to address the obstacles to collecting appropriate clinical evidence for decision making by 'ordinary' clinicians and patients, via regulation and health technology assessment. Finally, this additional complexity will need to be integrated into education, information and knowledge management systems to achieve the aim of safer and more effective use of medicines.

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# Appendices

## List of Participants

### UK/Europe

Dr Marisa Papaluca Amati	European Agency for the Evaluation of Medicinal Products
Dr Carly Anderson	Centre for Medicines Research International
Dr Mark Bale	Human Genetics Commission
Prof Martin Bobrow	University of Cambridge
Dr Celia Brazell	GlaxoSmithKline
Prof Morris Brown	University of Cambridge
Prof John Caldwell	University of Liverpool
Prof Ruth Chadwick	Lancaster University
Dr Kevin Cheeseman	AstraZeneca
Prof Angus Clarke	University of Wales
Dr Iain Cockburn	Esai Ltd
Dr John Connolly	Department of Health
Dr Oonagh Corrigan	University of Cambridge
Dr Ann Daly	University of Newcastle
Prof William Dawson	Royal Pharmaceutical Society
Dr Madeleine Devey	Arthritis Research Campaign
Jill Dhell	Medical Devices Agency
Dr Simon Festing	Association of Medical Research Charities
Dr Robert Garner	Department of Health
Dr Richard Gutowski	Medical Devices Agency
Dr Rhydian Hapgood	University of Sheffield
Sharon Hart	Drug and Therapeutic Bulletin
Dr David Jefferys	Medical Devices Agency
Dr Dianne Kennard	Department of Health
Alastair Kent	Genetic Interest Group
Prof Peter Lipton	University of Cambridge

Dr Martin Lunnon	GlaxoSmithKline
Dr Neil McAuslane	Centre for Medicines Research International
Dr Alun McCarthy	GlaxoSmithKline
Dr Duncan McHale	Pfizer
Dr John McMillan	University of Cambridge
Prof Miranda Mugford	University of East Anglia
Dr Claire Packer	National Horizon Scanning Centre
Dr James Raftery	University of Birmingham
Prof Martin Richards	University of Cambridge
Dr Justin Richards	PPD Inc
Dr Julia Riley	The Royal Marsden Hospital
Dr Paul Rolan	Medeval
Dr Rupert Sandbrink	Schering AG
Dr Rashmi Shah	Medicines Control Agency
Dr Saad Shakir	Drug Safety Research Unit
Dr Ian Smith	Lehman Brothers
Dr David Spiegelhalter	University of Cambridge
Karen Thomson	Diabetes UK
Prof Geoffrey Tucker	University of Sheffield
Kate Webb	National Asthma Campaign
Prof Andrew Webster	University of York
Dr Paul Whiteside	Department of Health
Prof Roland Wolf	University of Dundee
Dr John Wright	NHS Information Agency
Deborah Zarin	Health Technology Assessment

### **United States/Canada**

Dr Art Atkinson	National Institutes of Health
Nancye Buelow	Mindspring
Dr Michele Caggana	NY State Department of Health
Dr Robert Cook Deegan	Duke University
Dr John Eisenberg (deceased)	Agency for Healthcare Research and Quality
Dr David Feigal	CDRH/FDA
Prof Dave Flockhart	Indiana University
Dr Charles Grudzinskas	Georgetown University

Dr Steve Gutman	CDRH/FDA
Dr Joseph Hackett	CDRH/FDA
Dr Jane Henney	Association of Academic Health Centers
Prof Neil Holtzman	Task Force on Genetic Testing
Dr Shiew-Mei Huang	CDER/FDA
Dr Phil Jackson	Ontario Ministry of Health
Dr Larry Lesko	CDER/FDA
Dr Michelle Long	NIGMS/National Institutes of Health
Joseph McInerney	National Coalition for Health Professional Education in Genetics (NCHPEG)
Michael Murphy	Gentris Corporation
Prof Carl Peck	Georgetown University
Dr Sarah Radcliffe	PhRMA
Dr William Raub	Department of Health and Human Services
Dr Gaile Renegar	GlaxoSmithKline
Dr Patrice Rioux	Repligen Corporation
Dr Allen Roses	GlaxoSmithKline
Prof Mark Rothstein	University of Louisville
Dr Ronald Salerno	Wyeth
Dr Catherine Schaefer	Kaiser Permanente
Dr Peter Shaw	Bristol Myers Squibb
Dr Jeffrey Shuren	Center for Medicare and Medicaid Services
Barbara Slater	Ontario Ministry of Health
Dr Brian Spear	Abbott Laboratories
Dr Robert Temple	CDER/FDA
Sharon Terry	Genetic Alliance
Patrick Terry	Genetic Alliance International
Dr Scott Weiss	Channing Laboratories
Dr Janet Woodcock	CDER/FDA



## Glossary of Acronyms

ACGT	Advisory Committee on Genetic Testing (UK)
ADR	Adverse Drug Reaction
CDER	Center for Drug Evaluation and Research, FDA (USA)
CDRH	Center for Device and Radiological Health, FDA (USA)
CLIA	Clinical Laboratory Improvement Amendments (USA)
CMS	Centers for Medicare and Medicaid Services (USA)
CDC	Center for Disease Control (USA)
CPMP	Committee for Proprietary Medicinal Products (Europe)
CYP450	Cytochrome P450
DIA	Drug Information Association (UK)
DSRU	Drug Safety Research Unit (UK)
ELSI	Ethics, Legal and Social Implications (Research Program of the National Human Genome Research Institute, National Institutes of Health - USA)
EMA	European Agency for the Evaluation of Medicinal Products
EUDAMED	European Medical Device Database
FDA	Food and Drug Administration (USA)
HGC	Human Genetics Commission (UK)
HMO	Health Management Organisation (US)
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IVDD	In-Vitro Diagnostic Devices (Europe)
MCA	Medicines Control Agency* (UK)
MDA	Medical Device Agency* (UK)
MDD	Medical Device Directive (EU)
NEQAS	UK National External Quality Assessment Service (for laboratories)
NIGMS	National Institute of General Medical Services, National Institutes of Health (USA)
PGx	Pharmacogenetics
PMS	Post Marketing Surveillance
SACGT	Secretary's Advisory Committee on Genetic Testing, US Department of Health and Human Services

\* now merged into Medicines and Healthcare Products Regulatory Agency (MHRA)



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