False Positive?

The commercial & clinical development of pharmacogenetics

Paul Martin, Graham Lewis, Andrew Smart & Andrew Webster

The University of Nottingham

The University of York

Bath Spa University

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Paul Martin
IGBiS, University of Nottingham
Graham Lewis
SATSU, University of York
Andy Smart
Bath Spa University
Andrew Webster
SATSU, University of York

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Correspondence relating to this report should be sent to Dr Paul Martin, IGBiS, West Wing, Law and Social Sciences Building, University of Nottingham, NG7 2RD.
Email: paul.martin@nottingham.ac.uk

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Executive summary

1. Introduction

This report is based on the findings of a multidisciplinary social science research project which looked at the clinical and commercial development of pharmacogenetics (PGx), how the emerging technology is being regulated and the main social and ethical issues raised in this context.

1.1 Individuals differ in the way they respond to a given pharmaceutical therapy. One reason for this lies in the genetic variation between people. Pharmacogenetics (PGx) is an important new field of research that aims to apply new data about genetic variation to understanding the problem of differential drug response. Variations in drug efficacy mean that medicines do not provide the intended benefit for every patient, and differences with respect to drug safety can result in serious adverse drug reactions (ADRs). A significant proportion of ADRs and lack of efficacy may be attributed to genetic factors. One of the potential advantages of pharmacogenetics lies in matching the natural variation in a person's genetic make-up (their genotype) to their response to specific pharmaceutical products. This might in principle enable the prescription of medication to be tailored to an individual's genotype, allowing the development of so-called 'personalised medicine'.

1.2 The introduction of personalised medicine rests on two key ideas: 1) The stratification of patient populations according to their response to a particular medication; 2) The stratification of diseases into specific subtypes that are categorised according to genomic criteria and by their response to particular treatments. Some cancers and viral diseases have already been stratified into distinct disease subtypes. The potential benefits of disease stratification would be to improve diagnosis and in some cases link this more closely to therapeutic options.

1.3 PGx is mainly being developed by major pharmaceutical companies and dedicated biotechnology firms, with more limited input from academic researchers. The main potential benefits for the pharmaceutical industry are improvements in the speed and efficiency of the drug development process, and the creation of new markets for existing drugs and for conditions that were previously untreatable. However, to gain these benefits, pharmaceutical companies might have to make major changes: namely, a restructuring of operations to account for genetic variability. Furthermore, disease and patient stratification would also involve the segmentation of drug markets, which might undermine the dominant business model within the pharmaceutical industry which is based on the development of 'blockbuster' drugs aimed at all patient groups. The technology also raises a number of important ethical issues, such as which groups will be targeted for research and how treatment options for excluded groups will be affected. Thus far, few PGx related products have received regulatory approval or entered routine clinical practice.

1.4 There is no single innovation model for the adoption of PGx technology. The field has developed in terms of a process of experimentation and the search for

scientifically and commercially viable techniques, with the technology being applied at multiple points in the drug discovery and development process. As a consequence, there are multiple 'technical options' for the design and application of the technology. Our research identified 12 specific options, under the six broad headings described below:

I. Pharmacogenetics to improve drug discovery
- *1) Discovering new drugs that work well in the entire population*
- *2) Discovering new 'pharmacogenomic' drugs aimed at genomic sub-populations*

II. Pharmacogenetics to improve the safety of drug in development
- *3) Pre-clinical testing and the redesign of early clinical trials*
- *4) 'Rescue' of products in late stage trials due to ADRs*

III. Pharmacogenetics to improve the efficacy of drug in development
- *5) Later stage trial design and monitoring to target 'good responders'*
- *6) 'Rescue' of products that fail late stage trials due to lack of 'efficacy'*

IV. Improving the safety of licensed drugs
- *7) Market (label) extension of products restricted by ADRs*
- *8) Pre-prescription screening to identify patients at risk of ADRs*
- *9) Post-marketing surveillance of approved drugs*

V. Improving the efficacy of licensed drugs
- *10) Pre-prescription screening to identify 'good responders'*
- *11) Use of efficacy data in drug marketing and extending patent life*

VI. Disease stratification
- *12) Stratification of diseases and infectious agents into sub-types*

1.5 The early stages of the design and selection of these different options for PGx technology are shaped by the activities and needs of the different groups involved in the innovation process, including commercial firms, regulatory authorities, clinicians, and health policy makers. Each of these factors will be considered in the following sections.

2. The industrial development of pharmacogenetics

The main findings of the research regarding the commercialisation of PGx are that:

2.1 PGx technology is being developed by ~50 small biotechnology firms and ~30 large pharmaceutical companies. However, less than 20 of the small firms are solely dedicated to the development of this technology.

2.2 The relatively small number of dedicated firms, a high attrition rate of companies and signs of disinvestment from established firms previously working on PGx highlights the lack of a well-developed market for the technology. Despite this, the field continues to attract commercial interest.

2.3 A wide range of options for the technology is being pursued by industry, but some appear to be much more commercially attractive than others. Which ones are successful is contingent on a range of technological, regulatory and commercial factors, most notably around the issue of market segmentation. At present it is uncertain if business models based on segmented drug markets will be commercially viable for large companies, beyond a small number of successes in the oncology field.

2.4 Broadly speaking, there is an industrial division of labour with small firms mainly working on tests for licensed products, whilst large pharmaceutical companies

are working on new drugs. In particular, the latter are mainly applying PGx to established internal processes. However, there is some collaboration between large and small firms on the development of companion diagnostic tests.

2.5 PGx has a primary use within large firms as a technique in the design and analysis of clinical trials to develop safer and more efficacious 'conventional' blockbuster-type drugs. Nevertheless, despite a degree of caution, there is also some interest in disease stratification.

2.6 There is significant investment in the development of PGx tests mainly by small firms in four main areas: a) Drug metabolism enzyme (DME) testing for pre-prescription genotyping and drug development; b) viral genotyping of drug response; c) cancer PGx; d) testing for drug response in a number of common diseases. Of these applications, DME testing and different forms of cancer PGx are attracting the most commercial interest. However, it is small firms, rather than large pharmaceutical companies that are developing tests for generic medicines.

2.7 A significant number of industrial collaborations have been formed since the field started in the late 1990s, although the number of alliances created each year has decreased recently. Most collaborations between small genomics and platform companies and large pharmaceutical companies relate to internal drug development activities rather than diagnostics.

2.8 A small number of PGx products created by large companies have already reached the market, including targeted cancer therapies (e.g. Heceptin) and technology platforms (e.g. Amplichip) to enable PGx genotyping.

3. The regulation of pharmacogenetics

The main findings of the research regarding the regulation of PGx are that:

3.1 Regulators, most notably the US Food and Drug Administration (FDA), have taken the lead in encouraging the adoption of PGx, not least in terms of starting to institutionalise the technology in the drug assessment process. This is demonstrated by measures such as the development of industry guidelines for PGx data submission, the Voluntary Genomic Data Submission initiative for exploratory data, and work on issues around the co-development of drug and diagnostics.

3.2 The extent of industry commitment to the application of PGx and to data submission is largely unknown, but there is increasing evidence of PGx data being used throughout the drug development process. However, at present this is mainly in the early stages of clinical development.

3.3 PGx will not be applicable to all types of drugs and indications, but will be most likely where treatments are either non-existent or display a narrow therapeutic index.

3.4 The broad principles behind the regulatory framework governing PGx are now starting to become established, and a number of potential benefits have been identified, including more efficient clinical trials, and improved data on patient safety and drug efficacy leading to the prospect of more targeted treatment in certain therapeutic areas.

However, industry and regulators are moving cautiously and a number of important issues remain to be to be resolved, notably:

- The type of data required by regulators and the extent to which it will be used in the drug assessment and approval process;
- The process of assessing and approving diagnostic tests to be used with both new and established medicines;
- The relationship between the oversight of the therapeutic agent and (linked) diagnostic tests, and whether such tests will be made obligatory at the level of the clinic and how their use will be enforced;
- The nature of the pharmacovigilance regimes that will become associated with PGx products;
- The governance of 'off-label' prescribing of medicines licensed for use with a PGx test;
- The extent to which PGx testing will be mandated for already licensed medicines, including generics, and the robustness of evidence required to make label changes. Related to this are questions about the basis for regulatory decisions on whether available PGx data warrants mandatory testing or merely the provision of information on the drug label;
- Development of policies to tackle the possibility of 'orphan genotypes' arising, where some groups would have little access to therapy.

3.5 A number of broader ethical issues surrounding the general use of genetic testing also remain unresolved, especially those relating to consent, confidentiality, privacy and future use of personal genetic data and the banking of DNA samples.

4. The clinical use of pharmacogenetics

Within the context of clinical delivery our exploratory study among clinicians using four case study drugs with the potential to be used alongside a PGx test identified some of the key drivers and barriers shaping clinical adoption.

4.1 The main drivers behind the adoption of PGx included:

- Improving prescribing practice (including clinical decision-making) and patient experience;
- The potential to reduce health service costs or redeploy resources.

4.2 The main barriers facing clinical adoption of PGx include:

- The relative value of PGx information and its actual usefulness in practice, especially in relation to the multiple biological and environmental influences on drug metabolism;
- The complexity of drug response, genetic markers and clinical contexts;
- A lack of evidence surrounding the benefits of testing, the genotype-phenotype relationship and cost-effectiveness;
- Concerns about increasing time and workload burdens, and the difficulties of introducing a new drug into practice;
- Financial issues, including funding and resource allocation.

4.3 It must be stressed that the incorporation of the technique into everyday, routine practice (the utility of tests and what makes them 'workable') is not simply determined by how they measure up to the evidence based requirements of sensitivity and specificity. Stimulating a clinical demand will require convincing clinicians that there is clear and unequivocal evidence of the benefits, particularly how a test might improve clinical outcomes and add value to, and be integrated into, existing clinical

practice. This will be specific to a particular drug, disease and clinical context. Furthermore, practitioners are likely to weigh evidence of potential benefits regarding clinical outcomes in relation to the potential difficulties and drawbacks that may arise from altering current practice.

4.4 Certain requirements must therefore be fulfilled in order to create a clinical demand for PGx, including a strong evidence base in terms of patient outcomes and economic effectiveness, and the feasibility of integrating novel tests into current practice. The nature of the illness under consideration, the benefits and drawbacks of available treatment regimes and the practicalities of the current treatment process are all likely to influence the chances of a valid PGx test being widely adopted. Even in the best current examples of applying PGx to existing medicines, the potential is for incremental improvements to practice, rather than a wholesale revolution as implied in the idea of 'personalised medicine'.

5. The development of health policy to support pharmacogenetics

The main findings with respect to the development of policy are that:

5.1 An effective policy framework should see new technologies, health services, clinical practices, regulatory regimes and ethical issues as co-constructed. In particular, the adoption of PGx will be shaped by wider social and technical developments in genetics and biotechnology.

5.2 The field of PGx is marked by high level of technical, clinical and commercial uncertainty. As a consequence, we should expect to see an emerging policy agenda that is quite heterogeneous, mutable and highly context specific. Such a framework should be flexible and allow adjustment to be made as innovation proceeds.

5.3 The emerging policy, ethics and governance framework will therefore need to be quite broadly drawn if PGx is to be effectively managed on an ongoing basis. Private corporations and clinicians are having to work in a highly contingent innovation landscape and this may be an important reason why adoption has been slow.

5.4 Rather than placing an emphasis on the test-bedding or piloting of PGx application in established institutional settings, policy should explore how it can foster the creation of 'innovation niche spaces' in which new technologies might be nurtured by both public and private sector interests. A series of niche developments may appear as a result of competing innovation expectations, which for a time will generate more, rather than less, complexity.

5.5 The pattern of 'absorption' of PGx within healthcare systems will therefore critically depend on how far the existing knowledge base and professional practices open up to create institutional spaces through which PGx might be introduced.

5.6 PGx will be more likely to be successfully mobilised where commercial, professional and policy interests converge, and these in turn will be reflected in the creation of robust expectations about the utility and value of the technology.

5.7 At present there is no obvious policy model given the different perceived opportunities and risks of PGx; instead the key problem is how to build strategic

capacity without getting trapped into a policy/business model that will fail. This requires an approach that is highly *reflexive* and accepts the need for iteration and reflection about the way discrete policy elements need to be mobilised simultaneously and not sequentially.

5.8 Public policy will therefore need to adopt and develop a 'comprehensive framework', that not only requires a reflexive and cautious approach, but one that questions the allocation and resources to be devoted to PGx itself and the opportunity costs this might involve. This will ensure that any pay-off from PGx is perceived to meet genuine need.

6. Conclusions

6.1 As outlined in the introduction, a range of factors will determine which technological options are most likely to be commercially developed and clinically adopted, and which ones may fail. In broad terms, to be successful, a technology needs commercial investment and support (especially from larger companies), a permissive regulatory environment, significant clinical demand and relatively low barriers to diffusion and adoption within healthcare systems. Based on the data presented in the main body of the report, the 12 technological options for PGx can be divided into four groups as follows:

Group A: Applications of PGx that have a direct commercial benefit to the pharmaceutical industry and largely fit into established patterns of innovation and healthcare delivery. This group of applications includes:

- Option 1. Discovering new drugs which work well in the entire population;
- Option 3. Pre-clinical testing and early stage trial design/ monitoring of new drugs;
- Option 12. Stratification of diseases into sub-types.

It seems likely that these applications of PGx will continue to be integrated into established internal industrial processes and that disease stratification, most notably for cancer, will become widespread.

Group B: Applications of PGx that offer some commercial benefits to the pharmaceutical industry, but require new forms of innovation and the creation of new service and regulatory infrastructures. This group of applications includes:

- Option 2. Discovering new drugs aimed at genomic sub-populations;
- Option 5. Later stage trial design and monitoring of new drugs to target 'good responders';
- Option 7. Market (label) extension of licensed products restricted by ADRs.

The future development of these options is uncertain and largely contingent on the commercial strategies adopted by large pharmaceutical companies. However, two factors will be important in influencing commercial viability, namely the overall regulatory environment governing products targeting patient sub-populations and the availability of financial incentives to develop products for sub-populations, such as orphan drug legislation.

Group C: Applications of PGx that offer direct public health benefits, but are not commercially attractive to the pharmaceutical industry and require new forms of service infrastructure. This group of applications includes:

- Option 8. Pre-prescription screening to identify patients at risk of ADRs from licensed drugs;

- Option 9. Post-marketing surveillance of licensed drugs;
- Option 10. Pre-prescription screening to identify 'good responders' to licensed drugs.

The development of these options is likely to be driven by the actions of smaller diagnostic companies and health care providers, such as the NHS, and will be heavily influenced by public policy.

Group D: Applications of PGx that have little direct commercial or public health benefits, raise *regulatory* concerns and require new service infrastructures. This group of applications includes:

- Option 4. 'Rescue' of new products in late stage trials (ADRs);
- Option 6. 'Rescue' of new products based on efficacy;
- Option 11. Use of efficacy data in drug marketing.

It is unclear which set of actors in the innovation system will drive the adoption of these options. In the future there may be commercial proof of principle for drug rescue/repositioning or the use of PGx data in marketing, but until this is demonstrated the major regulatory barriers that face products that have failed clinical trials may prove insurmountable.

6.2 From this analysis it is clear that there is a serious risk that some of the options (listed under Group C), that have the greatest potential for improving public health, may not be developed due to lack of commercial support from large companies. This can be thought of as a form of market failure.

6.3 With respect to PGx, the primary aims of public policy should be to improve the health of the population by: supporting the creation of safe and effective medicines that meet unmet clinical need; improving the safety and efficacy of new and already licensed medicines; and promoting the cost-effective use of healthcare resources. In order to achieve this, we have argued that policy makers need to adopt a broad, comprehensive framework for PGx that is responsive to the emergent technology, commercial interest and regulatory and clinical responses. We suggest this framework is best developed from within a public health perspective.

7. Recommendations

Supporting industrial innovation

Recommendation 1: *Create greater regulatory certainty* in order to sustain long-term investment in PGx. In particular, this relates to the:

- Type of data required by regulators and how it will be used within the assessment process;
- Process of assessing and approving companion diagnostics;
- Oversight of the use of companion diagnostic tests;
- Nature of the pharmacovigilance regime associated with PGx;
- Extent to which PGx tests will be mandated for already licensed medicines; and the evidence required to make label changes;
- Resolution of the ethical issues surrounding the more general use of genetic testing and personal genetic information in healthcare systems.

Preventing market failure

Recommendation 2: *Extend orphan drug legislation* to provide incentives for companies to develop drugs for markets and patient groups segmented by PGx tests that may not otherwise be commercially attractive.

Recommendation 3: *Create public-private PGx partnerships* to develop diagnostic tests for a number of important and widely used already licensed medicines that are currently commercially unattractive.

Protecting the safety and rights of the public

Recommendation 4: *Enhance pharmacovigilance systems* to ensure that PGx technology and data are introduced into the monitoring of new medicines and already existing drugs where appropriate.

Recommendation 5: *Improve drug labelling, the oversight of off-label prescribing and the transparency of decision-making* on the inclusion of PGx data on drug labels, including whether such data is made mandatory or not.

Recommendation 6: *Ensure tight statutory regulation and oversight of the third party use of personal genetic information*.

Supporting clinical adoption of PGx

- **Recommendation 7**: *Include data on proof of clinical utility in the approval process for all PGx related diagnostic products.*
- **Recommendation 8**: *Give greater public funding to help create an evidence base on the clinical utility and cost-effectiveness of using PGx testing for important already licensed drugs*. Greater effort should also be made to improve the provision of information to clinicians on test availability and clinical utility.
- **Recommendation 9**: *Support the development of PGx delivery systems* that can be integrated in established patterns of professional practice. The process of translation could be stimulated by providing clear guidance on exactly how PGx tests might be used and interpreted by clinicians. This might be included in the design of the electronic patient record and computer-based decision support systems.

Create a PGx innovation platform in health delivery systems

- **Recommendation 10**: *Provide further investment in developing the overall structuring of genetic health service delivery* and especially the organisation, funding and governance of genetic testing. However, it must be stressed that it will be neither viable nor rational to adopt PGx in all therapeutic areas.
- **Recommendation 11:** *Explore alternative ways of providing PGx testing services*. It is not clear that the established structure of genetic testing laboratories either has the capacity or is best placed to carry out high volumes of routine PGx testing. Policy should explore a range of different service delivery models.
- **Recommendation 12:** *Fund ongoing and systematic evaluation* on the routine use and utility of medicines, the wider cause of ADRs, and the benefits of PGx in this context.

Recognise the contribution of social science in helping understand the development of PGx

- **Recommendation 13:** *Continue to support multidisciplinary social science research on emerging genetic technologies, such as PGx*.

Chapter 1
Introduction: Pharmacogenetics and 'personalised medicine'

1.1 The promise of pharmacogenetics

It has been known for many decades that individuals differ in the way they respond to a given pharmaceutical therapy. One reason for this lies in the genetic variation between individuals.[1] Following the sequencing of the human genome, the aim of much 'post-genomic' research is to translate DNA sequence information into useful medical knowledge, including novel therapeutic and diagnostic products. The promise of pharmacogenetics (referred to in this report by the abbreviation PGx) is to apply new data about genetic variation to understanding the problem of differential drug response.[2] Although most drugs are designed to work in the entire population, it is widely recognised that there are significant variations between individuals in both the safety and efficacy of medicines. Variations in drug efficacy mean that medicines do not provide the intended benefit for every patient, with a significant number of people simply not responding to treatment. Differences with respect to drug safety can result in serious adverse drug reactions (ADRs), which can cause major health problems or even result in death. It has been claimed that ADRs are the fourth biggest cause of death in the USA[3] and are a major cause of hospital admissions.[4] A significant, but as yet undetermined, proportion of ADRs and lack of efficacy may be attributed to genetic variation between individuals, although the influence of institutional, behavioural and environmental factors should not be underestimated.[5] One of the potential advantages of pharmacogenetics lies in matching the natural variation in a person's genetic make-up (their genotype) to their response to specific pharmaceutical products. This might enable the prescription of medication to be tailored to an individual's genotype, allowing the development of so-called 'personalised medicine'. In principle, this could both reduce safety problems and improve the effectiveness of treatment.

The introduction of personalised medicine rests on two key ideas: 1) *The stratification of patient populations according to their response to a particular medication*. This may include the identification of groups of patients who are at risk of adverse drug reaction (safety) or those patients who respond well to therapy (efficacy). 2) *The stratification of diseases into specific subtypes that are categorised according to genomic criteria*

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and by their response to particular treatments.[6] This has already been occurring in relation to several common diseases, most notably different forms of cancer (breast, lung and lymphoma), which have been stratified into distinct disease subtypes, as well as a number of viral diseases (HIV and hepatitis infection). The potential benefits of disease stratification would be to improve diagnosis and, in some cases, link this more closely to therapeutic options.

Pharmacogenetics is unusual in the context of medical innovation as it is mainly being developed by major pharmaceutical companies and dedicated biotechnology firms, with more limited input from academic researchers. This is partly due to the need to access large numbers of patients in clinical trials, something which few public sector researchers have access to. In addition, multifactorial genetics analysis involves heavy investment in instrumentation and informatics to enable the creation of large DNA sample collections and genotype databases, as well as the development of new diagnostic technologies, such as 'gene chips'. Only commercial firms working with clinical researchers have the resources to support these complex activities. The main potential benefits for the pharmaceutical industry are improvements in the speed and efficiency of the drug development process, and the creation of new markets for existing medicines and for conditions that were previously untreatable. Despite recent progress, the field is still surrounded by a high level of scientific and commercial uncertainty, as there are few PGx related products that have either received regulatory approval or entered routine clinical practice.

A key factor in the potential development of personalised medicine is that disease and patient stratification would also involve the segmentation of drug markets. This fundamentally threatens the cornerstone of pharmaceutical industry profits - the blockbuster drugs that are sold universally into an undifferentiated market. Fresh knowledge about human genetics has been heralded by some as a potential saviour for the industry, with claims that it could both greatly reduce the costs of drug development and supply thousands of new drug targets. To gain these benefits, however, pharmaceutical companies might have to make major changes: namely, a restructuring of operations to account for genetic variability. Implementing such changes will not be easy, and the pharmaceutical industry is faced with difficult decisions about the extent of its commitment to change in this area.

In addition to its potential benefits, the development of PGx and the possibility of patient/disease stratification and market segmentation raise *important new social and ethical questions*, including:

- Will the pharmaceutical industry move towards the development of highly segmented ‘orphan markets’? If so, will these be targeted at particular groups and will other groups be excluded?
- How might pharmacogenetics affect clinical practice? Where will it first be used and how will genotyping be integrated into the clinic? What forms of clinical governance will be needed? What are the implications for the future development of health services and health policy?
- How can informed patient consent be ensured in both prescribing and clinical trials? What implications does possessing the 'wrong' genotype have for the treatment a patient receives? What ethical issues are raised by the large-scale use of DNA samples and genetic data?

[6] Shah, J. (2004), Criteria influencing the clinical uptake of pharmacogenomic strategies, *British Medical Journal,* 328:1482-1486.

- How should regulators respond to proposals to redesign clinical trials on the basis of genotyping? How will drugs approved only for use with patients of a particular genotype be controlled? What changes might be needed in drug dispensing and post-marketing surveillance?

Great uncertainty surrounds many of these questions and the ethical and regulatory framework governing PGx is still emerging. In this context there is a real need for empirical evidence to guide policy making.

1.2 The research project

Given its significant potential to improve healthcare, and the important ethical, social and legal issues it raises, pharmacogenetics has recently been the subject of a number of studies,[7] several of which have focused on the ethics of PGx.[8] In contrast, there has been relatively little empirical social science research undertaken on these issues,[9] with a few notable exceptions.[10] Some previous work has focused on the pharmaceutical sector and its regulatory context. This has explored the relationship between regulators and the industry, the variation in regulatory practices between countries,[11] and ethical and safety questions associated with clinical trials and

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[9] Snedden, R. (2000), The challenge of pharmacogenetics and pharmacogenomics, *New Genetics and Society,* 19(2): 145-164.

[10] Hedgecoe, A. (2002), Reinventing Diabetes: Classification, Division and the Geneticization of Disease, *New Genetics and Society,* 21(1):7-27; Hedgecoe, A. (forthcoming), Terminology and the construction of scientific disciplines: the case of pharmacogenomics, *Science, Technology and Human Values;* Hedgecoe, A. and Martin, P. (2003), The Drugs Don't Work: Expectations and the Shaping of Pharmacogenetics. *Social Studies of Science*, 33(3):327-364; Webster, A., Martin, P., Lewis, G., and Smart, A. (2004) Integrating pharmacogenetics into society: in search of a model, *Nature Reviews Genetics* 5:663-669; Lewis, G. (2004), Tissue collection and the pharmaceutical industry: Investigating corporate biobanks, in Tutton, R. and Corrigan O. (eds), *Genetic Databases: Socio-ethical issues in the collection and use of DNA*, Routledge: London, 181-202.

[11] Abraham, J. and Lewis, G. (2000), *Regulating medicines in Europe: competition, expertise and public health*, Routledge: London and New York; Lewis G. and Abraham J. (2001), The creation of neo-liberal corporate bias in transnational medicines control: the industrial shaping and interest dynamics of the European regulatory state, *European Journal of Political Research,* 39:53-80; Abraham J. and Lewis G. (2003), Europeanization of Medicines Regulation, in: *The Regulation of the Pharmaceutical Industry*, Abraham, J. and Lawton-Smith, H. (eds), Palgrave Macmillan: Basingstoke and New York; Abraham, J. and Reed, T. (2002), Progress, innovation and regulatory science in drug development: the politics of international standard-setting, *Social Studies of Science*, 32:337-69.

'informed consent'.[12] These studies provide a general background to this project, but do not address the questions raised above.

1.2.1 Aims of the research

This project was therefore established as a detailed empirical study of how pharmaceutical companies and clinicians are developing pharmacogenetics, and the main social and ethical issues raised by these developments. Its original aims were to:

1. Describe the scale of activity in pharmacogenetics within the pharmaceutical industry, the main strategies which firms are adopting for its introduction and the possible impact of these strategies on clinical practice, the design of clinical trials, and the organisation of health services;
2. Identify the main social and ethical issues raised by the introduction of pharmacogenetics into the clinical testing of new medicines, particularly in relation to informed consent and the storage and use of genetic data;
3. Examine how pharmacogenetics is likely to be used in targeting established drug therapies to particular patient groups and what implications this might have for patient care, professional practice and clinical governance;
4. Assess the likely impact of pharmacogenetics on the regulation of medicines, including the design of clinical trials and post-marketing surveillance;
5. The project will conclude by mapping out a framework for public policy to manage the introduction of pharmacogenetics, including research oversight, clinical governance and the regulation of drugs.

During the course of the project some of the planned research relating to the second aim (on the practical ethics of clinical trials) became untenable due to major access problems. However, this topic has been relatively well covered by the studies mentioned above, so the focus of this report is on the other questions concerning commercial development, regulation and clinical practice.

1.2.2 Novel conceptual framework

Conceptually, the project aims to be innovative by drawing on and integrating two theoretical approaches. Firstly, the 'technology studies' work developed primarily by sociologists, especially those working within the European 'science, technology and society' tradition; and secondly, work which has a more specific focus on understanding the development of innovative health technologies.[13] These both show that the development, take-up, impact and social regulation of new technologies – such as pharmacogenetics - are intimately connected and can be thought to 'co-evolve' over time through a process of mutual shaping.[14] Thus there is no simple linear path from the laboratory to the clinic. The problems around introduction are shaped not merely by perceived clinical need, but by the intersection of different

[12] See e.g. Brown, R. F., Butow, P. N., Butt, D. G., Moore, A. R. and Tattersall, M.H.N. (2004), Developing ethical strategies to assist oncologists in seeking informed consent to cancer clinical trials, *Social Science & Medicine,* 58(2):379-390. Also see EU Directive on clinical trials: Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, *Official Journal of the European Communities,* May 2001.

[13] Webster, A. (ed). (2006) New Technologies in Health Care: Challenge, Change and Innovation, Palgrave Macmillan: Basingstoke

[14] MacKenzie D. and Wajcman J. (1999), *The Social Shaping of Technology,* Open University Press: Buckingham.

epistemological, institutional and cultural processes.[15] To be successful, innovators need to mobilise a wide range of social, technical, economic and political resources, and bring these together in a stable fashion around an emerging technology. Furthermore, during the innovation process, the meaning, applications and physical design of a new technology can change, being shaped and reshaped by the different social actors involved.

Of particular importance within these traditions is the concept of 'niche'. A number of authors have highlighted the importance of a 'niche' within an established drugs innovation system which can be opened up as an 'innovation space' for future growth. Innovations are often widely taken up when these niches branch and build, as costs fall and the technology becomes available to a wider market and variety of uses.[16] Inherent to this process of socio-technical change is the emergence of new social and ethical issues, and new forms of governance. In the case of pharmacogenetics this may depend on the stabilisation of new types of clinical trials and the acceptance of targeted drug regimes by physicians and patients. The 'niche' approach will enable us to see how the actors involved negotiate those social and ethical issues.

1.3 Options for development of pharmacogenetics

Before describing the empirical research findings it is worth defining more precisely what is meant by pharmacogenetics and mapping out the different ways (technology options) in which it might be used.

Pharmacogenomics and pharmacogenetics

In the last five years post-genomics research has focused increasingly on the function and expression of genes, and on studying the variations within and between different human populations. This has sparked growing interest in what has become broadly known as pharmacogenomics. This term is often used interchangeably with pharmacogenetics, but for the purposes of this report will be defined more carefully.

Pharmacogenetics is best understood as the study of the genetic basis of drug response and is mainly concerned with the assessment of a drug's clinical efficacy and/or safety profile. It is primarily focused on understanding how an individual's response to medication may be affected by their genetic make up (genotype).[17]

In contrast, ***pharmacogenomics*** is best described as being concerned with providing a comprehensive, genome wide assessment of the effects of pharmacological agents on gene expression patterns.[18] This information is used to evaluate the different effects of a number of chemical compounds during the process of choosing the best

[15] See e.g. Metcalfe, S. and James, A. (2003), Emergent systems and the delivery of clinical services: the case of intra-ocular lenses. Research Report. Centre for Research on Innovation and Competition (CRIC) and School of Economic Studies, University of Manchester; Gelijns, A.C. and Rosenberg, N. (1995), The Changing Nature of Technology Development, in Gelijns, A. C. and Rosenberg, N. (eds) *Sources of Medical Technology: Universities and Industry,* Institute of Medicine, Washington: National Academy Press.

[16] Kemp, R., Schot, J. and Hoogma, R. (1998), Regime Shifts to Sustainability Through Processes of Niche Formation: The Approach of Strategic Niche Management, *Technology Analysis and Strategic Management*, 10:175-196.

[17] Pirmohamed, M. (2001), Pharmacogenetics and pharmacogenomics, *British Journal Clinical Pharmacology* 52(4):345-347.

[18] Lindpaintner, K. (2002), Pharmacogenetics and the future of medical practice, *British Journal of Clinical Pharmacology,* 54:221-230.

one to develop (so called 'lead selection') and does not focus on differences between individuals.
Pharmacogenetics is therefore aimed at both drug development and clinical practice with the objective of finding the medicine best suited to a given patient (or to find the patients most likely to respond positively to a drug). In contrast, pharmacogenomic studies are used during the process of drug discovery and lead selection to find the most suitable drug candidate from a given series of compounds under evaluation. This report will very largely focus on pharmacogenetics, but will inevitably touch on pharmacogenomics where relevant.

1.3.1 Different approaches to pharmacogenetics and their potential benefits

Work in innovation studies and the sociology of technology has highlighted the wide range of different designs, strategies and applications that mark the early phase of the development of many new technologies. This is particularly true of radical or novel innovations that have few precedents. Under conditions of uncertainty, innovators engage in a process of search based on trial and error, experimentation and the testing of different prototypes. This is in order to find a design that is technically feasible, can be introduced into routine practice and is commercially viable. These general features mark the early development of pharmacogenetics, with firms adopting a range of distinct approaches to the application of genomic knowledge to the development and use of medicines.

There is no single or dominant model for adopting PGx technology. Instead, the development of the field should be understood in terms of a process of experimentation and the search for viable techniques, with the technology being applied at multiple points in the drug discovery and development process (see below). The early stages of the design and selection of different options for PGx technology will be shaped by the activities and needs of the different groups involved in the innovation process. The starting point for the project therefore involved the identification of a number of discrete innovation options for the application of PGx. These are summarised below and are divided into 12 options under six broad headings related to the discovery and development of new medicines, and the prescription and marketing of already licensed therapies.

It should be stressed that the description of these options is a heuristic device to enable a more powerful understanding of this emerging technology. These divisions are based on detailed empirical study of the PGx industry, but remain analytical categories. They do not represent all the ways in which PGx may be developed in the future, but provide an evidence-based description of the main strategies adopted at present.

Each of the options has different levels of scientific, clinical and industrial support and investment. Furthermore, each is also at a different stage of development, with some being used in daily practice, while others remain mainly as technical possibilities. By analysing the investment in each of the options and the barriers they face, it will become possible to make a more detailed assessment of which forms of PGx are most likely to be adopted in the short term.

I. Pharmacogenetics to improve drug discovery

Pharmaceutical companies are increasingly using PGx techniques and data to improve the drug discovery process. There are two main ways in which this is being done.

1) Discovering new drugs that work well in the entire population

Drug candidates can be screened for variable response against the most common variants (alleles) of a particular genomic target (i.e. a gene that is thought to be involved in disease). Only those candidates who show no significant variation in efficacy are then taken into drug development. This type of screening reduces the risk of drugs being rejected at a later stage and increases their likelihood of success.

2) Discovering new 'pharmacogenomic' drugs aimed at genomic sub-populations

A number of companies are developing strategies to create new drugs aimed at particular genomic sub-populations - what has been called 'pharmacogenomics' (see above). In most cases the target groups will be the individuals most likely to benefit from therapy, so called 'good responders'. These drugs would probably have to be approved as safe in all groups but would be licensed and marketed for good responders. In principle, this might increase the chance of an effective drug being approved, but at the expense of it having a restricted market. If such drugs were developed they would be more likely to be clinically effective in their target group.

II. Pharmacogenetics to improve the safety of drug in development

One of the main ways PGx may have an impact on drug development is in the design and analysis of clinical trials, with a number of authors claiming that this will lead to smaller, smarter and cheaper trials.[19] Others have suggested that drugs causing ADRs in particular genomic groups could be 'rescued' in late stage trials.

3) Pre-clinical testing and the redesign of early clinical trials

In early, pre-clinical studies or in early stage Phase 1 clinical trials, genotyping might be used to either exclude or include particular genomically defined groups in order to increase the chances of a drug being shown to be safe.[20] However, this type of pre-screening is likely to meet significant opposition from regulatory authorities due to the risk of missing serious ADRs. It seems more likely that companies will use PGx to ensure that trial populations are representative of the general population for particular genetic variants associated with drug metabolism (e.g. CYP2D6). This could greatly help to minimise the risk of trial bias, or reduce the risk of a drug failing at a later stage of development as a result of bias, and to improve the safety profile of the final product.

4) 'Rescue' of products in late stage trials due to ADRs

In later stage Phase II and III trials, PGx may be used retrospectively to identify particular genomically defined groups who are at higher risk of ADRs. This might be particularly important in 'rescuing' a therapy that was highly effective, but was associated with a small number of serious genetically based ADRs. These groups could be identified and excluded from subsequent pivotal trials. A drug developed in this way would only be licensed for use in specific sub-populations and would need careful monitoring, because of the risk of it being given to the wrong patient group. Consequently, it would have to be used in conjunction with a test for pre-prescription genotyping and have a restricted market. Regulators might license such a product solely for use in specialist secondary and tertiary settings, due to the higher risk of off-label prescribing in primary care.

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[19] Rothstein, M.A. and Epps, P.G. (2001), Ethical and legal implications of pharmacogenomics, *Nature Reviews Genetics* 2:228–231; Roses, A. (2000), Pharmacogenetics and future drug development and delivery, *The Lancet*, 355:1358-1361.

[20] Issa, A. M. (2002), Ethical perspectives on pharmacogenomic profiling in the drug development process, *Nature Reviews Drug Discovery* 1:300–308.

III. Pharmacogenetics to improve the efficacy of drug in development

A third possibility would be to target drug development at patients most likely to respond to a therapy.

5) Later stage trial design and monitoring to target 'good responders'

In later stage Phase II and III trials, PGx might be used to improve efficacy in two ways. First, prospective studies could test new drugs in sub-populations of patients believed to be good responders. This might significantly increase the chance of a drug reaching the market. Second, where the overall benefit of a drug across the whole population is shown to be marginal, PGx might be used retrospectively to identify a particular genomic subgroup composed of particularly good responders to the therapy. These groups could be specifically included in subsequent pivotal trials. In both cases this would lead to the development of new drugs licensed for use purely in a specific genomic group. The breast cancer therapy trastuzumab (Herceptin) is an example of a very successful product developed for a genetically defined group of patients whose tumours over-express the HER-2 gene product. Whilst this drug is largely safe in all patients, it is only effective in this sub-population.

6) 'Rescue' of products that fail late stage trials due to lack of 'efficacy'

In later stage Phase II and III trials, PGx may be used retrospectively or prospectively to identify specific genomically defined groups composed of particularly good responders. This might be particularly important in 'rescuing' a therapy that was unable to demonstrate efficacy in the whole population, but that was highly effective in a subgroup. Subsequent pivotal trials of the drug could then be targeted at this sub-population. A drug developed in this way would only be licensed for use in the defined sub-populations and would have to be used in conjunction with a test for pre-prescription genotyping and have a restricted market.

IV. Improving the safety of licensed drugs

Much attention has been given to the ways in which PGx might benefit the pharmaceutical industry in the discovery and development of new drugs. However, the technology offers significant advantages to clinicians, healthcare providers, patients and companies by improving the purchase, prescription, use, marketing and surveillance of licensed products. This might be achieved in a number of ways:

7) Market (label) extension of products whose use is limited by ADRs

A number of approved drugs already have restricted markets as a result of safety problems. For example, approximately 5% of patients treated with the HIV/ AIDS drug Abacavir (see Chapter 2) develop a hypersensitivity reaction that requires permanent discontinuation of the drug. This has limited the clinical use of the therapy. Research is underway to identify the genomic sub-group most at risk of this ADR and to determine if prospective screening will identify patients who will benefit from abacavir therapy. As no genetic marker is likely to be fully predictive, genetic screening is best thought of as an adjunct to established clinical management of patients who receive abacavir therapy. Such strategies might be used to extend the use of drugs with treatment-limiting ADRs, and result in improved patient outcomes and increased product sales.

8) Pre-prescription screening to identify patients at risk of ADRs

One of the most widely publicised applications of PGx is the development of 'personalised medicine' in which patients are genotyped before medication to enable physicians to give 'the right drug to the right person'. Attention has focused particularly on the possibility of pre-prescription testing to identify patients at greatest risk of genetically based ADRs resulting from the use of a given drug. These patients could either be offered an alternative therapy or be closely monitored, if no alternative exists. A number of laboratories and private companies in the USA already offer thiopurine methyltransferase (TPMT) genotyping (e.g. Prometheus Labs http://www.prometheuslabs.com) to identify patients most at risk of severe adverse reactions as a result of their inability to metabolise the chemotherapy drug 6-Mercaptopurine (see case study in Chapter 4). This type of application of PGx could in principle lead to safer prescription and reduce the burden posed by serious ADRs.

9) Post-marketing surveillance of approved drugs

Pharmacogenetics could also be incorporated into improved post-marketing surveillance of medicines. Patients who have suffered an ADR could be genotyped to see if there was a genetic basis for their response. This might lead to the creation of a test to identify people at high risk of rare ADRs. Rather than leading to drug withdrawal, the introduction of this form of PGx testing might also enable some products to remain on the market[21] or to be 'rescued' after withdrawal.[22]

V. Improving efficacy of licensed drugs

10) Pre-prescription screening to identify 'good responders'

In a similar fashion to pre-prescription patient safety testing, PGx could be used to identify those most likely to respond positively to a specific drug. It is already well established that some patients fail to respond to common prescription medicines such as fluoxetine (Prozac). There have been claims that testing for non-responders would be cost-effective for health-care providers, as the expense of genotyping would be more than offset by savings from reducing ineffective prescription.[23] In some cases this might lead to an overall reduction in healthcare costs. However, the use of PGx by purchasers to reduce the overuse of ineffective drugs in groups of non-responders clearly conflicts with the interests of the pharmaceutical industry, as it is predicated on reduced drug sales[24].

11) Use of efficacy data in drug marketing and extending patent life

Pharmacogenetic information could allow doctors to make a more informed choice about the use of one medicine compared to another in the same drug class. This might also provide some pharmaceutical companies with a powerful marketing tool if they could demonstrate that their medicine was more effective in a particular patient group than a rival product. Such a prospect would be particularly attractive to companies whose products were lower ranked by sales volume.

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[21] Robertson, J.A., Brody, B., Buchannan A., Kahn, J. and McPherson, E. (2002), Pharmacogenetic challenges for the health system, *Health Affairs*, 21(4):155-167.

[22] Issa, A.M. (2002), Ethical perspectives on pharmacogenomic profiling in the drug development process. *Nature Reviews Drug Discovery,* 1:300–308.

[23] Lichter, J.B. and Kurth, J.H. (1997), The impact of pharmacogenetics on the future of healthcare. *Current Opinions in Biotechnology,* 8: 692-695.

[24] Robertson, J. A., Brody, B., Buchannan A., Kahn J. and McPherson E. (2002), Pharmacogenetic challenges for the health care system, *Health Affairs* 21**:**155–167.

VI. Stratification of diseases and infectious agents into sub-types

12) Stratification of diseases and infectious agents into sub-types

As mentioned above, pharmacogenetic testing can be used to stratify diseases into sub-types according to how they respond to particular drugs. For example, some types of breast cancer respond more positively to certain forms of chemotherapy than others. Knowing this information helps in the clinical management of the disease.

1.4 Structure of the report

This report is divided into an introduction, four main data chapters and a conclusion. Chapter 1 sets out a definition of pharmacogenetics (PGx) and describes the main ways (options) in which it is currently being developed. Chapter 2 presents a detailed survey of the commercial development of PGx in Europe and North America, describing the activities of both small biotechnology firms and larger pharmaceutical companies in this area. In particular, it focuses on the range of strategies adopted by companies, the development of diagnostic tests and the division of labour between small firms and large companies. Chapter 3 provides a description of the role of regulatory agencies in promoting PGx and the current regulatory framework surrounding the use of PGx data in the drug development, assessment and approval process. It also outlines the key issues relating to drug labelling and the development and use of companion diagnostic tests. Chapter 4 presents a qualitative empirical study of the potential application of PGx in the prescribing of four commonly used licensed medicines. Each case study looks at the drivers and barriers to the adoption of PGx in clinical practice. Chapter 5 gives an analysis of the policy issues surrounding the translation and integration of pharmacogenetics into health services. In particular, it focuses on the UK Genetics White Paper and makes the case for developing a comprehensive framework. In conclusion, Chapter 6 summarises the findings from each of the main chapters and sets out an assessment of how PGx might develop in the short- to medium-term and the different factors shaping the technology. It concludes with a series of recommendations for how public policy can support the development of the technology in a manner that maximises public health gain.

Chapter 2
The Commercial Development of Pharmacogenetics

2.1 The key role of industry

Whilst the public sector plays an important role, pharmacogenetics is very largely an industrially driven technology due to the high cost of genotyping equipment and the large-scale research needed to conduct association studies and stratified clinical trials. The commitment of biotechnology and pharmaceutical firms, their strategies and investment decisions, will therefore be critical in shaping which options for the technology outlined above are most likely to be developed. This chapter presents a detailed survey of the companies working on PGx, the structure of the industry, the main commercial strategies, the level of interest they have in different options for the technology, and the products and services they are developing.

There are two broad groups of companies involved in the commercial development of pharmacogenetics.[25] Firstly, approximately 50 small biotechnology and genomics firms are involved in conducting PGx association studies, developing specific genetic tests, and selling a range of specialist services to the pharmaceutical industry. In addition, some 32 large pharmaceutical companies are working on pharmacogenetics, either internally or in collaboration with smaller specialist firms. Whilst data on the work of small and medium sized enterprises (SMEs) is relatively easy to obtain, information on the activities of large companies is much more difficult to access due to issues of commercial confidentiality. As a consequence, this chapter will initially present data on small firms working on PGx, including their products and collaborations with large companies. In later sections of the chapter these data will be analysed to infer some conclusions about the development of PGx within large companies.

2.2 Development of PGx by SMEs

In common with most biotechnology and genomics firms, the SMEs working on pharmacogenetics are generally small, young and research intensive. As described in Table 2.1, the smaller specialist firms have been broken down into a 'core universe' of 43 companies with a significant interest in developing the technology, and a further 18 with a minor interest in this area (See methodology section Appendix 2 for details of this distinction). The main firms are split roughly 60/40 between North America (27 firms) and Europe (16 firms), with five UK firms and three German firms.

Of the core group, 17 are focused solely on developing PGx diagnostic tests, eight are both developing diagnostics and supporting drug development, either internally or through partnerships with other companies, nine are involved in providing PGx related support services and another eight are producing specialist tools, kits and software. Firms that have PGx as their sole or main focus are highlighted in bold in the Table 2.1. As can be seen, only a relatively small proportion of the core universe (17 or ~ 40% of the 43 firms) can be described as dedicated pharmacogenetics companies.

[25] It should be noted that, in addition to these two main groups, a number of specialist diagnostic companies (e.g. Beckton Dickinson) and US healthcare providers (e.g. Kaiser Permanente) are also investing in the technology through the formation of collaborations with smaller firms (see below).

Table 2.1 Genomics and biotechnology companies working on PGx

North American firms		European / other firms	
PGx drug development & diagnostics (5)		***(3)***	
Curagen	US	Astex Technology	UK
Egeen	US	deCODE/Encode	Iceland
Clinical Data (including former Genaissance)	US	**Epidauros AG**	Germany
Millennium	US		
Myriad Genetics	US		
Diagnostics only (11)		***(7)***	
Celera Diagnostics	US	Axis-Shield	UK/Norway
DNAPrint Genomics	US	DAKO	Denmark
Genelex	US	**Epigenomics AG**	Germany
Genomas	US	Ipsogen	France
Genomic Health	US	Jurilab	Finland
Gentris	US	LGC	UK
Interleukin Genetics	US	Vita Genomics	Taiwan
Monogram Biosciences (ViroLogic)	US		
Prediction Sciences	US		
Prometheus Laboratories	US		
Third Wave Technologies	US		
PGx service firms (inc samples) (5)		***(4)***	
Gene Logic	US	**The Brain Resource Company**	Austria
Genizon Biosciences (Galileo Genomics)	US	**CXR Biosciences**	UK
Perlegen Sciences[1]	US	**DxS**[2]	UK
SeraCare Life Sciences (Genomics Collaborative)	US	**Medigenomix**	Germany
Seryx	US		
PGx tools, kits and software (6)		***(2)***	
Affymetrix	US	Biotage	Sweden
Golden Helix	US	GE Healthcare	UK
Nanogen	US		
Sequenom	US		
Tm Biosciences[3]	Can		
Waban Software	US		
Firms with a minor interest in PGx (10)		***(8)***	
Amgen	US	AdnaGen	Germany
ARCA Discovery	US	Exon Hit	France
Cardinal Health	US	GeneScan Europe (cyp chip)	Germany
Ellipsis	Can	IQur (viral genotyping)	UK
GeneOhm Sciences	US	IntegraGen	France
InSite Vision	US	Memorec Biotec	Ger
NeoPharm	US	PharmaMar	Spain
Panacea Pharmaceuticals	US	Solvo Biotechnology	Hungary
PolyGenyx	US		
TriPath Imaging	US		

Note: firms marked in bold have PGx as their sole or main focus

[1] Perlegen are currently a service firm, but have a long-term commitment to drug development.

[2] DxS have recently announced their intention to develop PGx diagnostics.

[3] Tm Biosciences is primarily a service firm, but is also developing diagnostic products.

This illustrates the fact that PGx is often only one of a number of commercial activities being undertaken by these companies. For example, in the group of firms working on both diagnostics and drug development, several companies are relatively large and well-established biotechnology and genomics firms involved in drug discovery and development (e.g. Curagen, Millennium, deCODE). The same is true of firms working only on diagnostics, with several larger diagnostic companies involved in nucleic acid testing investing in PGx (Celera Diagnostics, Axis-Shield, DAKO, LGC). In contrast, the bulk of the firms providing PGx services, such as genotyping, DNA banking etc., are focused exclusively on this area.

Of the 17 dedicated PGx firms all were formed between 1997-2004, three are public companies (Clinical Data; DNAPrint Genomics; The Brain Resource Company) and most are small, with only two (Clinical Data and Epigenomics) having more than 100 staff.

It is interesting to compare these data with an earlier survey and industry mapping exercise conducted as part of this project in 2002. One of the most striking features is the high attrition rate, with 22 firms (i.e. ~50% of total) who had been in the core PGx universe in 2002 no longer being active in the field. Of these, one (DNA Sciences) was acquired by another firm listed in the core universe and one (Visible Genetics) by a large pharmaceutical company, nine had ceased trading altogether, and seven had disinvested from the technology, with no evidence of work on PGx in any of their public documents. A further four were acquired by other biotechnology firms and none of which had current R&D programmes on PGx listed in their public documents

Furthermore, a further three firms still in the core universe (Curagen, Millennium, and ExonHit) have significantly reduced their investment in the technology, as demonstrated by the information contained in their public documents, including SEC filings. However, during the same period another 19 firms have entered the core universe, leaving the total size of this industrial sector working on PGx only slightly reduced.

In conclusion, the relatively small overall number of firms in the core universe, the lack of a large group of dedicated PGx companies, the high attrition rate and signs of disinvestments from incumbents all highlight the lack of a well-developed market for PGx and the problem of establishing a commercially viable business model for the technology. Despite this, the field continues to attract commercial interest, as demonstrated by the significant number of new firms that have been created to work on PGx in the last four years.

2.3 The emerging market for PGx - technical options being developed

The different technological options for PGx described in Chapter 1 are elaborated in more detail with respect to their industrial development in Table 2.2. Each option is described in terms of the commercial aims behind its development, as well as the types of services and products that are being designed and developed to achieve this aim.

A detailed description of the main technological options that each firm in the core universe is working on was undertaken. This provides data to establish which technological options currently have the most commercial interest. Although it is a crude index, the number of firms working on a given option provides a useful indicator

of its prospects of being successfully developed in the near term, as options with little investment stand a poor chance of being introduced into practice. These data have been summarised in Table 2.3 and a number of key points can be drawn from it:

a. Commercial interest in pharmacogenetics is spread across the whole process of drug discovery and development, with 10 of the 12 options being developed by more than two firms. Furthermore, many firms are working on multiple options. However, the great majority of interest is shown in just seven of these options, with little commercial investment in drug rescue for either safety or efficacy, market extension strategies, post-marketing surveillance or the use of efficacy data in drug marketing;

b. There are two broad markets, with an additional smaller one, that can be identified as having the greatest numbers of firms working on them (highlighted in bold). Firstly, most investment is being made in services and products supporting pre-clinical and clinical drug development. This is followed by the development of diagnostic tests to aid prescribing (mainly of already licensed drugs) and to enable disease stratification. A smaller number of firms are also providing services to support drug discovery;

c. Firms supporting the application of PGx to clinical drug development are focused on both safety and efficacy. They are offering a range of services (including ADME testing, toxicity screening, genotyping and association studies) and products (genetic tests for ADRs, ADME/CYP assays and chips, database of ADRs, and software tools). These are very largely being sold to large integrated pharmaceutical firms;

d. Firms developing technologies to support pre-prescription genotyping are almost entirely focused on developing diagnostic tests as distinct products, rather than selling services. It is therefore unsurprising that almost all of these firms are dedicated diagnostic companies, with only a few firms also working on drug development (Clinical Data, Egeen, deCODE). Most interest is being shown in developing tests for efficacy (16 firms), with slightly less support for safety testing (11 firms) and disease stratification (10 firms). These products are described in greater detail in the next section;

e. The smaller group of firms supporting drug discovery mainly provide support services to large pharmaceutical companies with the emphasis on ADME, CYP and toxicity analysis and testing;

f. Table 2.3 also shows that there are two firms in the core universe that are looking to develop their own new drugs internally explicitly using pharmacogenetic knowledge (Millennium, Perlegen). However, Perlegen efforts are still at a very early stage of development.

Table 2.2 The main technological options for PGx being developed by industry

	Aims	Services	Products
Drug discovery (I)			
1. Discovering new drugs which work well in entire population	Screen leads to see if metabolised by ADME genes. Use to eliminate drug candidates that are poorly metabolised in particular genotypes e.g. CYP variants. Eliminate leads that are differentially metabolised.	1. Genotype-based toxicity studies 2. Association studies to identify ADME gene polymorphisms	1. Assays of ADME gene variants 2. Libraries of screened leads that are not metabolised in particular genotypes
2. Discovering new drugs aimed at genomic sub-populations	Identify drug candidates that respond well in particular genotypes. In cases where diseases can be stratified and sub-typed, drugs can be discovered which target the genetic variants responsible for the most common forms of the disease e.g. drugs for HER positive breast cancer.	1. Association studies of drug response	1. Genotyped assays that model particular disease sub-types 2. Libraries of screened leads that target particular genotypes
Safety of drugs in development (II)			
3. Pre-clinical testing and early stage trial design/ monitoring	Use of panels of ADME gene variant assays (e.g. liver cells) to identify drugs that are poorly metabolised and are toxic in particular genotypes. Screen out drugs with high levels of toxicity. Also use genotyping to ensure a representative patient population (e.g. correct distribution of CYP variants) so that rare genetically based ADRs can be detected.	1. Pre-clinical studies of drug metabolism and toxicity 2. Genotyping of clinical trial population 3. Support services for clinical genotyping (e.g. sample banking)	1. Panels of ADME gene variant assays 2. Diagnostics and chips for clinical genotyping
4. 'Rescue' of products in late stage trials (ADRs)	Retrial drug in population selected by genotype.	1. Clinical association studies. 2. Support services for clinical association studies (genotyping, sample banking)	1. 'Rescued' drugs
Efficacy of drugs in development (III)			
5. Later stage trial design and monitoring to target 'good responders'	Association studies in clinical trials to identify genomic sub-populations who are 'good responders'. Stratification of disease and identification of subtypes. Develop drug for particular sub-populations of good responders e.g. Herceptin.	1. Clinical association studies. 2. Support services for clinical association studies (genotyping, sample banking)	1. New drug targeted at genomic sun-population 2. Diagnostics and chips for clinical genotyping
6. Drug rescue (efficacy)	Retrial drug in population selected by genotype.	1. Clinical association studies. 2. Support services for clinical association studies (genotyping, sample banking)	1. 'Rescued' drugs

Safety of licensed drugs (IV)			
7. Market (label) extension of products restricted by ADRs	Improve safety of prescribing by identifying sub-populations at risk of serious ADRs from polymorphisms in ADME genes (e.g. CYP). Expand indications through association studies to define sub-population at risk of genetic ADR (e.g. Abacavir).	1. Clinical genotyping services (e.g. TMPT) 2. Association studies of safety. 3. Support services for clinical association studies (outsourcing of studies, genotyping, sample banking)	1. Assays and chips for CYP testing 2. Diagnostic tests to identify sub-populations most at risk of ADRs
8. Pre-prescription screening to identify patients at risk of ADRs	Identify patients most at risk of genetic-based ADRs for particular drugs/ classes of drugs. Avoid giving drug to these subgroups.	1. Clinical genotyping services 2. Association studies of safety 3. Support services for clinical association studies (outsourcing of studies, genotyping, sample banking)	1. Diagnostic tests to identify sub-populations most at risk of ADRs
9. Post-marketing surveillance	Analyse genetic basis of rare ADRs	1. Association studies of safety 2. Support services for clinical association studies (outsourcing of studies, genotyping, sample banking)	1. Diagnostic tests to identify sub-populations most at risk of ADRs
Efficacy of licensed drugs (V)			
10. Pre-prescription screening to identify 'good responders'	Identify good responders for particular drugs/ classes of drugs. Target therapy at sub-group most likely to benefit. Stratification of disease and identification of genotype subtypes.	1. Clinical genotyping services 2. Association studies of efficacy 3. Support services for clinical association studies (outsourcing of studies, genotyping, sample banking)	1. Diagnostic tests to identify sub-populations who will benefit most from particular drugs
11. Use of efficacy data in drug marketing and in extending patent life	Identify good responders for particular drugs/ classes of drugs. Target marketing of therapy at sub-group most likely to benefit. Stratification of disease and identification of genotype subtypes.	1. Clinical genotyping services 2. Association studies of efficacy 3. Support services for clinical association studies (outsourcing of studies, genotyping, sample banking)	1. Diagnostic tests to identify sub-populations who will benefit most from particular drugs
Stratification of diseases and infectious agents into sub-types (VI)			
12. Stratification of diseases and infectious agents into sub-types	Stratification of diseases and infectious agents into genomic subtypes according to drug response (e.g. HIV drug resistance). Use to guide drug prescribing.	1. Clinical genotyping services 2. Association studies of efficacy 3. Support services for clinical association studies (outsourcing of studies, genotyping, sample banking)	1. Diagnostic tests to identify sub-populations who will benefit from a particular drugs

Table 2.3 Industrial interest in the main technological options for pharmacogenetics

Drug discovery		Internal	Services	Product
1. Discovering new drugs which work well in entire population	**7**	Millennium	**Gene Logic, Astex, Brain Resource, CXR (CYP), DxS (ADME)**	Epidauros, CXR (CYP)
2. Discovering new drugs aimed at genomic sub-populations	**8**	Millennium, Perlegen	**Curagen, Gene Logic, Genizon, Genomics Collaborative, Sequenom, Brain Resource**	
Safety of drugs in development				
3. Pre-clinical testing and early stage trial design/ monitoring	**22**		**Clinical Data, Curagen, Gentris (ADME), Prediction Sciences, Gene Logic, Genizon, Genomics Collaborative, Sequenom, Epidauros, Brain Resource, CXR, DxS, Medigenomix**	**Clinical Data, Gentris (CYP), Affymetrix (Chip), Golden Helix (sw), Nanogen (Chip) Tm Biosciences (CYP), Waban, Epidauros, Jurilab (ADME chip), LGC (ADME), CXR (CYP), GE Healthcare (CYP chip), Biotage (CYP chip)**
4. 'Rescue' of products in late stage trials (ADRs)	5		Gene Logic, Perlegen, Astex, Epidauros, CXR	Epidauros
Efficacy of drugs in development				
5. Later stage trial design and monitoring to target 'good responders'	**21**	Millennium	**Clinical Data, Egeen, Genomic Health, Gentris, Prediction Sciences, Gene Logic, Genizon, Perlegen, Sequenom, deCODE, Epidauros, Ipsogen, Brain Resource, DxS, Medigenomix**	**Genaissance (2), Affymetrix (Chip), Golden Helix (sw), Nanogen (Chip), Waban (sw), Axis-Shield, Vita Genomics**
6. Drug rescue (efficacy)	4		Gene Logic, Perlegen, Epidauros	Affymetrix (Chip), Epidauros

Safety of licensed drugs				
7. Market (label) extension of products restricted by ADRs	1		Perlegan	
8. Pre-prescription screening to identify patients at risk of ADRs	**11**		Genelex (CYP), Perlegen, Seryx	**Clinical Data, DNAPrint, Genomas, Gentris (CYP), Prediction Sciences, Prometheus (TPMT), Third Wave (UGT assay), Tm Biosciences (CYP)**
9. Post-marketing surveillance	1		Perlegen	
Efficacy of licensed drugs				
10. Pre-prescription screening to identify 'good responders'	**16**		Seryx	**Clinical Data, Egeen, Celera, DNAPrint, Genomas, Gentris, Interleukin, Prediction Sciences, deCODE, Axis-Shield, Epigenomics, Jurilab, LGC, Vita Genomics, DxS**
11. Use of efficacy data in drug marketing and in extending patent life	3			Clinical Data, Egeen (patent), Axis-Shield (patent)
Stratification of diseases and infectious agents into subtypes				
12. Stratification of diseases and infectious agents into subtypes	**10**	Millennium	Perlegen, Epigenomics, Vita Genomics	**Myriad, Celera, Genomic Health, Third Wave (HCV), DAKO, Epigenomics, Ipsogen (Chips), Vita Genomics**

Diagram 2.1 Different points of intervention in the innovation process

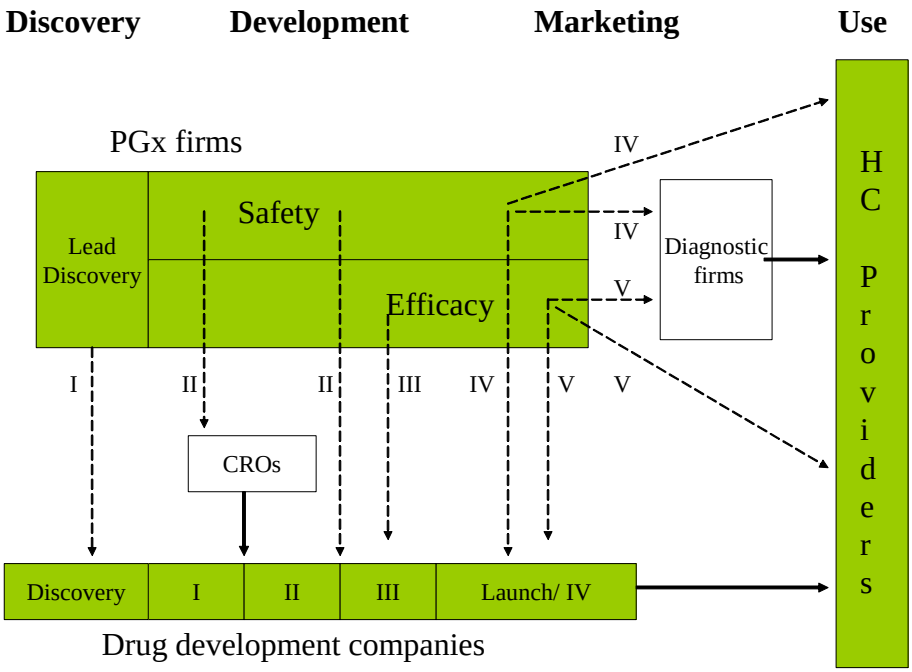


Diagram 2.1 schematically illustrates the different points at which the various options for PGx technology can intervene in the innovation process, as well as the division of labour between the three main types of company. In particular, it highlights that PGx can be used across the entire process of discovering, developing, marketing and using medicines.

2.4 The development of diagnostic products

Detailed analysis was undertaken of the diagnostic products being developed by the firms in the PGx universe and included all diagnostic products that are currently being offered for some kind of research or clinical use, and all new tests that are in development. It should be noted that it is difficult to make a clear distinction between general services offered, discrete tests, and stand-alone products. The data therefore include some tests that may only be available in a particular company's laboratory. In total, some 49 tests are either in use or under development. Of these 60% (30), are already available for some kind on experimental or clinical application. However, many of the products listed as being in use, especially those for cancer and 'other diseases', are only available for research purposes and have not received formal regulatory approval. Furthermore, the extent to which they are used in practice is very difficult to assess, as some tests that are available have been developed purely as 'proof of concept' diagnostics and are not likely to be marketed as commercial products. These data are summarised in Table 2.4 overleaf.

Table 2.4 Commercial PGx tests available for use or in development

	In use			In development			All
Type of test	**US tests**	**EU/ other tests**	**Total**	**US tests**	**EU/ other tests**	**Total**	**Total**
Drug metabolism	7	8	15	1	1	2	17
Anti-viral drug resistance	4	1	5	2	1	3	8
Cancer (disease stratification)	3	3	6	3	3	6	12
Other conditions	3	1	4	5	3	8	12
TOTAL	17	13	30	11	8	19	49

Note: This summary includes the two products produced by large pharmaceutical companies (Bayer's HIV genotyping test acquired via Visible Genetics and Roche's Amplichip).

The tests described in Table 2.4 can be broken down under four broad headings:

2.4.1 PGx tests for drug metabolism

The largest group of established tests are for drug metabolising enzymes (DMEs - mainly Cytochrome P450 alleles), which are being sold in the two main markets described above: studies of drug metabolism during pre-clinical and clinical drug development, and pre-prescription patient testing (for already licensed drugs). They are offered in a number of different forms, including in house laboratory testing, assays and kits for use in third party laboratories, DNA microarrays (chips) for use in point-of-care diagnostics, and even direct-to-consumer testing services (Genelex). The growing number of chip-based diagnostics is a significant development, as this technology offers the possibility of lower-cost/higher throughput analysis in the longer term. There is only one commercial provider of DNA-based TPMT testing, largely as a result of the patent on it.

In addition to these tests offered by firms in the core PGx universe, it should be noted that in 2003 Roche launched its Amplichip as a technology platform for PGx and related testing (see below). The first application is CYP testing for the 2D6 and 2C19 alleles.[26] The CYP2D6 gene is believed to be involved in metabolising 25% of all currently prescribed medicines including beta-blockers (for heart disease) and anti-depressant/anti-psychotics.[27] Understanding drug metabolism is important because slower than normal metabolism can cause a drug to remain in the body for longer than it otherwise would and concentrations may build up to harmful levels. Alternatively, a very fast metaboliser would eliminate the same drug from their system before it could have a full therapeutic effect and so they would not gain much benefit from the treatment. Knowledge of a patient's CYP status could therefore be a

[26] Roche's AmpliChip was launched in 2003 and approved for clinical use in September 2004 in the EU and December 2004 in the US. The AmpliChip distinguishes 20 known polymorphisms in the 2D6 gene and 2 major polymorphisims in the 2C19 gene. See http://www.roche-diagnostics.com/media/pdf/presskit/final_technology_behind_cyp450.pdf]

[27] Nuffield Council on Bioethics (2003), Pharmacogenetics: ethical issues. Available at, http://www.nuffieldbioethics.org/go/ourwork/pharmacogenetics/introduction/

useful prescribing aid and might help doctors to choose the right dose of a medication to give to particular individuals (see Chapter 4).

In terms of tests for DMEs there are very few new ones in development. This probably reflects the relatively large number of established providers of these products and services, and the presence/entry of large incumbent diagnostics firms (e.g. GE Healthcare, Roche), which have strong marketing capabilities.

2.4.2 Anti-viral drug resistance testing

Another group of relatively well-established PGx tests are for viral genotyping, in order to identify anti-viral drug resistant sub-types as a means of guiding therapy. Assays and testing kits are currently marketed for both HIV and hepatitis C (HCV), and are also in development for hepatitis B. In addition to the tests produced by the firms in the core universe, Bayer also markets a test in HIV drug response tests following its acquisition of Visible Genetics. These tests are currently targeted at the use of already licensed medicines, but are also being used during the development of new drugs by large companies.

Although these tests do not measure any human genetic characteristic, they are used to detect viral strains that are resistant to a particular drug and have the effect of stratifying patient groups according to therapeutic response. However, metabolic profiling tests are limited in their utility as drug response and toxicity are often the result of complex interactions between genes, the environment and behaviour, including poor compliance with treatment regimes.[28]

2.4.3 Cancer PGx testing (disease stratification)

One of the areas that is attracting increasing commercial attention is the possibility of using somatic genetic profiling of tumours as a means of stratifying cancers into subtypes based on their response to new and existing chemotherapies. The tests offered by Genomic Health and Myriad, and in development by DNAPrint Genomics, Epigenomics and Ipsogen are largely aimed at improving the use of established drugs, such as taxol, Tamoxifen, and Carboplatin. In contrast the tests offered by DAKO and Ipsogen, and in development by DxS, are designed to guide the development and use of the new generation of 'targeted' cancer therapies, including Herceptin, Glivec, Iressa and other drugs aimed to the EGFR gene (see below).

The Oncotype test (Genomic Health) and testing for HER-2 status for use with the drug Herceptin, are attached to a particular marketed product. These tests are generally used to stratify patients to identify particular response groups. In the case of the HER-2 test, it identifies a genetic subset of breast cancer patients whose tumours are susceptible to Herceptin. The Oncotype test works slightly differently by genetically stratifying breast cancer patients on the drug tamoxifen, according to their likelihood of a future relapse of the disease. Both tests share the aim of focusing treatment where it is most effective and avoiding unproductive drug use.

In August 2005 the FDA approved Third Wave's Invader UGT1A1 Molecular Assay for *in vitro* diagnostic use. This is the first pharmacogenetic test to be approved by the FDA for use as a companion diagnostic to a specific drug therapy and will be used to identify patients who may be at increased risk of adverse reaction to the chemotherapy drug irinotecan (Camptosar, Pfizer), originally approved in 1999.

[28] Tucker, G. (2004), Pharmacogenetics--expectations and reality, *British Medical Journal,* 329:4-6.

Irinotecan is used to treat colorectal cancer and was relabelled recently to include dosing recommendations based on a patient's genetic profile.

2.4.4 PGx tests for other diseases

A number of other PGx tests are also currently available. These include tests to guide the use of albuterol therapy (asthma), and licensed drugs to treat rheumatoid arthritis (RA) and glaucoma. In addition, Clinical Data have created a test to assess an individual's risk of getting Long-QT syndrome, a rare form of serious ADR. There are also a relatively large number of tests in development for licensed drugs used to treat important common conditions, including response to statins (hyperlipidemia), clozapine (schizophrenia) and SSRIs (depression) (see Table 2.5). However, many of these are still at an early stage of development. Some of these tests are being designed to work with a specific drug – e.g. Clozapine - or with particular classes of drug, such as the statins. These tests aim to detect genetic subgroups within the patient population for the relevant condition. Clozapine, a schizophrenia treatment, also affects a sub-group of patients with a potentially life threatening ADR involving white blood cells (see Chapter 4). In this case a test is being sought to genetically identify individuals at greatest risk. All of these tests being developed for existing drugs are intended as pre-prescription tests to aid clinical decision-making.

2.4.5 Other applications of PGx

It should be stressed that the main focus of commercial activity amongst the firms described in this survey, as opposed to large integrated pharmaceutical companies, is on diagnostic products and services. However, in addition to Millennium (see above) two other firms in the core universe (NeoPharm and Clinical Data) are using PGx studies to assist in the internal development of drug products they have in-licensed. Tests being developed in conjunction with new drugs are being used in a different way, as these tests are intended to assist the development of the new products. Clinical Data's Vilazodone is an anti-depressant of a similar type to Prozac, currently in Phase I/II clinical trials. At this stage it appears to have a suitable safety profile and shows signs of efficacy. According to Clinical Data, initial development of Vilazodone by Merck KGaA and GlaxoSmithKline took the compound into Phase II, with over 1,000 patients between them. Development was discontinued because the response in the Phase II studies was not significantly better than placebo.[29]

However, many drugs in clinical development prove safe, but fail large-scale Phase III clinical trials because they simply do not show a significant level of health improvement in patients. With Vilazodone, Clinical Data are profiling patients before the later stages of clinical testing to identify genetic subgroups that may have a good response profile to the drug. Unlike other examples given in Table 2.5, this search for good responders is occurring before drug approval is sought. NeoPharm are also using pharmacogenetic profiling in the development of their anti-cancer drug LE-SN38. In this instance the profiling is used to find groups with different rates of metabolism of the drug, based on variations in a liver enzyme known to break down LE-SN38. In this way, dosage levels can be set to avoid ADR's during the early safety testing stages of clinical development. Both these tests could help companies to get approval for their

[29] Reed, C., Kalnik, M., Rakin, K., Athanasiou, M. and Judson, R. (2005), Restoring value to stalled Phase II compounds: the case for developing a novel compound for depression using pharmacogenetics, *Pharmacogenomics* 6(2):95-100. Of note is finding that in those studies in which an active comparator was used, the comparator drugs also failed to demonstrate superiority to placebo.

Table 2.5 Examples of pharmacogenetic tests currently in use

Test	Factor Measured	Company	Applications
CYP2D6/ CYP2C9/ CYP2C19/ CYP1A2	Metabolism rates of many common drugs	Genelex	Genelex offers laboratory screening for variation in the genes CYP2D6, CYP2C9, CYP2C19, and CYP1A2. Knowledge of variants in these genes can help physicians predict individual responses to many prescription, OTC (over-the-counter) and herbal medicines, including Warfarin, Prozac, Zoloft, Paxil, Tamoxifen, and Valium. The aim is to prevent adverse drug reactions by classifying patients as having poor, intermediate, extensive and ultra-extensive rates of metabolism for a variety of common drugs.
PRO-PredictRx TMPT Genetics	Rheumatic Disease	Prometheus Laboratories	PRO-PredictRx TMPT Genetics measures the level of TMPT enzyme activity in patients with rheumatic disease to determine patient candidacy and dosage for IMURAN therapy.
Onco*type* DX	Likelihood of breast cancer recurrence in women treated with tamoxifen	Genomic Health	Onco*type* DX is a diagnostic assay that quantifies the likelihood of breast cancer recurrence in women with newly diagnosed, stage 1 or 2, breast cancer who will be treated with tamoxifen. The test involves assessment of a patient's tumour tissue sample for variation in a panel of 21 genes associated with recurrence or non-recurrence in particular subtypes of breast cancer. The aim of the test is to provide enhanced treatment planning by stratifying patients according to likelihood of recurrent disease.
ViroSeq	Viral genotyping	Celera Diagnostics	HIV-1 genotyping in human blood samples to detect drug resistant strains and mutations. Allows patient stratification for appropriate treatment regimen selection.
UGT1A1 Molecular Assay	Chemotherapy	Third Wave	The UGT1A1 assay is the first pharmacogenetic test to be approved by the FDA for use as a companion diagnostic to a specific drug therapy and will be used to identify patients who may be at increased risk of adverse reaction to the chemotherapy drug irinotecan (Camptosar).

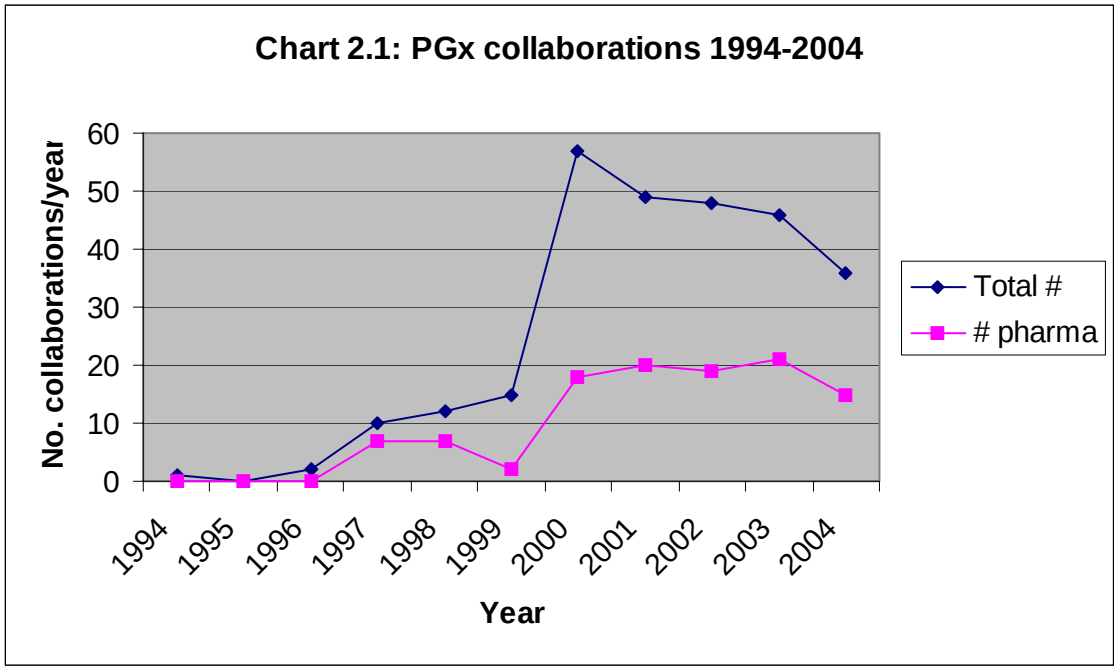
Table 2.6 Examples of commercial PGx tests and drugs currently in development

Test	Disease	Company	Application	Stage of development
Ovanome	Ovarian Cancer	DNAPrint Genomics	Genomic-based diagnostic tool to match ovarian cancer patients with the most suitable form and dose of chemotherapy. Detects SNP alleles that are predictive for non-response to the Taxol and Carboplatin drug chemotherapy combination.	Awaiting clinical testing
Statinome	Various cardiac disease, high cholesterol		PGx test to classify patients as adverse responders or good responders to the statin class of drugs. Statins are used to treat patients who are at increased risk of heart disease.	Awaiting clinical testing
Vilazodone & test	Depression	Clinical Data	Vilazodone is a small molecule compound licensed from Merck KGaA for the treatment of depression. In 2005 the company began pharmacogenomic characterisation of depression patients to find genetic markers that identified a population of patients who will respond to the drug.	Entered phase II clinical trials in 2005 and start of test development
Hypertension R_x	Hypertension	Prediction Sciences	Pre-prescription testing to predict which anti-hypertensive medication therapy (ACE, Ca-Channel or ARB Inhibitor, diuretic, ß-Blocker, combination) would be most effective for lowering the patient's blood pressure upon diagnosis.	Pre-clinical
Neurological R_x	Depression, bipolar disorder and schizophrenia		Pre-prescription testing to predict response for treatments in depression, bipolar disorder and schizophrenia.	Pre-clinical
LE-SN38 Genotyping	Cancer	NeoPharm	NeoPharm have employed the genotyping of patients in the early pre-clinical and clinical development of their anticancer drug LE-SN38. Genotyping splits responders into regular and slow metabolisers and allows for dose safety adjustments.	LE-SN38 in phase 1/2 clinical trials

respective drugs by structuring clinical trials in such a way as to target good responders or avoid poor ones.[30]

2.5 Industrial collaborations in PGx

The biotechnology and genomics industrial sector is heavily networked, with all companies seeking to establish alliances and partnerships with other firms in order to develop their products and generate income. The pattern and growth of alliances is therefore an important indicator of industrial interest in the technology, as each collaboration represents a market transaction. Some 273 collaborations were established in the field of PGx between 1994-2004. The growth in the total number of these alliances is shown in Chart 2.1, as is the number of collaborations involving large pharmaceutical companies. The year 2000 marked the rapid expansion of the field, but this activity has declined in subsequent years. This pattern indicates that some of the momentum behind the technology might have been lost in the last four years, not least because of the difficulty of translating new knowledge into clinically useful tests.



Of the 273 alliances, some 92 (~33% of total) are involved the development of diagnostic products. Chart 2.2 shows the growth of collaborations in this area, which followed a similar pattern to the general trend identified above. However, of these 92 collaborations, only 23 involved large pharmaceutical companies and of these 15 (5% of total) were focused wholly or in part on tests for already licensed drugs. The pharmaceutical companies having the most collaboration in the diagnostics area were Abbott (2), Bristol-Myers Squibb (3), Boehringer Ingelheim (2), GSK (2), Bayer (3), and Roche (2)[31], although it should be noted that a significant number of these alliances are no longer active.

[30] Lichter, J.B. and Kurth, J.H. (1997), The impact of pharmacogenetics on the future of healthcare. *Current Opinions in Biotechnology,* 8:692-695.

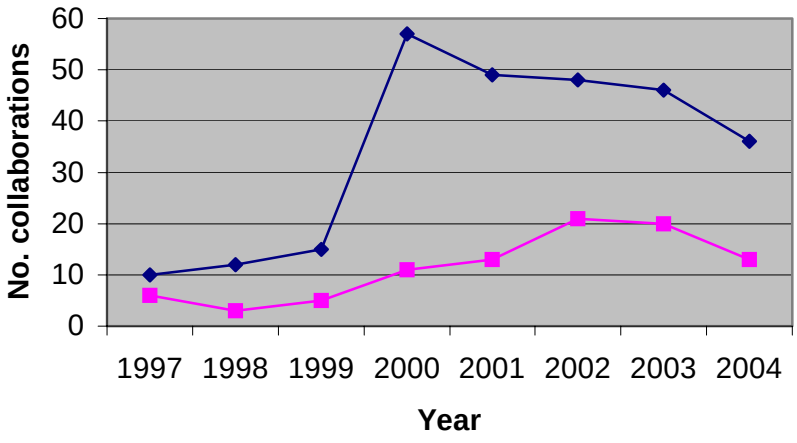
[31] Roche has a separate molecular diagnostics division, which is included here as a diagnostics company.

Similarly, just 13 collaborations were with large diagnostic firms, with 10 of these (~3.5% of total) focused on already licensed products. Of the latter group, three companies (Roche Diagnostics, Quest, and Becton Dickinson) accounted for nine of these collaborations. There were also four collaborations with US HMOs working on the development of diagnostic tests for licensed medicines.

The data indicate that whilst a significant percentage of industrial investment has been in the development of diagnostic products, relatively little of this has come from the large companies that have the resources to successfully develop and market new tests. It also appears that large pharmaceutical companies are making little investment in applications of PGx aimed at already licensed medicines, reflecting the lack of a strong commercial incentive to introduce genetic screening where it might reduce drug sales. Taken together, dedicated PGx firms, specialist diagnostic firms and healthcare providers (such as HMOs in the US context) have made greater investment in pre-prescription genotyping of established products, as this offers the prospects of new diagnostic markets and reduced healthcare costs. However, the larger diagnostic companies are making relatively limited investment in this area, with smaller firms playing the lead role.

While this might point to a clear division of labour, with the smaller firms leading the development of PGx diagnostics, the situation is more complicated in relation to the development of new products, as larger firms will inevitably be involved. New drugs approved after going through stratified clinical trials based on PGx-test results will often require a dedicated drug-test combination in order to be approved. In such cases, it is in the interests of pharma companies to undertake drug-test development, either themselves or through collaboration with specialist companies. However, at the present time, very few of these combinations have reached the market (see next section).

Chart 2.2
Diagnostics collaborations



Source: www.recap.com; www.newsanalyzer.com; and company documents.

2.6 The development of PGx by large companies

As mentioned above, it is very difficult to measure large companies' level of interest in PGx directly, as few give any details of their internal programmes on their web sites, news releases or public documents. As a consequence it is only possible to draw conclusions from their activity from a limited number of data sources, including the pattern of their industrial collaborations, data from regulatory submissions, the marketing of PGx related products and interviews with company scientists and managers.

Table 2.7 Large firms investing in pharmacogenetics

Firm	Location	Total alliances 97-04
US companies	**(13)**	**(48)**
Pfizer (includes Pharmacia & Parke-Davis)	US	15
Bristol-Myers Squibb	US	8
Biogen	US	4
Abbott Laboratories	US	3
Lilly	US	3
Merck	US	3
Millennium	US	3
Wyeth	US	3
Amgen	US	1
Genzyme	US	1
Johnson &Johnson (Janssen)	US	1
Proctor and Gamble	US	1
Schering Plough	US	1
EU companies	**(13)**	**(54)**
GlaxoSmithKline	UK	16
AstraZeneca	UK/Sweden	8
Bayer	Germany	7
Roche (inc. Roche Diagnostics)	Switzerland	7
Sanofi-Aventis (inc. RPR)	France/ Germany	7
Boehringer Ingelheim	Germany	2
Novartis	Switzerland	2
bioMerieux–Pierre Fabre	France	1
Ferring	Switzerland	1
Novo Nordisk	Denmark	1
Merck KGaA	Germany	1
Schering AG	Germany	1
Serono	Switzerland	1
Japanese companies	**(6)**	**(7)**
Ono Pharmaceuticals	Japan	2
Fujisawa	Japan	1
Sumitomo	Japan	1
Daiichi	Japan	1
Mitsubishi Pharma	Japan	1
Sankyo Pharma	Japan	1

2.6.1. PGx collaborations involving large companies

A summary of large company collaborations in the field of PGx is given in Table 2.7. In total, 32 large companies were involved in 113 (41%) of the 273 PGx collaborations. These were split between the development of internal capabilities through the acquisition of equipment and services (27), the application of PGx to drug discovery and development (63), and the development of diagnostics (23). These data suggestthat the main firms investing in PGx are: GlaxoSmithKline (16 alliances), Pfizer (15), Bristol-Myers Squibb (8), AstraZeneca (8), Bayer (7), Roche (7) and Sanofi-Aventis (7). It is notable that there are the same number of US and European pharmaceutical companies investing in PGx, with a similar overall number of collaborations. A detailed analysis of PGx collaborations reveals that the majority of large pharmaceutical companies are mainly investing in options aimed at improving internal processes, reducing costs and enhancing the efficiency of drug discovery and development, and have relatively little commercial interest in applications of PGx aimed at already licensed medicines except where markets can be expanded by extending product licences (e.g. Abacavir – see below).

2.6.2. Clinical development involving PGx

Data from regulatory submissions provide a crude estimate of the number of new drugs that are being developed using pharmacogenetic data (see Chapter 3 for details). In summary, it appears that a large number of early stage (Phase I) clinical trials are now collecting PGx data, mainly on drug metabolism. However, it is likely that the number of late stage (Phase III) trials with a significant PGx dimension is probably less than 10. The evidence available in the public domain therefore suggests that PGx is now an important part of the early stage drug development process in the majority of leading pharmaceutical companies. Given the length of time taken to move products from these early stages through to marketing approval (typically as much as 10 years), it is not surprising that there are relatively few PGx-related products close to getting regulatory approval.

2.6.3. Products on the market

There are three broad classes of PGx-related products that have been marketed by large companies as of May 2006: 1) Targeted cancer therapies that use a test to stratify patient populations, 2) Tests to extend the label of drugs with limited markets or to ‘rescue’ withdrawn products, and 3) technology platforms for genetic testing.

A. Pharmacogenomic disease stratification and the development of new cancer therapies

Whilst not strictly part of classical pharmacogenetics, an important application of pharmacogenomic gene expression profiling has been to help understand the precise molecular mechanisms involved in causing particular diseases, most notably cancer. For example, during the development of cancer a number of complex genetic changes occur to the cells in the tumour. These include mutations in the DNA caused by environmental factors (such as pollution and smoking), as well as more complex chromosomal rearrangements. They are referred to as ‘somatic mutations’ and are distinguished from inherited genetic defects, as they cannot be passed on to the next generation. Such genetic changes lead to altered patterns of gene expression, which can be detected by pharmacogenomic studies and this information has been successfully used to develop a new group of targeted (or so called ‘designer’) cancer therapies.

Case study: Imatinib mesylate (Glivec/Gleevec in US)

Imatinib mesylate, sold as Gleevec in the United States and as Glivec elsewhere is produced by Novartis. It is available in oral capsule form as a treatment for Chronic Myeloid Leukaemia (CML), which accounts for some 15-20% of leukaemia cases. 95% of all CML patients have a chromosomal abnormality known as the 'Philadelphia chromosome', which produces a mutant and overactive protein. This abnormal protein is responsible for triggering the excessive cell proliferation characteristic of cancer. It is as a result of this genetic abnormality that the resulting overactive protein causes excessive cell proliferation and destabilisation. With CML the affected cells are clonal hematopoietic stem cells and the white blood cells they produce. Glivec acts by blocking and inhibiting the activity of the mutant protein (known as bcr-abl) thus negating its effects. It acts as a highly specific enzyme inhibitor.

Glivec has had considerable clinical success in treating CML, with the vast majority of patients who are treated in the initial chronic phase of the disease achieving a complete remission This compares to lower remission rates and high side effects following alpha interferon treatment, and poor long-term prospects with chemotherapy alone. Aside from Glivec, the only cure for CML is a bone marrow transplant, which relies on a suitable donor being found and on the patient being in a robust enough condition to survive surgery. Due to the fact that a known chromosomal abnormality is directly involved in causing the disease, CML can be diagnosed, even before symptoms appear, through routine blood testing and a DNA test that can reveal the presence of the Ph chromosome. This allows more patients to be identified while still in the early stages of the condition. Early detection is important because late stage leukaemias often develop resistance to Glivec and other drugs, and prove incurable.

Glivec has also received attention because of the mechanism of its action. As well as being a rationally designed drug, it may also target a disease pathway common to other cancers during their development. It was initially designed to target a different mutant protein of a similar type to bcr-abl – a tyrosine kinase – which was thought to be involved in the development of gastrointestinal tumours. Other tumours, including types of breast, lung, prostate and skin cancer, may use similar pathways, although it is unlikely that a mutant tyrosine kinase is the sole agent responsible for the malignancy in many of these tumours. Even if Glivec does not prove as successful in treating these other forms of the disease, it can be seen as an endorsement of the model of targeting the molecular basis of pathogenesis in cancer and identifying those molecular features which can help target specific therapies at the patients they will help most.

Glivec was approved for use in the US in May 2001 for CML therapy for all stages of the disease, once interferon alpha treatment has failed. By November 2001, US approval had been followed by Switzerland, Australia and the EU. Glivec was one of the first molecularly targeted anti-cancer drugs. In 2004 Novartis recorded worldwide sales of Gleevec/Glivec of $1.6 billion, making it the company's second best-selling pharmaceutical product.

Examples of these therapies are the drugs, trastuzumab (Herceptin, Roche/Genentech) and imatinib (Glivec, Novartis - Gleevec in the US), which require pre-prescription testing to identify patients with specific somatic mutations and are designed to specifically target the molecular mechanisms involved in causing particular cancers. Details of these products are shown in the two case study boxes. Whilst Herceptin, Glivec and a related product, cetuximab (Erbitux, Merck

KGaA/ImClone/BMS) have enjoyed some measure of success, other targeted cancer therapies (e.g. Avastatin) have proved less viable.

Case study: Trastuzumab (Herceptin)

Trastuzumab is a monoclonal antibody developed by the US biotechnology company Genentech and marketed as Herceptin by Genentech in North America and Roche elsewhere. Herceptin is a humanised (human-mouse) monoclonal antibody produced using recombinant DNA technology. The drug was granted regulatory approval by the US FDA in September 1998 and by the European Commission in 2000. Reported worldwide Herceptin sales were $1200M in 2004.

Herceptin bonds with high specificity to a human protein called HER2, which is known to be over-expressed in 25-30% of human metastatic breast cancers. This over-expression causes the affected cells to be overly sensitive to the effects of growth factors, and to grow and proliferate at an elevated rate, contributing to the development of a cancerous state. Herceptin is thought to block the activity of the HER2 protein thus negating the effects of its over-expression. Herceptin binding can also target abnormal cells for destruction by the body's own immune system.

The HER2 test (HercepTest, DAKO) is an immunohistochemical (IHC) that identifies the subset of breast cancer patients who have amplified HER2 genes and are receptive to treatment with Herceptin.[32] The FDA subsequently approved the more sophisticated FISH (fluorescence in situ hybridization) test (Vysis PathVysion, Abbott), based on proprietary DNA technology, which measures the HER-2 protein expression at the genetic level, and as a consequence is more accurate. Due to its cost, however, current clinical practice is to use the latter test to eliminate possible false positives thrown up by the standard IHC test.[33]

Herceptin is approved for use as a treatment for women with metastatic breast cancers, which affect some 10% of women diagnosed with the disease. Herceptin is indicated for use on its own in women who have already had chemotherapy treatment, and for use in combination with paclitaxel (an anti-cancer drug produced by Bristol Myers Squibb) in women who have not had a previous course of treatment. Herceptin can reduce the size of the tumour in a patient, usually over the course of a 24-week treatment regime, but it is not a cure for metastatic breast cancer. Herceptin can significantly extend the lifespan of women suffering this type of cancer, but ultimately survival is unlikely to be increased for longer than one year.

In May 2005 at the 41st Annual meeting of the American Society of Clinical Oncology clinical data were presented suggesting that Herceptin might be effective in the treatment of early stage (HER2-positive) breast cancer[34] and in May 2006 it was approved by the EMEA for this indication.[35]

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[32] http://www.gene.com/gene/products/information/oncology/herceptin (accessed 11 October 2002).

[33] http://www.pathvysion.com/BreastCancerTests_221.asp (accessed 18 December 2002). NCCN Practice Guidelines in Oncology, v.2.2005: Breast Cancer. National Comprehensive Cancer Network. Available at: http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf (accessed 10/07/06).

[34] Editorial, (2005). Herceptin and early breast cancer: a moment for caution L*ancet*, 366: (p1673; Genentech Press Release, (2005), Pivotal Herceptin data in the New England Journal of Medicine showed significant improvement in disease-free survival in early-stage HER2-positive breast cancer, available athttp://www.gene.com/gene/news/press-releases/display.do?method=detail&id=8987> (accessed 09/01/2006).

[35] http://www.emea.eu.int/humandocs/Humans/EPAR/herceptin/herceptinM2.htm; NICE draft guidance on NHS use, June 2006. http://www.nice.org.uk/page.aspx?o=328789

In 2003 another product, gefitinib (Iressa, AstraZeneca) was initially fast tracked for approval as a drug of final resort for lung cancer patients for whom all other therapies had failed. However, in December 2004 AstraZeneca reported to the FDA that, following a post-marketing clinical trial, Iressa had failed to show any survival advantage compared to a placebo.[36] The product was removed from the market, but in a striking example of the benefits of targeted treatment based on genetic variation, it has since been discovered that Iressa exhibits efficacy in about 10% of patients with a particular somatic mutation in the EGFR gene. The company is now reportedly proceeding to develop the drug for this genetically defined sub-population.[37]

B. Genetic tests to rescue or extend the label of existing products

One of the most widely discussed examples of pharmacogenetics is the drug Abacavir, an anti-HIV-1 drug manufactured by GlaxoSmithKline (GSK) and marketed as Ziagen (abacavir sulfate), and in combination products, Trizivir, Epzicom and Kivexa. It received approval from the FDA in 1998 and in Europe in 2000. Abacavir belongs to a class of drug known as nucleoside reverse transcriptase inhibitors (NRTI). The HIV-1 virus uses an enzyme, reverse transcriptase, to replicate when it invades a host body cell. Abacavir binds to the active site of the viral reverse transcriptase enzyme and inhibits production of a function viral DNA molecule. This effectively stops the HIV virus from replicating and infecting additional host cells. Worldwide sales of Ziagen were $274 Million in 2003. Approximately 5% of HIV-1 patients experience a hypersensitivity reaction to treatment with Abacavir that, in rare cases, has proved fatal. As a consequence, there is a high medical need to identify patients at risk of fatal toxicity. There are good reasons for assuming there is a genetic component to this susceptibility, which could be identified by pharmacogenetic methods.

A number of studies have been carried out including those by GSK and by researchers in Australia and the UK to investigate associations between prospective gene candidates and the incidence of hypersensitivity reactions. All three groups have identified an association between the HLA-B5701 allele and hypersensitivity to abacavir. However, the sensitivity of HLA-B*5701 varies between 43-78% in white populations and has lower sensitivity in non-white patient populations. The clinical utility of a test depends on avoiding both false positive results (where people would be wrongly identified as being at risk for experiencing a hypersensitivity reaction and perhaps denied access to the drug) and false negatives (where individuals would be assessed as safe and still be at risk of suffering an ADR). Furthermore, as clinical risk management has been effective in limiting serious outcomes, it is important that clinical vigilance is not be reduced in patients who lack the HLA-B*5701 allele as the delayed diagnosis of a hypersensitivity reaction is likely to lead to more severe problems. Some diagnostic labs do offer a genotyping service based on the HLA-B5701 allele, but this is not endorsed by GSK as HLA-B*5701 as screening has not been prospectively validated and because of the concern that use of the marker as a diagnostic may prompt inappropriate re-administration of abacavir to patients with suspected hypersensitivity reactions. It is hoped that an accurate test can be developed for use with the product, so that the drug label can be rewritten enabling it to be given to a greater number of patients without risk of serious side effects.

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[36] FDA Statement on Iressa, December 17, 2004, available at, http://www.fda.gov/bbs/topics/news/2004/new01145.html.

[37] Anon. (2005), Iressa Study Finds Response Markers as Abbott Courts AstraZeneca for Dx Alliance, *Pharmacogenomics Reporter*, 5 May 2005. See also Zamiska, N. and Whalen, J. (2005), Cancer Drug, Deemed Failure, Helps Asians, *Wall Street Journal. 5* May 2005. pB1.

There has also been some limited investment in so-called 'drug rescue', the only real example being the case of alosetron (Lotronex, GSK), a drug for irritable bowel syndrome. Lotronex was approved in the US in early 2000, then quickly withdrawn voluntarily by the manufacturer in late 2000 because of a number of serious adverse drug reactions. It was subsequently approved again in 2002 under 'restricted marketing' terms as a result of doctor/patient demand. Subsequently the manufacturer has conducted research that identifies the relationship between ADRs and individuals' genetic profile as part of the FDA-imposed risk management programme. [38]

C. Technology platforms for genetic testing.

In December 2004 the FDA gave marketing approval to the Roche Amplichip Cytochrome P450 Genotyping Test for use with the Affymetrix GeneChip Microarray Instrumentation System, after obtaining approval in the EU in September 2004, allowing marketing in the US and Europe.[39] The Amplichip CYP450 test analyses a patient's DNA for 29 polymorphisms and mutations of the 2D6 gene, and 2 polymorphisms of the 2C19 gene. These two genes produce enzymes that help metabolize up to 25% of all prescription drugs (see above). The system is primarily aimed at pre-prescription genotyping and can assess whether a patient is a poor, efficient, intermediate or ultrarapid metaboliser. Initially the technology will be restricted for use in reference laboratories, but Roche plans to develop the technology into a fully automated system that can be moved closer to the patient for use in clinical laboratories or even at the point of care.

Roche has a commercial partnership with Affymetrix and is developing the Amplichip as a pharmacogenetics testing platform through the introduction of additional microarray-based diagnostic tools in the areas of HIV-1 resistance genotyping, p53 cancer resequencing, colorectal cancer risk prediction, cystic fibrosis and human papilla virus genotyping.[40]

A number of other companies are looking to develop similar technology platforms. Tm Bioscience received approval for a similar microarray test for cystic fibrosis (Tag-It CFTR40+4 mutation detection kit). They also produce Tag-It P450-2D6, Tag-It P450-2C9 and Tag-It P450-2C19 arrays. Affymetrix recently bought ParAllele giving the company access to the MegAllele DME-T, a drug-metabolism assay with the potential

[38] FDA (2000), Glaxo Wellcome Decide to Withdraw Lotronex from the Market, http://www.fda.gov/bbs/topics/answers/ANS01058.html Office of Public Affairs: Washington (accessed 23/04/05); FDA (2002), FDA Approves restricted marketing of Lotronex'http://www.fda.gov/bbs/topics/NEWS/2002/NEW00814.html, (accessed 23/04/05); Houn, F. (2002), letter from FDA Office of Drug Evaluation II, Centre for Drug Evaluation and Research to GlaxoSmithKline, refNDA-21-107/S-005, http://www.fda.gov/cder/foi/appletter/2002/21107s5ltr.pdf FDA to GlaxoSmithKline, (accessed 23/04/05); Roses, A. D. (2003), Unpublished research presented at DIA Pharmacogenetics Workshop London, 29 October 2003. On the Risk Management Program for Lotronex, see http://www.fda.gov/cder/drug/infopage/lotronex/lotronex-qa_0602.htm and http://www.lotronex.com (accessed 23/04/05).

[39] EU approval was granted in Sep. 2004 and FDA approval in Dec. 2004. FDA News, (2004) FDA Clears First of Kind Genetic Lab Test. Dec 23, 2004. http://www.fda.gov/bbs/topics/news/2004/new01149.html (accessed 22/06/05).

[40] The leukemia classification microarray is slated for rollout during 2005 and into 2006, while the AmpliChip p53 test has been targeted for research use in 2006. Womack C., (2005), Roche Official: Leukemia, p53 Microarrays Next on the Agenda, *Pharmacogenomics Reporter*, 22 Feb. 2005. Roche is also collaborating with LabCorp on evaluation studies of the AmpliChip test, including work on these future developments. LabCorp press release (2005), LabCorp To Begin Validation And Evaluation Of Roche Diagnostics' Amplichip Cyp450 Test , Burlington: NC, 29 July 2005.

to become a competitor to Roche's CYP450 AmpliChip. The Amplichip is the only FDA and EU approved in vitro device of this kind that has been approved as of August 2005. Roche have recently admitted that they do not expect widespread uptake of the AmpliChip system in clinical practice for several years.[41]

At present there appears to be relatively little demand for expensive devices of this kind. However, in the long term the development of technology platforms of this sort by large diagnostic companies such as Roche will greater reduce the cost of PGx genotyping as well as making testing more widely available.

2.6.3 Interviews with company managers

As part of the project, a series of interviews were undertaken with key managers in both pharmaceutical companies and smaller PGx firms during 2003. However, given the rapidly changing nature of the pharmacogenetics field, many of the views expressed by the interviewees may have been overtaken by events and these data has not been presented here in detail. Despite this limitation, interviewees confirmed a number of the key findings from the data presented above, including:

- Large companies have been making significant investment in PGx, although there are large variations between companies in their commitment to the field and their expectations of potential benefits;

- Large companies are already applying PGx to their internal processes, including developing drugs for specific genomic groups, but more importantly, they are using PGx to ensure that drug candidates are not differentially metabolised by DME alleles. This will ensure that potential variations between patients are minimised;

- There was significant interest in disease stratification and the idea of designing drugs for specific disease subtypes. Some managers saw this as the most important long-term benefit of PGx. However, it was acknowledged that considerations of market size would play an important role in the adoption of this strategy;

- There was very little commercial incentive to apply PGx to already marketed products. The only exception was in a few cases where it might be used as a marketing tool to increase the relative sales ranking of a drug against its rivals.

2.7 Summary and conclusion

Significant numbers of SMEs and large integrated pharmaceutical companies are working on PGx in both Europe and the US. The SMEs are small, and relatively few are dedicated solely to the development of PGx and only a handful are investing in their own internal drug development programmes. Instead, most are either selling services to large pharmaceutical companies to support drug development or are developing their own gene-based diagnostic PGx tests for already licensed medicines. In contrast, large pharmaceutical companies are focused on applying PGx knowledge and technology to improving their own internal processes, particularly in drug development. As a consequence, their focus is mainly on new products, as they have little commercial incentive to apply PGx to their already licensed medicines. It

[41] BioarrayNews, (2005),Defending Decision to Ride Arrays Into the Clinic, Roche Dx Lays Out IVD Agenda for Next 10 Years:. Interview with Roche Molecular Diagnostics' CEO, Heiner Dreismann. BioarrayNews,6(10) www.bioarraynews.com.

therefore appears there is a significant division of labour within the industry, with SMEs leading the application of PGx to licensed products.

The relatively small overall number of firms in the core universe, the lack of a large group of dedicated PGx companies, the high attrition rate and signs of disinvestments from incumbents all highlight the lack of a well-developed market for PGx and the problem of establishing a commercially viable business model for the technology. The pattern of industrial collaborations indicates that there was a rapid growth of interest in PGx between 1997 and 2000, but this has declined since then. Despite this, the field continues to attract commercial interest, as demonstrated by the significant number of new firms that have been created to work on PGx in the last four years.

Approximately 50 PGx-based diagnostic tests are currently available for use or are in development. However it is unclear how many of these are actually being actively marketed by the industry. The main applications of PGx are: 1) tests for drug metabolism; mainly CYP testing); 2) antiviral drug resistance testing; 3) cancer disease stratification and pharmacogenetics; 4) PGx testing for a range of established drugs for the treatment of a range of common conditions, including depression, high cholesterol and rheumatoid arthritis. With the exception of CYP testing, which is also used in drug development within the pharmaceutical industry, the main focus of these tests is on pre-prescription genotyping.

Evidence on the activities of large companies is hard to obtain, but it is clear that over 30 companies (i.e. most of the major firm) have some interest in the technology. However, the level of investment varies considerably, with several leading companies (GSK, Pfizer, BMS, AstraZeneca, Bayer, Roche and Sanofi-Aventis) being the most committed. These companies appear to be mainly interested in applying PGx to help improve the efficiency of their internal processes, particularly in the pre-clinical and early clinical stages. Whilst not strictly pharmacogenetics, the development of targeted cancer therapies, such as Glivec, has demonstrate that patient stratification based on somatic genotyping, can deliver commercially successful products.

In conclusion, the pharmaceutical and biotechnology industries are making significant but varied investments in PGx, which can be pictured as lying along a ‘spectrum’ of commitment, with some companies more invested in PGx than others. However, exactly which technical options for the development of PGx are adopted depends on a number of critical factors, including technical feasibility, commercial attractiveness, regulatory considerations and the ability to integrate the technology into routine clinical practice. Thus, while the application of PGx to the development of new drugs seems likely given the backing of big pharmaceutical companies, the introduction of pre-prescription genetic testing for drug response in regard to existing drugs is much less certain. It is here that investment by smaller diagnostic firms and healthcare providers is likely to be important. Even with this investment, however, there is the real prospect of ‘market failure’ more generally in the sense that the priorities of large firms might not deliver the greatest public health benefits (e.g. testing for non-responders to widely used already licensed drugs, such as the SSRIs or warfarin).[42]

[42] In an effort to counter possible ‘market failure’, the UK Department of Health funded six PGx studies in 2004 on licensed drugs including a prospective study on variability in response to warfarin, and TPMT genotyping in the management of patients prior to commencement of azathioprine treatment. For details, see: http://www.genres.org.uk/prp/projects.htm.

Chapter 3
The regulation of pharmacogenetics

3.1 The emerging regulatory regime

The behaviour of regulatory authorities will be an important influence on industry decisions on which PGx development options to adopt and on clinical uptake.[43] Chapter 1 described six broad options that encompass possible routes to commercialisation of PGx and the development of PGx-based products, with different opportunities within these options. The present chapter analyses the approach adopted by regulators to date towards pharmacogenetics and likely developments in the future based on documentary evidence and interview data, focusing on each of these six broad options.[44]

In the main, the development of PGx is industry-driven, with the primary interest being the use of the technology to improve innovation rates and reduce attrition during product development. But it is important to note that whilst research-based industry is the primary 'driver', introduction may take place via routes other than pharmaceutical innovation and new drug development. For example, recently there has also been interest in the application of PGx to a number of generic drugs, such as warfarin. This has largely been generated by concerns that whilst the application of PGx to widely used generic drugs may offer major public health benefits, these may not be realised because of a lack of commercial interest (i.e. market failure). Another related aspect increasingly highlighted is the lack of evidence relating to clinical utility and the introduction of PGx based prescribing into long-established clinical regimes (See Chapter 4).[45] There are also examples where PGx is already used to direct prescribing decisions, particularly in the treatment of certain forms of cancer. Both areas are returned to below in the context of regulation.

Industry objectives with regard to the development of PGx reflect continuing concerns about the size and robustness of development pipelines and the decline in the number of products submitted for regulatory approval, coupled with the exponential increase in costs as one moves through the development process.[46, 47] Any reduction in

[43] Here we restrict the terms 'regulatory agency' and 'regulatory authority' to agencies responsible for the assessment of safety, efficacy and quality and subsequent licensing decisions. Cost-benefit, reimbursement decisions, and evidence and perceptions of wider public health benefits will, of course, also influence uptake of PGx.

[44] The present chapter has been complemented by additional findings from two further studies: Lewis, G., Pharmacogenomics, diagnostic tests and clinician acceptance (2004-2006) UK ESRC Science in Society programme project, RES-151-25-0049 Details at http://www.york.ac.uk/res/pgx/ and Hopkins, M.M., Lewis, G. et al. (2005), Regulatory and Quality Assurance Frameworks for PGx: A Comparative Study of the US, EU and Four Member States – Part 3 of the European Science and Technology Observatory (ESTO) Study on Pharmacogenomics and Pharmacogenetics: State of the Art and Social and Economic Impacts. European Commission Joint Research Centre, Institute for Prospective Technological Studies (IPTS): Seville, Spain. Technical Report EUR 22214EN, available at, http://www.jrc.es/home/pages/detail.cfm?prs=1387.

[45] Perhaps the best demonstration of such concerns is the UK Department of Health's decision in 2004 to fund six studies on PGx including a large prospective study on variability in patient response to warfarin, available athttp://www.genres.org.uk/prp/projects.htm.

[46] FDA (2004), *Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products*, US DHHS, Food and Drug Administration (March); Gilbert, J, Henske, P. and Singh, A. (2003),

development costs through the adoption of new technologies such as PGx is therefore highly attractive to industry. Chapter 2 concluded that the application of PGx techniques to already marketed products (Options IV and V in Chapter 1) will, if developed at all, rely heavily on the activities of diagnostic companies and health care providers (such as the NHS in the UK and HMOs in the US). Furthermore, large pharmaceutical companies see little commercial benefit in applying PGx principles to drugs previously withdrawn ('drug rescue'), although other smaller firms may step into this niche.[48] The most suitable areas for the application of PGx from a commercial point of view will be those in which new treatments are being developed[49] and where existing treatments have a narrow therapeutic index.[50] However, whatever the eventual 'shape' of PGx commercialisation and introduction, the technology raises a series of quite difficult clinical and policy challenges for regulatory authorities and other policy makers such as health service managers.

The procedures for assessing conventional 'one size fits all' medicines are well developed, with regional and, increasingly, international harmonisation of standards and guidelines for safety and efficacy testing.[51] Regulatory authorities approve drugs on the basis of population data on efficacy and safety – in practice by assessing the

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Rebuilding Big Pharma's Business Model, *InVivo, the Business & Medicine Report*, Windhover Information, 21(10) November; Tufts Center for the Study of Drug Development (2001), *Backgrounder: How New Drugs Move Through the Development and Approval Process*, Boston (November).

[47] Interestingly, a recent report commissioned by the European Commission concludes that such fears, which have now become commonplace, probably do not reflect a trend and are likely to be reversed over the next few years. Charles River Associates (2004), *Innovation in the pharmaceutical sector: a study undertaken for the European Commission* (8 November). A recent contribution from industry also contests the view that innovation rates are in steep decline (although not the increase in development costs). Schmid, E.F. and Smith, D. A., (2005), Is declining innovation in the pharmaceutical industry a myth? *Drug Discovery Today*, 10(15):1031-1039.

[48] This view is supported by the comment of a leading industry proponent of PGx who, when asked about the possibility, commented: "PGx and withdrawn products? That's for the generics [companies]". Presentation by A.D. Roses, to Drug Information Association (DIA) 4th Pharmacogenetics Workshop, October 2003, London. This view has been specifically linked to the observation that such products would normally be out of patent by time of development and therefore of no interest to research-based industry – see e.g. Roses, A.D. (2004), Pharmacogenetics and drug development: The path to safer and more effective drugs, *Nature Reviews Genetics,* 5:645-656. Interestingly this 'Big Pharma' view is not held by US regulators, who expect to see submissions involving PGx data on withdrawn products at some point (Interview with senior staff member US Food and Drug Administration, Rockville MD, 18 April 2005 for G. Lewis, 'Pharmacogenomics, diagnostic tests and clinician acceptance', UK ESRC Science in Society programme project (2004-2006). Details at http://www.york.ac.uk/res/pgx). Also, GSK is itself conducting PGx safety studies on Lotronex, a drug withdrawn because of serious adverse events but subsequently allowed back on the market with tight controls over use coupled with studies to identify the genetic basis of these events.

[49] Brazell, C., Freeman, A. and Mosteller, M. (2002), Maximizing the value of medicines by including pharmacogenetic research in drug development and surveillance. *British Journal of Clinical Pharmacology,* 53: 224–231.

[50] Pirmohamed, M., and Lewis, G., (2004), Implications of Pharmacogenetics and Pharmacogenomics for Drug Development and Health Care, in Mossialis E., Mrazak M. and Walley T. (eds), *Regulating Pharmaceuticals in Europe: Striving for Efficiency, Equity and Quality, (European Observatory on Health Systems and Policy/WHO Regional Office for Europe)*, Open University Press: Maidenhead. The therapeutic index of a drug is the ratio of the toxic dose to the therapeutic (i.e. effective) dose, often used as a measure of the relative safety of the drug for a particular treatment. PGx is more likely to be clinically useful where the therapeutic index is narrow (i.e. when there is a smaller amount of difference between toxic and efficacious doses).

[51] Abraham, J. and Lewis, G. (2000), *Regulating medicines in Europe: competition, expertise and public health,* Routledge : London and New York; Abraham, J., and Lewis, G., (2004), Europeanization of Medicines Regulation, in: *The Regulation of the Pharmaceutical Industry*, Abraham, J., and Lawton-Smith, H. (eds), Palgrave Macmillan: Basingstoke, pp. 42-81.

results from randomised clinical trials on a standardised group of patients. As a result the prescribing physician cannot predict with any certainty the likely reaction of any given patient to a particular drug. In other words, conventional prescribing practice is a process of 'trial and error'. Unexpected responses arise because of the use of relatively rigid standardised dose schedules and a disregard for the diversity and inter-individual variability within a population during the drug development process. This can be particularly problematic in regard to prescribing for children and also older persons, who often experience the adverse effects of poly-pharmacy, but the principle applies to all patients.

One of the central questions explored in this study was whether the development and incorporation of PGx products into medical practice will change existing assessment methods and lead to the development of new regulatory procedures, and if so what form these procedures will take. The fundamental principle of PGx is targeted treatment based upon an individual's genetic profile. What are the implications for safety and efficacy standards, and hence regulatory approval, of this paradigmatic shift? The introduction of PGx in the clinic will also involve routine use of genetic testing or the use of a combined therapeutic agent and diagnostic test in some form or another.[52] Will the prospect of routine genetic testing and the introduction of drug/diagnostic combinations raise new concerns or pose new challenges for regulators?

In Europe, marketing authorisation for innovative products is achieved through the European Medicines Agency's[53] centralised procedure, which effectively provides a European-wide licence, while other 'non-innovative' medicines are approved by a process of mutual recognition, also known as the decentralised procedure.[54] However, European regulators expect both procedures to be used for PGx products. Regional harmonisation is also increasingly underpinned by international harmonisation through the International Conference on Harmonisation (ICH), which comprises industry representatives and regulators from the three largest markets, USA, EU and Japan.[55] The existence of harmonised standards and the globalised nature of pharmaceutical markets would add a layer of complexity to any regulatory changes required by PGx development.

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[52] It is important to recognise that the diagnostic component may already be available, and that the same genetic test may be applicable to more than one drug, or even more than one therapeutic category. This possibility becomes more likely as our understanding of the molecular basis of disease increases, with the possibility of re-defining some diseases.

[53] From May 2004, the European Medicines Evaluation Agency was re-named as the European Medicines Agency, although the acronym EMEA continues to be used. The Committee on Proprietary Medicinal Products (CPMP) was changed to the Committee on Human Medicinal Products (CHMP). See http://www.emea.eu.int/ for details.

[54] These two long-standing authorisation procedures have recently been extended to provide for separate mutual recognition and decentralised procedures and a centralised procedure, plus establishment of a formal Coordination Group for mutual recognition, following a review of existing arrangements and new legislation adopted in 2004. See Regulation (EC) No 726/2004) of the European Parliament and the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. *Official Journal of the European Union* L136/1. For details of European regulatory procedures, see the European Commission's site http://pharmacos.eudra.org/F2/home.html

[55] Abraham, J. and Lewis, G. (2000), *Regulating medicines in Europe: competition, expertise and public health,* Routledge: London and New York; Abraham J., and Lewis, G., (2004), Europeanization of Medicines Regulation, in: *The Regulation of the Pharmaceutical Industry,* Abraham J., and Lawton-Smith, H., (eds), Palgrave Macmillan: Basingstoke.

As reported elsewhere, the approach that agencies such as the EMEA and FDA are adopting towards PGx in terms of genetic tests, clinical trials, licensing, and labelling policy remains unclear, although in the past few years both agencies have began to engage with the subject in a much more pro-active manner.[56] The FDA and, increasingly, the EMEA, are now actively supporting the introduction of pharmacogenetics into both drug development and medical practice, with regular meetings with industry and joint discussion of the 'meaning' and interpretation of PGx data. In the case of the FDA, these moves have been highlighted by development of a series of formal guidances and operating procedures aimed at encouraging incorporation of PGx into drug development plans.[57]

There are a number of existing regulatory guidelines and recommendations that reflect some of the clinical issues around pharmacogenetics in clinical studies and data submission for marketing approval. These include guidelines on pharmacokinetic (PK) studies in man, drug interactions, ICH guidelines on acceptability of foreign clinical data, bioavailability and bioequivalence, dose response information, and variability in pharmacodynamic (PD) response.[58] Indeed, some regulators point to the existence of such guidelines in order to dismiss claims that agencies have been reluctant to engage with PGx until relatively recently. Nonetheless, both regulators and industry have recognised the need for new guidelines not least because of the 'paradigmatic shift' inherent in the routine use of genetic profiling and the introduction of drug/diagnostic combinations noted above. In the US especially, new guidelines are also seen as key to enabling innovation and allaying industry concerns about how the FDA will handle submissions in the future. Even so, there is still considerable uncertainty about the implementation of such guidelines.

3.2 Regulatory authorities encourage the adoption of PGx

Over the past four years, both the EMEA and the FDA have started a process of direct engagement with industry on issues around the introduction of PGx into drug development and approval procedures and this process is now well developed. The FDA now publicly advocates the use of pharmacogenomic strategies to optimise clinical trials, with numerous interventions and statements to this effect by senior staff.[59] Active encouragement of PGx by regulatory agencies is in stark contrast to the

[56] Pirmohamed, M., and Lewis, G., (2004), Implications of Pharmacogenetics and Pharmacogenomics for Drug Development and Health Care, in Mossialis, E., Mrazak, M. and Walley, T. (eds), *Regulating Pharmaceuticals in Europe: Striving for Efficiency, Equity and Quality,* Open University Press: Maidenhead; Webster, A., Martin, P., Lewis, G., and Smart, A. (2004), Integrating pharmacogenetics into society: in search of a model *Nature Reviews Genetics* 9:663-669.

[57] Lesko, L., and Woodcock, J. (2002), Pharmacogenomic-guided drug development: regulatory perspective, *The Pharmacogenomics Journal* 2:20-24., FDA (2005), Guidance for Industry. Pharmacogenomic Data Submissions, US DHHS; FDA, CDRE, CBER, CDRH, March 2005, FDA (2005), Management of the Interdisciplinary Pharmacogenomics Review Group (IPRG) Manual of Policies and Procedure, MAPP4180.2, FDA/CDER (effective date: 16 March 2005); FDA (2005), Drug-diagnostic Co-Development Concept Paper - Draft, DHHS, FDA, April 2005,available at http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf.

[58] Shah, R.R. (2003), Regulatory aspects of pharmacogenetics and pharmacogenomics. *Bundesgesundheitsbl-Gesundheitsforsch-Gesundheitsschutz*, 46:855-867.

[59] One of the first interventions was by FDA officials Larry Lesko and Janet Woodcock in 2002: "we believe that the central issue is not whether pharmacogenetics or pharmacogenomics-guided drug prescriptions will happen, but when and how". Lesko, L., and Woodcock, J. (2002), Pharmacogenomic-guided drug development: regulatory perspective, *The Pharmacogenomics Journal* 2:20-24. (p.20). On release of the FDA's draft Pharmacogenomics Guidance document in 2003, Mike McClellen, then FDA

position at the start of this project in 2001 when there was little indication of regulatory engagement and little or no information in the public domain as regards the attitude of regulatory agencies towards PGx.

In the case of the FDA, this positioning as an active encourager of PGx is a reflection of the agency's belief that the correlation of patients' genetic variations to clinical outcomes could help bring certain drugs to market more rapidly and efficiently, thereby boosting the industry's current low R&D productivity rate and improving public health. This policy is part of the FDA's Critical Path initiative, which views PGx as an important avenue for speeding up drug development and approval process.[60] Expressed in more political terms, the FDA has adopted an approach which says: we will help industry bring innovative products to the market faster in return for improvements in public health brought about by developing products that target treatment more effectively and reduce ADRs. There is a similar impetus in Europe to boost innovation and the competitiveness of the pharmaceutical industry,[61] although specific policy initiatives with regard to encouraging PGx are less developed than in the US.

The earlier lack of engagement by regulatory agencies reflects, in part at least, a lack of available data. Apart from the commonly cited examples of Herceptin and Glivec, and the more recently approved Erbitux, all products in the oncology area, regulators in both Europe and the US have not received any new drug approval submissions (Marketing Authorisation Applications (MAAs)/Investigational New Drugs (INDs) in Europe/US respectively) that rely on PGx data. In other words, there are few PGx products on the market, although there are a number of PGx tests available to direct prescribing decisions for existing drugs (See Chapter 2). This in turn reflects the fact that there is relatively little PGx data from late stage clinical trials in the hands of industry since the primary focus to date has been on Phase I and II studies, although reportedly some industry-sponsored Phase III trials are underway. One reason for the paucity of data with regard to new drug development is simply the time is takes to develop a drug. For PGx data from Phase III studies to be available and then included in product applications, the decision to adopt a 'PGx approach' to development would have been taken several years ago. Accordingly it is only a matter of time before such data 'feeds through' to regulatory submissions, although of course there are other factors affecting the decision process, such as industry perceptions of the likely commercial benefits of PGx, clinician and payer acceptance etc., as discussed elsewhere in this report.[62]

The evidence suggests that the industry has, at least up until now, been very cautious as regards drug development involving patient stratification. But this may change over time, and whilst little data is available at present, in the longer term regulators expect

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Commissioner, stated: "pharmacogenomics is a new field, but we intend to do all we can to use it to promote the development of medicines" (GenomeWeb News 3 Nov. 2003).

[60] FDA (2004), *Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products*, US DHHS, Food and Drug Administration (March).

[61] Charles River Associates (2004), *Innovation in the pharmaceutical sector: a study undertaken for the European Commission* (8 November).

[62] As Nicholas Dracopoli, vice president of clinical discovery technology at Bristol-Myers Squibb, recently noted in answer to question 'why are there so few examples of genomics-based drugs?': "Because drug development takes 8 to 15 years. Genomic drugs are just now moving into development". Davies, K., (2005), Medicine Gets a Personal Touch, Bio-IT World, 30 May at http://www.bio-itworld.com/newsitems/2005/05/05-30-05-news-dracopoli (Accessed 31/05/05).

to have to grapple with a massive increase in genetic data. There is also the possibility of 'regulatory dependence' and 'conflict of interest' situations developing, where the main source of knowledge about a treatment or indication resides in industry. Regulators may become ever more reliant on company sources for expertise as genomics-based technologies become the dominant development model. Improving internal understanding of PGx and related technologies and knowledge of how genetic information relates to treatment claims is one of the drivers for the FDA's Voluntary Genomic Data Submission (VGDS) initiative (initially known as the 'safe harbor' proposal) introduced in early 2005.[63] By means of this initiative the desire to understand the meaning and potential regulatory significance of complex genetic data is being progressed in practical terms by encouraging the submission of pharmacogenomic data (defined by the FDA as data from pharmacogenomic or pharmacogenetic tests) early in the development process for the purposes of discussion and mutual learning and understanding. The initiative also attempts to address industry concerns about the use of such data; these focus on the possibility that voluntarily submitted data may, for one reason or another, eventually form part of formal assessment procedures, and fears about commercial confidentiality. For example, a potential safety issue might emerge and it is unclear how regulators would react to such a finding. They cannot ignore information once it has come to light since it may present a public health issue and, in the US context, federal law compels sponsors to divulge to the FDA all data that is likely to impact on the assessment of safety and efficacy.

The FDA's voluntary data submission proposal emerged in May 2002 when the first joint FDA/industry meeting on PGx was held. The agency organised further joint workshops in November 2003 and July 2004 followed by release of an official pharmacogenomics guidance document prior to the most recent workshop in April 2005.[64] The FDA also organised a workshop with industry focused specifically on the co-development of drug, biological, and device products in 2004.[65] Following this meeting, a Concept Paper on co-development was released, which is expected to result in a formal FDA guidance document[66]

In summary, the Guidance for Industry: Pharmacogenomic Data Submissions, (see footnote 63) introduces a classification for genomic biomarkers; clarifies what type of genomic data needs to be submitted to the FDA and when; introduces a new data submission pathway to share information with the FDA on a voluntary basis (i.e. the VGDS scheme); and encourages the voluntary submission of exploratory genomic

[63] FDA (2005), Guidance for Industry. Pharmacogenomic Data Submissions, US DHHS, FDA, CDRE, CBER, CDRH, March 2005, available at: http://www.fda.gov/cder/genomics/GDS.htm (Accessed 25 April 2005); FDA (2003), Guidance for Industry: Pharmacogenomic Data Submissions. Draft Guidance (November). Available at: http://www.fda.gov/cder/guidance/5900dft.doc.

[64] 'The second workshop in November 2003 was designed to disseminate the Agency's ideas and gauge industry response to the proposal, and resulted in the joint writing and publication of a Draft Guidance document [FDA (2003b) Guidance for Industry Pharmacogenomic Data Submissions - Draft Guidance. Available at: www.fda.gov/cder/guidance/5900dft.pdf]. The final Guidance document was published in March 2005. [FDA (2005) Guidance for Industry Pharmacogenomic Data Submissions. Available at: www.fda.gov/CDER/guidance/6400fnl.pdf]

[65] FDA/DIA (2004), Pharmacogenomics Workshop: Co-Development of Drug, Biological, and Device Products; July 29, Arlington, VA.

[66] FDA (2005), Drug-diagnostic Co-Development Concept Paper - Draft, DHHS, Food and Drug Administration, April. http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf

data. The document also introduces a new agency-wide review group and clarifies how the FDA will review genomic data submissions.[67]
Voluntary genomic data submission (VGDS) is overseen by a specially created interdisciplinary group separate from the agency's formal assessment division, the Interdisciplinary Pharmacogenomics Review Group (IPRG).[68] The purpose of the IPRG is to bring together relevant expertise from across the FDA whilst at the same time distancing the Group from assessment activity in order to help assuage industry fears. What type of data is submitted and how participative companies will be in the longer term remains an open question but as of March 2006, some 25 submissions had been made under the scheme, with fifteen meetings with sponsors including two meetings held jointly with the EMEA. The indications are that submitted data are likely to be related most closely to gene expression data and data related to the definition and interpretation of potential biomarkers although published figures show discussion of a wide range of scientific and PGx topics.[69] [70]

European regulators face a similar 'trust problem' to that confronting the FDA as regards the status of submitted data. In the European case, care is taken by the EMEA to distinguish between 'Briefing Sessions' and the formal Scientific Advice procedure under which companies can seek guidance on the type of data the regulators are likely to want included in a MAA.[71] So far there appears to be relatively little interest on the part of industry in the Briefing Sessions, despite the EMEA encouraging companies to come forward and use the facility.[72] Prior to the introduction of the PGx Briefing Sessions, EMEA efforts had been mainly focused on developing common PGx terminology through the CPMP PGx Expert Group, now replaced by the Pharmacogenetics Working Party (PGWP),[73] and conducting informal meetings with industry representatives.

Regulatory authorities are seeking the best method to assess proof of value and clinical benefit, especially if alternative treatment is available. The EMEA is presently seeking to understand the type of support required for PGx development and the implications of this. The Agency has adopted standardised terminology, which is seen as an essential step prior to entering discussion with both industry and other

[67] Frueh, F. (2005), HHS Efforts and Future Directions in Pharmacogenomics – An Update on FDA Guidances Related to Pharmacogenomics. Presentation to Secretary's Advisory Committee on Genetics, Health and Society (SACGHS), Bethesda MD, 16 June 2005, available at http://www4.od.nih.gov/oba/SACGHS/meetings/June2005/Freuh.pdf, (accessed 22/06/05). It is important to note that FDA guidance documents are recommendations, not legal obligations.
[68] FDA (2005), Guidance for Industry. Pharmacogenomic Data Submissions, US DHHS, FDA, CDRE, CBER, CDRH, March 2005; FDA (2005), Management of the Interdisciplinary Pharmacogenomics Review Group (IPRG) Manual of Policies and Procedure, MAPP4180.2, FDA/CDER (effective date: 16 March).
[69] Frueh, F.(2006) Qualification of Genomic Biomarkers for Regulatory Decision Making, 18th Annual DIA EuroMeeting, Paris, France – March 7, 2006, available at: http://www.fda.gov/cder/genomics/presentations/DIA_Eur4.pdf (accessed 10/05/06).
[70] Interview with senior FDA staff member 15/04/05 for Lewis (2004 – 2006) op. cit. (see note 41).
[71] EMEA (2004), Mandate, Objectives and Rules of Procedure of the Scientific Advice Working Party (SAWP). EMEA/CHMP/SAWP/69686/04 (23 September); EMEA (2005), Committee on Medicinal Products for Human Use (CHMP) Draft Guideline on Pharmacogenetics Briefing Meetings. EMEA/CHMP/20227/2004. (17 March), available at: http://www.emea.eu.int/.
[72] Figures provided by EMEA sources suggest that there had been no requests for Scientific Advice for products involving PGx by late 2003, suggesting little late stage PGx product development, but there had been 3 or 4 requests for the informal Briefing Sessions immediately after announcement of the scheme, with this rising to approx. 10 by early 2005 (Additional data from Hopkins, M.M. and Lewis, G et al. (2006) – see note 44).
[73] EMEA (2005), Mandate, Objectives and Rules of Procedure for the CHMP Pharmacogenetics Working Party, EMEA/CHMP/101592/2004 (17 February).

regulatory authorities.[74] It has also been active in ensuring that relevant expertise is available to the CHMP (which replaced the CPMP in 2005), including 'in-house' education and training needs. The latter task is particularly challenging because of the devolved nature of the European regulatory system. And finally, like other agencies, it must also consider how to manage data submission within the CTD (Common Technical Document) model and how to keep labelling up to date with respect to PGx data as the information available and, equally as important, its interpretation of changes over time. The EMEA is also concerned to set out the principles required in order to maximise the potential benefits from secondary research whilst maintaining patient privacy. The key issue here revolves around how long companies should be permitted to keep coded samples to allow sufficient time for secondary research to be undertaken.[75]

Another area the project examined was the possible relationship between regulatory authorities' positions towards PGx and issues of clinical introduction. Interestingly, senior FDA staff are on record as having stated that product assessment that incorporates PGx data will include what can broadly be defined as 'clinician acceptance' issues, particularly with regard to the question of whether a product requiring genetic testing prior to prescription can and will be used as specified.[76] Such issues clearly connect with labelling decisions when approval is granted for a PGx-based treatment regime, and whether to 'recommend' or 'require' PGx testing prior to treatment and how such rulings would be encouraged or enforced accordingly. Also, whilst the subject of off-label prescribing is not peculiar to PGx it may pose some particular challenges. The emergence of additional information post-approval may also present quite specific challenges to regulators in the context of PGx. These topics are discussed in more detail below.

3.3 PGx and clinical development

Current regulatory approval is based on assessment of the efficacy and safety of medicinal products, based on data generated by a series of clinical trials (CTs). These begin with dosage and PK studies using a small number of healthy volunteers (Phase I); a larger number of patients (50 - 100) for proof of efficacy (Phase II), and finally large scale clinical studies utilising several hundred to several thousand patients and matched controls on either placebo or comparator drug (Phase III). Post-marketing studies (such as to provide additional safety data and increase knowledge of the drug's action, extend indications, and provide marketing information) comprise what are called Phase IV studies.

CTs are based on the notion of 'generalisability' of response. Evidence provided by CTs is extrapolated to the wider patient population, irrespective of the fact that groups exposed to the drug did not form part of the trial. In contrast, the fundamental principle of PGx is that the drug regimen is targeted at patients according to their genetically determined (at least in part) response, whether in efficacy terms or ADRs.

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[74] EMEA (2004), Understanding the terminology used in pharmacogenetics. EMEA 3842/04/Final (29 July) available at: http://www.emea.eu.int/pdfs/human/pharmacogenetics/384204en.pdf; EMEA (2002), Committee for Proprietary Medicinal Products (CPMP) Position Paper on Terminology in Pharmacogenetics. EMEA/CPMP/3070/01 (21 November).

[75] Interview data from senior EMEA official for Hopkins, M.M. and Lewis, G. et al. (2006) op cit. (see note 44)

[76] Lesko, L., and Woodcock, J., (2002), Pharmacogenomic-guided drug development: regulatory perspective, *The Pharmacogenomics Journal* 2:20-24.

What does this mean for regulation in terms of the introduction of PGx? The drug development process can be divided into stages and this question is discussed below with regard to each stage.

PGx offers potential benefits for all aspects of the drug development process. Increased knowledge of gene-receptor and gene-pathway interaction at the pre-clinical development stage could lead to lower attrition rates, improved targeting, and higher throughput. In fact, pre-clinical application is the area where most benefits from PGx have been realised to date, with application of knowledge of drug absorption, distribution, metabolism and excretion (ADME) to drug candidate selection, and development of in vitro screens to identify molecular defects underlying phenotypic variability.[77]

A number of claims have been made with regard to clinical trials (CTs) in terms of both clinical and cost benefits. In clinical terms, in Phase I trials, healthy volunteers could be genotyped and, with increased sample size, this may lead to better focused later studies. In Phase II studies, increased sample size based on information gleaned from Phase I could be matched by lower attrition rates. Phase III could see smaller sample size, coupled with reduced cost, faster throughput and therapeutic indication according to genotype. Finally, Phase IV might see a more structured collection of data including DNA for pharmacovigilence purposes, with a resultant improvement in safety.

Once again, it is very difficult to obtain accurate data on the extent to which CTs are being designed to include a PGx component due to the general unavailability of industry data in the public domain for reasons of commercial confidentiality. By 'PGx component' we mean prior genotyping of trial participants in order to correlate subsequent outcomes with genetic profiles. Interview evidence suggests that this is being conducted by a number of companies either themselves or through contract laboratories responsible for the clinical trial. One recent industry report claimed that there are thousands of such CTs underway at the Phase I and early Phase II stage.[78] Whilst it is clear that such genotyping is becoming more common, it is not possible to confirm such a figure from data available in the public domain, nor obtain a clear picture of the extent to which such studies involve either prospective or retrospective screening. The number of Phase III PGx CTs is small – there were probably no more than ten underway in 2003 based on evidence from the Centre for Medicines Research, the industry sponsored research organisation, at the time. This figure broadly accords with our interview data from senior industry scientists.[79] As noted already, with regard to new drug development, the apparent paucity of trials is due in large part to the time required for drug development.

Earlier commentators made more expansive claims. In 2002, analysts at PriceWaterhouseCoopers (now IBM Life Sciences) suggested that 70% of patients

[77] Pirmohamed, M. and Lewis, G. (2004), Implications of Pharmacogenetics and Pharmacogenomics for Drug Development and Health Care, in Mossialis, E. Mrazak, M. and Walley, T. (eds) *Regulating Pharmaceuticals in Europe: Striving for Efficiency, Equity and Quality*, (European Observatory for Health Systems and Policy/WHO Regional Office for Europe), Open University Press: Maidenhead.
[78] Acorn, G. (2004), *Clinical Genomics: the impact of genomic technology in clinical trials and medical practice. Executive summary*, Cambridge Health Institute, Boston MA., available at http://www.chadvisors.com/.
[79] Centre for Medicines Research (2003), Workshop on personalised medicine, CMR International Institute for Regulatory Science, Surrey, UK 14-15 April.

participating in clinical trials were going to be genotyped prior to participation by 2004.[80] Such claims seem highly unlikely to have occurred when by all accounts the actual proportion of Phase III trials doing this is small. The research carried out for this and related studies suggests that this area is much more complex.[81] Most activity remains restricted to early clinical studies, with routine collection of samples from trial participants for possible future use. Companies are unlikely to introduce prospective genotyping to CTs unless they see clear clinical *and* commercial benefits. For example, it is not obvious that the promised cost savings are as high as early claims make out. Companies may also want to avoid stratified markets. Internal 'power relations' with regard to decision-making and long term company strategy and positioning are also likely to play a part in such decisions. Overall, the industry is moving quite cautiously, apart from a small number of firms who have opted to make a major commitment, such as GSK and Roche.

3.3.1 Toxicology and early clinical development

Considerable efforts are being expended by the pharma industry on the application of PGx to both toxicology (toxicogenomics) and early clinical development. The principal use of PGx in early clinical development is to reduce attrition and generate data to aid the design of Phase II trials through genotyping – echoing the key industry (and regulatory) concern about low R&D productivity. Having said this, it is important to realise that existing development practice includes extensive examination of drug metabolism and to this extent PGx techniques based on CYP450 analysis are an extension of current practice. Indeed, the bulk of 'PGx data' submitted to the FDA (which by 2003 amounted to more than 100 examples and is now so large that they have reportedly 'stopped counting') is likely to be CYP450 data, although the recently established voluntary submission of research data scheme will alter this to some extent.

In addition, as already noted, all the major drug companies are routinely collecting samples from clinical trials participants for possible future genotyping. Although not directly relevant to regulatory agencies' assessment procedures, this practice has implications for EMEA interest in these issues[82] as well as the wider regulatory environment of genetic testing, sample storage, informed consent and ethics.[83]

3.3.2 Late clinical development

Late clinical development provides the basis for assessment of clinical efficacy and is central to decisions on whether to grant marketing authorisation. Data collected for this study suggests that regulators are likely to take a case by case approach to submissions that contain PGx data from late stage development (i.e. products targeted at specific population groups), according to parameters such as indication, existence of other treatments, and therapeutic index. The cautious stance adopted by regulators here reflects the general conclusion that PGx will not be applicable to all types of drug and all indications for both therapeutic and commercial reasons. The

[80] Arlington, S. Peakman, T., Salvatore, A. and Peachey, J. (2001), Custodians in Crisis: the Impact of Genomics on Regulation, *Drug Discovery World,* Fall 2001, available at http://www.ddw-online.com/.
[81] Lewis, G. 'Pharmacogenomics, diagnostic tests and clinician acceptance', ESRC Science in Society programme project (2004-2006) and Hopkins M. M. and Lewis, G. (2005) – see note 44.
[82] Interview with senior EMEA official for Hopkins, M.M., Lewis, G. et al (2006) op. cit. (see note 44).
[83] Lewis, G. (2004), Tissue collection and the pharmaceutical industry: investigating corporate biobanks, in Tutton, R. and Corrigan, O. (eds), *Genetic Databases: socio-ethical issues in the collection and use of DNA*,Routledge:London, pp181-202.

most likely areas are those where treatments are either non-existent, or if they do exist, display a narrow therapeutic index, e.g. cancer therapy and perhaps widely used drugs that exhibit serious side effects in a relatively small proportion of exposed patients, such as warfarin.[84]

3.3.3 Pharmacovigilance and post marketing surveillance

For statistical reasons, the frequency of rare ADRs cannot be determined prior to marketing given the conventional size of clinical trials (CTs). It is often the case that a drug will have been exposed to no more than 1,500 individuals prior to marketing. Drug safety relies on wide exposure over time through marketing to obtain a comprehensive safety picture. Pharmacovigilance (PV) has been given far less attention than pre-marketing safety assessment, and there is general recognition that more needs to be done as regards collection and interpretation of post-marketing safety data.[85] In this sense, treatment based on PGx relates to wider concerns about strengthening existing PV systems, as PGx offers the opportunity of improving both efficacy and safety information through data collection, interpretation, and then better patient targeting in the post marketing environment.

What form are improvements in PV likely to take and what is the response of regulatory agencies likely to be? Allen Roses of GlaxoSmithKline has proposed that samples from the first quarter of a million patients receiving a new drug should be routinely banked with appropriate safeguards for possible future analysis.[86] However, at this point in time regulators in the EU are looking to collect post-marketing PGx information retrospectively, if and when needed. In other words, if a safety problem emerges, collection and profiling of samples would be undertaken, and genotyping data would be related to ADRs. However, this is a task that presents considerable practical difficulties.

3.4 PGx and labelling issues

The assessment of safety and efficacy, which can be viewed as a drug's benefit/risk ratio, is the basis upon which drug approval decisions are made.[87] Such decisions are usually quite complex and may involve a series of 'trade-offs' depending on the type of drug, the therapeutic index and the availability of other treatments. This complexity is 'translated' for use in the clinical setting by means of the drug 'label'– prescribing instructions formally recommended to doctors by the regulatory authority. In Europe, information on licensed indications and prescribing directions is contained in the Summary of Product Characteristics (SPC). The challenge to labelling policy that PGx poses is summed up in the US federal regulation which states that: 'labelling shall describe the evidence and identify specific tests needed for selection and monitoring

[84] DIA (2003), 4th Pharmacogenetics Workshop: Moving Towards Clinical Application. 29-30 Oct., London; Pirmohamed, M. and Lewis, G., (2004), Implications of Pharmacogenetics and Pharmacogenomics for Drug Development and Health Care, in Mossialis, E., Mrazak M. and Walley, T. (eds), *Regulating Pharmaceuticals in Europe: Striving for Efficiency, Equity and Quality, (European Observatory for Health Systems and Policy/WHO Regional Office for Europe)*, Open University Press: Maidenhead.

[85] Abraham, J. and Lewis, G. (2000), *Regulating medicines in Europe: competition, expertise and public health*, Routledge, London and New York.

[86] Roses, A. D. (2004), Pharmacogenetics and drug development: The path to safer and more effective drugs, *Nature Reviews Genetics,* 5:645-656.

[87] In addition to safety and efficacy, regulatory assessment also includes quality, which is not discussed here.

of patients who need the drug'.[88] As the predictive power of pharmacogenetic testing increases labelling is likely to become more prescriptive.[89] The introduction of PGx into clinical practice will further demonstrate the complexity of labelling decisions and in addition raise a range of ethical questions for regulators as well as doctors.

Many drugs currently marketed have prescribing information relating to polymorphic drug metabolism, such as when they are metabolised by CYP2D6, one of the cytochrome P450 metabolising enzymes responsible for the metabolism of many common drugs. There are no barriers to the inclusion of PGx related information in drug labels. Trastuzumab (Herceptin) is the best known example, but according to FDA figures, around 35% of US approved drugs have PGx information on the label.[90] In the future, there are likely to be many more examples where the label may reflect findings that a drug has been shown to be (only) efficacious in patients with a certain genotype. A drug would then be licensed not only for a particular condition but recommended for use in patients with a certain genotypic profile. There are already a number of such examples, but the development is perhaps best exemplified by examining the prescribing instructions for trastuzumab (Herceptin) in breast cancer (See Chapter 2), which is licensed for use only in women who have been shown to over-express the HER2 gene by means of a biochemical test. Prescription to patients without the particular genotype is therefore outside the licensed indication – what is known as 'off-label' prescribing. Whilst this test is now routinely used in breast cancer treatment, in general terms it seems unlikely that doctors will automatically refuse to prescribe a drug indicated for a serious or life threatening condition on the basis of a patient's genotypic profile. The probability is that PGx prescribing information will be mediated according to the nature of the disease, availability of other treatment options, and patient circumstances. A key point here is that the association between genotype and drug response is probabilistic, so doctors cannot be certain that a patient will not benefit from treatment, thus making denial difficult.

Labelling regulations will presumably also have to disclose recommended dosage based on stratified patient groups according to genotypic profiles and there are already a number of examples.[91] There are major issues here concerning how instructions for use will be encouraged or enforced (if, indeed, they should be enforced). Doctors have the right to prescribe 'off-label' and it is difficult to see why this would change in the future. Indeed, regulatory agencies are increasingly aware of off-label use for patient groups not included in the original approval.[92] How regulatory

[88] Federal Regulation (2004), Code of Federal Regulations, Title 21, Volume 4 (revised April 1, 2004] Title 21--Food and Drugs Chapter 1 -- Food and Drug Administration, Department of Health and Human Services, Subchapter C - Drugs: General [cited as 21CFR201.57]. Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.57 (accessed 23/06/05).
[89] Robertson, J, A., Brody, B., Buchanan, A., Kahn, J. and McPherson, E. (2002), Pharmacogenetic challenges for the health care system, *Health Affairs*, 21(4):155-167.
[90] Lesko, L. (2004), How Is FDA Enabling the Use of PGx in Drug Development and Product Labels of Approved Drugs? Paper presented at Scientific American Targeted Medicine conference, 11 Nov. 2004, New York, USA.
[91] A controversial example of this approach is the recently FDA-approved drug BiDil for heart failure which is indicated for Afro-Americans, where it appears that self-defined racial characteristics are serving as a surrogate for as yet unproven genotypic differences effecting drug response. *FDA News* FDA Approves BiDil Heart Failure Drug for Black Patients, 23 June 2005. Available at: http://www.fda.gov/bbs/topics/NEWS/2005/NEW01190.html (accessed 25 June 2005).
[92] But this is being called into question with calls for greater attention to patient diversity. See e.g. the controversy over GSK's anti-depressant drug, Seroxat (Paxil in the US), which was never licensed for use in children, yet is prescribed by some doctors 'off-label'. Regulators on both sides of the Atlantic recently

agencies ensure appropriate prescribing of medicines based on pharmacogenetic principles remains an outstanding question. Predictions about future labelling policy, or more accurately, the series of complex questions surrounding labelling in the context of PGx, also imply a number of assumptions regarding the availability of genetic testing, the capacity of doctors to interpret the results, and 'infrastructure questions' such as provision of genetic counselling. These issues are returned to later in the report.

However, as already noted, it is unlikely that PGx testing will be a regulatory requirement for all drugs. The need for testing prior to prescribing a particular drug will depend upon several variables, in particular the genetic factors determining its disposition, the drug's pharmacodynamic characteristics and therapeutic index, and, of course, the availability of a suitably validated diagnostic test. A drug that has a high degree of efficacy in a large proportion of the population and that shows little inter-individual variability in kinetics and dynamics, and has a wide therapeutic index, should not necessarily require PGx testing. Indeed, it would not be cost effective to test every patient prior to drug prescription. By contrast, a drug that is efficacious in (say) 30 per cent of the patient population and displays a narrow therapeutic index, such as is typical with some current psychiatric drugs, would be a strong candidate for PGx testing of potential patients prior to prescription. Again, the extent to which regulatory agencies will adopt such a policy and how they will enforce it is unclear at this time. Pre-clinical studies should be able to identify the routes of metabolism and disposition of any particular drug, and its mechanism of action. If any of these parameters are subject to genetic polymorphism that could theoretically or in practice affect the response to the drug, then pharmacogenetic testing should be encouraged.[93] This suggests that, with regard to drug development, constant dialogue between pharmaceutical companies and regulatory agencies will be important to ensure that the development process is as efficient as possible and yet does not lead to a reduction in regulatory standards.

Regulators are also likely to be concerned that PGx may lead to a situation where patients who are non-responders or who are susceptible to a particular adverse reaction (i.e. individuals who possess the 'wrong' genotypic profile) will be faced with the prospect of non-treatment. Such 'excluded patients' may in some cases be based on ethnicity, since there is variation in the response of different ethnic groups to certain drugs.[94] Exclusion of large numbers of people from treatment possibilities based on 'ethnicity' or 'race' – both contested concepts socially and in scientific terms - through the use of pharmacogenetics is likely to be of concern to regulatory authorities as well as to wider political institutions.

This 'orphan genotype' problem will, by definition, represent a relatively small proportion of the overall population in a country but may still amount to considerable numbers of people. Pharmaceutical companies may be reluctant to develop new medicines to treat small groups of 'orphan patients'. Wider policy concerns may

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banned its use in children after it was linked to an increase in suicidal thoughts and, according to some analysts, an increase in suicides.

[93] Pirmohamed, M. and Lewis, G. (2004), Implications of Pharmacogenetics and Pharmacogenomics for Drug Development and Health Care, in Mossialis E., Mrazak, M. and Walley, T (eds), *Regulating Pharmaceuticals in Europe: Striving for Efficiency, Equity and Quality,* Open University Press: Maidenhead.

[94] Weinshilboum, R. (2003), Inheritance and Drug Response, *New England Journal of Medicin*e, 348(6):529-537.

require the expansion of commercial incentives to encourage drug development in such areas, with the extension of present policy towards orphan drugs to include development of medicines for populations excluded from treatment by genotypic profile.

Alternatively, it is possible that smaller genomics or drug development companies will enter the market in a similar way to what has occurred in the orphan drug market. However, it is not possible at this stage to predict the role that dedicated PGx and/or small biotech firms are likely to play in practice. As described in Chapter 2, whilst there are a few small genomics companies that claim to be engaged in drug development, their efforts draw mainly upon 'in-house' proprietary genetic information and mostly focus upon early-stage development, often in collaboration with large pharma companies.

It is also possible that PGx will reduce the cost of clinical trials and thereby stimulate development of products that are not commercially viable at present. To qualify for orphan drug status[95] in the USA, companies must demonstrate there are less than 200,000 potential users of the drug, and similar legislation exists in the EU. However, defining the prospective patient population is often not straightforward. Hence a potential source of conflict exists between regulators and industry. Interestingly, Genentech, the makers of Herceptin, the monoclonal antibody active against certain forms of breast cancer where it has been shown there is over-expression of the HER2 gene, sought orphan drug status in the USA but this was refused.

Much of this report focuses on commercially-driven options being developed by global pharmaceutical companies. However, it is possible that important health benefits from PGx will come from targeted therapy using existing generic drugs, such as warfarin, the statins, 6-mercaptopurine and so on (see Chapter 4). From a regulatory perspective, PGx offers the opportunity to enhance patient benefit by improved targeting and more effective prescribing. In some cases, most notably in cancer therapy, genetic testing is already routinely used to aid treatment decisions. The FDA has now adopted a policy of actively considering whether PGx can provide such benefits more widely such as when new PGx data changes the risk/benefit ratio of an already approved treatment. Such information might lead to re-assessment and trigger the review of the drug concerned.[96] Widespread adoption of such a policy could have important implications for both industry and medical practice generally. For example, the FDA has already re-visited recommended practice and labelling requirements for drugs for childhood leukaemia, such as 6 mercaptopurine (6MP) and other treatments.

In the example of 6MP, the existing label has been revised in conjunction with the manufacturer to inform clinicians of the option of using thiopurine methyltransferase (TPMT) testing to guide treatment with 6MP.[97] The FDA has also made a series of

[95] Orphan drug status provides market exclusivity for a stated number of years and a reduction in registration and other fees, including development costs, depending on the country or region concerned.
[96] Lesko, L. and Woodcock, J. (2004), Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective, *Nature Reviews Drug Discovery*, 3:763-769.
[97] For label details see: www.fda.gov/cder/foi/label/2003/12429slr021_tabloid_lbl.pdf See also: Summary Minutes of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee July 15, 2003 – available at: http://www.fda.gov/ohrms/dockets/ac/03/minutes/3971M1.htm; Weinshilboum, R. (2001), Thiopurine pharmacogenetics: clinical and molecular studies of thiopurine methyltransferase, *Drug Metabolism and Disposition*, 29:601-605.

changes to prescribing recommendations for the proprietary anti-colorectal cancer agent irinotecan (Camptosar, Pfizer) based upon PGx data collected post approval, indicating that regulatory intervention is potentially wide ranging and not restricted to generics.[98] In the case of irinotecan, the absence of PGx information on the label despite growing evidence of a link between a specific UGT1A1 allele and risk of severe toxicity was highlighted in 2004. According to the FDA, insufficient evidence is presently available to recommend exact dosing according to genotype, but the label has been changed to reflect the increased risk of severe neutropenia for individuals with the relevant genotype. In parallel with this development, in August 2005 Third Wave Technologies received US approval for a test to determine UGTA1A status prior to prescribing.[99]

These examples signal a clear willingness on the part of regulators and the FDA in particular to incorporate PGx information as it becomes available, yet this position is coupled with a degree of cautiousness and lack of prescriptiveness at the present time, reflecting both scientific and wider clinical and social uncertainties. This ambiguity is demonstrated by differences in the extent to which testing is recommended or whether clinicians are merely informed about genotype-phenotype relationships and test availability. Thus in most cases to date, information is provided in the label but tests are not recommended or mandatory.

From a practical point of view, this broadening of the role of PGx will also mean that regulators will have to manage a massive increase in data, on a much wider range of treatments. At present, it is unclear how regulators might use PGx data. As noted above, indications are that gene expression data, as well as the currently more common CYP450 data (both of which affect drug response) are featuring in 'voluntary data submissions' and in formal clinical trial applications (INDs) and/or MAA/NDA submissions. However, both the technology and more importantly its interpretation are at an early stage. Technologies are available to survey the expression levels and variability in genes involved in drug response but the question for both industry and regulators is how to use them. At present, the FDA does not always have the understanding or expertise to interpret such data, although, as discussed previously, it is taking steps towards resolving this by encouraging voluntary data submission and establishing the IPRG.

3.5 PGx and diagnostic tests

Diagnostics will be key to the deployment of PGx in both clinical trials and clinical practice. The primary interest of regulators is the safety and accuracy of genetic tests. In theory, PGx tests should be 100% sensitive (true positives) and 100% specific (true negatives), but in practice they will be much lower than this on both fronts. The regulatory regime will also be complicated by the fact that the therapeutic agent and

[98] The label history for any FDA-approved drug can be found at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ (accessed 06/05/06). The current label for irinotecan is at: http://www.fda.gov/cder/foi/label/2005/020571s024,027,028lbl.pdf (accessed 06/05/06).

[99] FDA (2005), FDA Clears Genetic Test That Advances Personalized Medicine Test Helps Determine Safety of Drug Therapy, FDA News, 22 August, available at http://www.fda.gov/bbs/topics/NEWS/2005/NEW01220.html. In April 2005, DxS announced the development and validation of an assay for the UGT1A1*28 allele. See also: McLeod, H. and Watters, J. W. (2004), Irinotecan pharmacogenetics: is it time to intervene? Journal of Clinical Oncology 22(8):1356-1359.

diagnostic test are not always regulated by the same agency in different countries. Also, there is little regulatory harmonisation in the area of diagnostics with different regulatory structures operating in different parts of the world. In the UK, for example, medicines and in vitro diagnostic tests have historically been evaluated and regulated by distinct agencies that have different regulatory procedures and domains of operation. However, this arrangement changed in April 2003 with the merger of the Medicines Control Agency (MCA) and Medical Devices Agency (MDA) to create the Medicines and Healthcare products Regulatory Agency (MHRA). In the USA, the Food and Drug Administration (FDA) has been responsible for marketed products of both types for many years, and operates a much tighter diagnostics/devices regime. In Japan, the independent administrative organisation, the Pharmaceuticals and Medical Devices Agency, started operating on 1 April 2004, again bringing together medicines and devices. While there is some pressure for a EU-wide devices agency akin to the EMEA, the UK government is opposed to such a development at present.

Historically, diagnostics have been subject to less scrutiny than medicinal products, and this remains the case today, with responsibility for approval often residing with a different agency than that for drugs.[100] As noted above, medicines are now effectively harmonised across Europe, and to a large extent in other regions. In contrast, in the EU responsibility for diagnostic products remains with national agencies, although adoption of the European In Vitro Diagnostics directive will bring about greater coordination.[101] In the United States, tests developed by commercial labs — so-called 'home-brew' tests — are exempt from regulations that apply to marketed tests, although this dual approach to diagnostics review in the US continues to be a subject of debate. The expectation is that controls on lab-developed tests in general may be tightened in the future.[102] The extent to which PGx testing will rely on commercial labs and proprietary 'home brew' tests, or upon marketed drug/test combinations developed by pharma and/or diagnostics companies is unclear. The most likely scenario is that there will be a mix of the two modes depending on the therapeutic area, test sophistication and commercial factors, although the prominence of the former over time will also depend upon future decisions with regard to regulatory policy towards 'in-house' tests.

As shown in Chapter 2, a variety of development models are emerging for PGx tests. Large pharma companies themselves may develop tests, particularly if they are already major players in the diagnostics market through wholly owned diagnostics divisions, such as Roche, Abbott and Johnson and Johnson. In contrast, many are likely to be developed by dedicated diagnostics companies, whilst others may emerge via (collaborative ventures with) genomics firms.

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[100] Jeffreys, D.B. (2001), Comparison of the regulatory controls for medical devices and medicinal products, *International Journal of Pharmaceutical Medicine* 15:125-130; Mansfield, E., O'Leary, T.J. and Gutman, S. I. (2004), Food and Drug Administration Regulation of in Vitro Diagnostic Devices, *Journal of Molecular Diagnostics,* 7(1):2-7.

[101] Jeffreys, D.B. (2003), An overview of recent developments in the European Regulation of Medicine/Medical Device Combination Products, *Drug Information Journal*, 37:39-43; European Commission (1998), The in vitro diagnostic medical devices directive (98/79/EC). *Official Journal European Communities* L331/1 (27 October).

[102] Interviews with senior staff member at FDA Center for Diagnostics and Radiological Health (CDRH), and with US diagnostics industry associations, Washington DC., April 2005, for Lewis, G., Pharmacogenomics, diagnostic tests and clinician acceptance, UK ESRC Science in Society programme, 2004-2006. Details at: http://www.york.ac.uk/res/pgx.

As noted in the discussion of labelling, regulatory agencies will have to decide whether to make a PGx test compulsory, and if so under what conditions, or to allow it to be voluntary and at the discretion of the medical practitioner. This area is made more complex by the availability of diagnostic tests direct to patients, either over-the-counter (OTC) or via the Internet. Both doctors and regulators will also confront the issue of patient-sourced genetic information in the future and the impact that greater patient involvement in treatment decisions may have in relation to PGx.

The introduction of routine genetic testing as a fundamental part of PGx prescribing confronts regulators with a number of issues. Regulators will need to examine at least four aspects of the diagnostic test: analytic validity, clinical validity, clinical utility (does the test really matter in practice), and ethical, legal and social issues generated by the test. The requirement to ensure the analytical validity of a PGx test; and for the test sponsor to demonstrate clinical validity, which in Europe means evidence of performance, is now required by the EU's IVD Directive. However, the crucial issue for adoption is clinical utility – whether use provides real patient benefit compared to other action.

3.6 Ethical issues raised by clinical development and use of PGx

Ethical issues relating to the use of patient DNA samples obtained during clinical trials by drug firms have been a major source of debate, and in anticipation of statutory legislation, a number of major pharmaceutical companies, such as Roche, have developed local regimes for the management of data that they present as "ensuring the optimal protection of the privacy of trial participants".[103] In Europe, there appears to be a steady tightening of the trials regime that might well conflict with the interests of commercial organisations to which it is mostly directed. For example, the EU Directive on Good Clinical Practice requires all trials at Phase I (and beyond) to be formally approved by the appropriate regulatory authority in addition to the present ethics committee approval.[104] However, there are questions about the extent to which ethics committees themselves are 'up to speed' on the implications of trials that are designed around a PGx approach.

In addition, there is the question of whether doctors should be compelled to offer a test prior to prescription if one is available. And will patients be obliged to take a PGx test in order to receive treatment?[105] These issues overlap with both formal regulatory concerns and professional standards and autonomy, and connect with wider public policy on genetic testing and privacy. There must also be a mechanism for updating the labelling of both medicine and diagnostics as more knowledge becomes available.

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[103] Roche (2002), The role of ethics in clinical trials, *Roche Facets* 18:3, available at http://www.roche.com/pages/facets/18/ethicstriale (accessed 15 November 2002).

[104] European Parliament and Council Directive on Clinical Trials, 2001/20/EC on the approximation of the laws, regulations and administrative provisions of Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. *Official Journal of the European Communities* (L121, pp34-44) 1 May 2001.

[105] Pirmohamed, M. and Lewis, G. (2004), Implications of Pharmacogenetics and Pharmacogenomics for Drug Development and Health Care, in Mossialis E., Mrazak, M. and Walley, T. (eds), *Regulating Pharmaceuticals in Europe: Striving for Efficiency, Equity and Quality* (European Observatory for Health Systems and Policies/WHO Regional Office for Europe), Open University Press: Maidenhead.

These practical and ethical questions are linked with other issues confronting regulators, such as PGx testing and quality assurance systems. How they will ensure that patient risks are properly listed and who will have access to this information? For example, will all hospitals and GPs have access to PGx data in order to make prescribing decisions, or will such information be restricted to 'centres of excellence' or specialist clinics? PGx-directed prescribing is already used to some extent in cancer treatment, but proponents envisage much broader use including incorporation into primary care. Currently, most diagnostic tests are carried out by hospitals or commercial laboratories, often using 'home brew' tests, the latter situation being particularly prevalent in the US context. As noted above, 'home brew' tests are generally not regulated to the same extent as other diagnostic products and this would be a key area where test validation would be crucial.[106] According to some observers, the introduction of PGx testing is also likely to see an increase in point of care (POC) testing and even desktop machines located in doctors surgeries. Such developments will also require careful consideration by regulators.

The introduction of PGx into clinical practice will also require increased levels of genetics education and understanding. Decisions taken by regulators with regard to labelling and test requirements will have to take into account doctors' knowledge of genetics and their understanding of PGx, as well as the level of provision of the required testing capacity.[107] It may also require new ways of securing information from patients through post-marketing studies.[108] Genomics has until now been characterised by large amounts of data from relatively small number of people with rare diseases. However, the application of genotype-specific medications in daily clinical practice will bring new complexities. Together, these challenges may justify re-examining present assessment procedures, with a shift towards 'provisional approval' and greater demand for post marketing studies. As Arlington and Peakman comment: "Why not replace [marketing approval] with a living document – a continuous record that includes post marketing studies, adverse event reports and feedback for patients. After all they are the industry's ultimate customers".[109]

The routine banking of DNA samples in clinical trials by pharmaceutical companies and other research organisations provides opportunities for secondary use of such samples and refinement of the science.[110] Besides future drug development, other potential uses include improved pharmacovigilance and post-marketing risk/benefit analysis, and improvements to PGx tests. This is a difficult area to negotiate because of informed consent requirements and the need to obtain renewed consent depending on the planned research. Regulators must also take into account wider societal perceptions and concerns about genetic banking generally and commercial (proprietary) use and ownership of samples. Another policy issue that may impinge on regulatory concerns and approval procedures is that relating to incorrect prescription

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[106] Mansfield, E., O'Leary, T. J. and Gutman, S. I. (2004), Food and Drug Administration Regulation of in Vitro Diagnostic Devices, *Journal of Molecular Diagnostics,* 7(1):2-7.

[107] Frueh, F. and Gutwitz, D. (2004), From pharmacogenetics to personalized medicine: a vital need for educating health professionals and the community, *Pharmacogenomics* 5(5):571-579.

[108] Roses, A. D. (2004), Pharmacogenetics and drug development: The path to safer and more effective drugs, *Nature Reviews Genetics,* 5:645-656.

[109] Arlington, S. and Peakman, T. (2002), Custodians in Crisis: the Impact of Genomics on Regulation, *Drug Discovery World,* Winter 2001-2002, p4.

[110] Lewis, G. (2004), Tissue collection and the pharmaceutical industry: investigating corporate biobanks, in Tutton, R. and Corrigan, O. (eds), *Genetic Databases: socio-ethical issues in the collection and use of DNA,Routledge:London,* pp181-202.

and professional liability, whether the result is failure to reduce ADRs or improve efficacy.

3.7 Conclusion

Both national and regional regulatory agencies, and international bodies such as the ICH and WHO, confront a range of issues in relation to PGx. These include the technical classification and management of PGx through the development of new guidelines, its safe and effective implementation within the drug development and delivery process (especially with regard to post-marketing surveillance), broader questions about information provision, training, and the ethical implications of PGx-based treatment for specific patient populations.

Industry and regulators have both sought to create new institutional processes, such as voluntary data submission and discussion of concepts like 'provisional approval' to handle the uncertainties surrounding PGx technology. To many observers, the FDA in particular is leading the way on encouraging PGx innovation – a novel and possibly ambiguous position for a regulatory agency to occupy. At the same time there is a delicate balancing act to play here between such accommodations and encouragements, and the proper review of the safety and efficacy of PGx development. In the medium to long term there may be significant changes in the ways in which clinical trials data are produced and reviewed, while the relation between trial results, generalisability to stratified patient populations, and the position of 'orphan patients' is likely to prove particularly problematic. Such issues are not restricted to new drugs and diagnostic devices developed within industry but relate also to generic drugs already used widely in the clinical setting. Here, regulators will have to work closely with other health agencies to assist in guiding the review of widely used, off-patent drugs, such as warfarin. In turn, such advice will be drawn upon to help shape procurement and professional decision-making within the clinic itself. Regulation is, of course, part of a wider process of governance and health policy. These issues will be addressed in Chapter 5, but first the issues raises by the potential adoption and use of PGx tests in the clinic will be considered.

Chapter 4
The adoption of PGx in clinical practice

4.1 Introduction

In this section new data are presented from a study of UK practitioners' views on the adoption of PGx into clinical practice. Very little is known about this, as PGx testing is not currently in widespread clinical use. It is practitioners who can illuminate the potential drivers and barriers facing introduction of PGx into practice. The study was based on a series of case studies of established drugs that are widely cited as being possible candidates for the introduction of PGx testing. Qualitative interviews were also undertaken with practitioners to explore the issues surrounding adoption. The potential use of PGx testing in relation to these drugs relates mainly to Options IV and V described in Chapter 1 (pre-prescription testing for safety and efficacy of already licensed medicines).

An in-depth descriptive study of this sort is a necessary first step in identifying the key issues raised by practitioners concerning PGx. This research was small in scale and the design therefore has unavoidable limitations with respect to generalisability. However, the findings provide a starting point to direct thinking and research on the factors that might influence the use of PGx in specific clinical settings and could identify key issues that will have to be addressed if practitioners are to successfully adopt PGx into routine practice.

4.1.1 Pharmacogenetics in principle and practice

In principle, if administered before prescription a genetic test could allow doctors to identify people who are either at risk of reacting adversely to a specific drug or to identify those likely to have a particularly beneficial response. This could make drugs more effective and safer[111] by improving patient care, providing doctors with a valuable decision-making aid and generating useful cost-effectiveness information.

To date, discussions about the practical introduction of pharmacogenetics into clinics have encompassed a wide set of issues.[112] These include questions about effectiveness, such as the 'quality' of the tests (e.g. their sensitivity, specificity and positive/negative predictive values) and their outcome benefits (e.g. the scale of negative effects that might be avoided or the additional value for treatment

[111] Roses, A. (2000), Pharmacogenetics and the practice of medicine, *Nature*, 405:857-865; McCarthy A. (2001), Pharmacogenetics. *British Medical Journal*, 322:1007-1008; Lindpaintner, K. (2002), Pharmacogenetics and the future of medical practice, *British Journal of Clinical Pharmacology*, 54:221-230.

[112] Barash, C.I. (2001), Role of the laboratory in leveraging adoption of pharmacogenetics. *Amercian Clinical Laboratory*, September 2001 35-37; Goldstein, D. B. (2003), Pharmacogenetics in the Laboratory and the Clinic *New England Journal of Medicine*, 348:553-556; Holtzman, N. A. (2003), Clinical Utility Pharmacogenetics and Pharmacogenomics, in M.A. Rothstein (Ed), *Pharmacogenomics: social, ethical, and clinical dimensions*, Wiley-Liss: Hoboken N.J.; Melzer, D., Raven, A., Detmer, D. E., Ling, T. and Zimmern, R. (2003), *My Very Own Medicine: What Must I Know? Information Policy for Pharmacogenetics*, University of Cambridge:Cambridge; Omenn, G. and Motulsky, A. (2003),. Integration of Pharmacogenomics into Medical Practice, in Rothstein, M.A. (Ed), *Pharmacogenomics : social, ethical, and clinical dimensions*. Wiley-Liss: Hoboken, NJ; Shah, J. (2004), Criteria influencing the clinical uptake of pharmacogenomic strategies. *British Medical Journal*, 328:1482-1486.

objectives). Other factors relate directly to the context of practice, such as the existence of alternative treatments or other testing methods, the size of a patient population, the degree of dosage adjustment and whether the therapy is for unusual or non-acute conditions. A further set of issues relate to working practices, for example the ability of clinicians to understand and interpret genetic test information and use it in situations where there are time and workload pressures. In addition, there have been separate discussions of the health economic and ethical implications of pharmacogenetics.[113]

The range of topics covered in these discussions illustrates a key point: decisions relating to the usefulness, benefits and drawbacks of pharmacogenetics in clinical practice involve multiple, overlapping and potentially competing factors. These include not only questions about effectiveness and resources, but also a broader range of matters relating to the context of care, professional work practices and service delivery. This study explores these issues further by gathering data from practitioners who might be expected to integrate PGx into day-to-day practice.

4.1.2 Study design and methodology

One of the main aims of the research was to identify practitioners' views about the drivers and barriers facing the use of pharmacogenetics in routine practice. The study focused on four drugs: *clozapine*, *warfarin*, *6-mercaptopurine* and *isoniazid*. These drugs were chosen because patients are known to have variability in their responses, some part of which has been shown to be associated with genetic factors. Importantly, they are all in everyday use in the health service and, due to concerns about patient safety, require monitoring regimes. Furthermore, these examples allowed for some variation in disease areas and patterns of use, as they came from a range of clinical contexts. *Clozapine* is used to treat schizophrenia, *warfarin* is used to treat thromboembolic disorders, *6-mercaptopurine* is used to treat acute lymphobalstic leukaemia and *isoniazid* is used to treat tuberculosis.

Qualitative (semi-structured) interviews with practitioners were used to gather the necessary in-depth information. Relevant literature was first gathered about the drugs in question, such as prescribing guidelines and highly cited scientific articles. This provided information on the disease area; the drug's history, characteristics and usage; the current prescribing practice including governance and monitoring regimes; and the potential influence of pharmacogenetics. The interview schedule was then designed to gather information about current routine practice, and elicit views and opinions about the likely drivers and barriers to change.

A cohort of practitioners (mainly from two hospitals in the East Midlands in the UK) were selected, approached and interviewed using a snowball sampling strategy.[114] The interviewees were mainly clinicians, but also included specialist nurses,

[113] Veenstra, D. L., Higashi, M. K. and Phillips, K. A. (2000), Assessing the cost-effectiveness of pharmacogenomics, *Pharmaceutical-Sciences*, 2(3): Article 29; Danzon, P. and Towse, A. (2002), The economics of gene therapy and of pharmacogenetics, *Value in Health*, 5:5-13; Rothstein, M.A. and Epps, P.G. (2001), Ethical and legal implications of Pharmacogenomics. *Nature Reviews Genetics*, 2:228-231; Nuffield Council of Bioethics (2003), *Pharmacogenetics: Ethical Issues,* Nuffield Council of Bioethics: London.

[114] Initially we identified and contacted local Clinical Directors who were responsible for the prescribing of the case study drugs. They were asked to recommend local practitioners, who were subsequently invited to take part in a one-hour interview. Those who agreed to interview we also asked to recommend other colleagues who were also invited to take part.

pharmacists and clinical scientists. The majority were not pharmacogenetic specialists, but were instead asked to discuss, in principle, the kinds of issues that may arise in their practice. A total of twenty-one interviews were completed. Given the small sample size and the regional bias, this research is best seen as a purely descriptive study that identifies key issues for further investigation.

4.2 Case study 1: Clozapine

4.2.1 The drug and its treatment context

Clozapine[115] is an 'atypical' antipsychotic[116], indicated in cases of treatment resistant schizophrenia.[117] Treatment resistance is defined when patients prove to be non-responsive to, or intolerant of, at least two other neuroleptics. There are approximately 200,000 diagnosed schizophrenics in the UK.[118] NICE estimates that it is an illness that affects about 1 in every 100 people at some time in their lives, having a serious impact on life experience and opportunities.[119] While ~20% of suffers will only experience a single attack, others have prolonged problems, with 70% of people having at least two 'acute' episodes. Following treatment most patients tend to improve or recover, although only about 25% of people recover completely. Those who experience persistent symptoms require intensive support and treatment.

Pharmacological interventions are usually required at each stage of treatment, with atypical medications being increasingly favoured.[120] Although conventional neuroleptics can be effective, patients can develop resistance to treatment and approximately 15% of patients experience profound side effects when on these medicines.[121] Clozapine has proved a very effective treatment in up to 30-50% of resistant patients and 80% of those who suffer from intolerable adverse events.[122] There are, however, concerns about safety. In light of these concerns, clozapine was not approved for clinical use in the USA between 1974-1990.[123]

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[115] Sold under the trade name Clozaril by Novartis Pharmaceuticals.

[116] The antipsychotic, or 'neuroleptic', drug class can be divided into 'conventional' and 'atypical'.

[117] Clozapine Study Group (1993), The safety and efficacy of clozapine in severe treatment-resistant schizophrenic patients in U.K., *British Journal of Psychiatry*, 163:150-154; Kerwin, J. R. and Taylor, D. (1996), New antipsychotics a review of their current status and clinical potential, *Drugs*, 6: 71-82.

[118] Clozapine Summary Sheet, MTRAC, Department of Medicines Management (Oct 1995), ss95/09. available at www.keele.ac.uk/depts/mm/MTRAC/ProductInfo/summaries/C/CLOZAPINEs.html, (accessed 16/12/02).

[119] National Institute of Clinical Excellence (2002) Schizophrenia. Core interventions in the treatment and management of schizophrenia in primary and secondary care NICE:London

[120] The NICE (2002) guidelines divide the treatment and management of schizophrenia into three stages: initiation, acute phase and promoting recovery. They recommend that atypical antipsychotics are prescribed for all newly diagnosed cases, and existing cases are transferred where it is useful.

[121] Johnstone, E. C. (1995), Schizophrenia: Problems in Clinical Practice, *Lancet* 345:557-562; Farmer, A.E. and Blewett, A. (1993), Drug Treatment of Resistant Schizophrenia. Limitations and Recommendations. *Drugs*, 43:374-383. References taken from Clozapine Summary Sheet, MTRAC (Midlands Therapeutic Review Advisory Committee), Department of Medicines Management (Oct 1995), ss95/09, available at www.keele.ac.uk/depts/mm/MTRAC/ProductInfo/summaries/C/CLOZAPINEs.html (accessed 16/12/02).

[122] Coffey, I. (1994), Options for the Treatment of Negative Symptoms of Schizophrenia. *CNS Drugs*, 1: 107-118.

[123] Iqbal, M.M., Rahman, A., Husain, Z., Mahmud, S.Z., Ryan, W.G. and Feldman, J.M. (2003), Clozapine: A Clinical Review of Adverse Effects and Management. *Annals of Clinical Psychiatry*, 15(1): 33-48.

Clozapine has side effects that can occur in ~70% of cases; these are serious enough to warrant withdrawal of treatment in ~6% of cases. The major concern is the haematological (blood) disorder neutropenia, particularly its more severe form agranulocytosis. These can impair the functioning of the immune system and leave a patient open to infection. Problems usually occur during the first 18 weeks of treatment. Patients with neutropenia are generally asymptomatic, while those with agranulocytosis may show signs of infection. Once identified, problems can be clinically managed by the withdrawal of clozapine and appropriate observation to minimise the risk of potentially fatal infections. However, as it is not possible to predict who may be 'at risk', all patients are monitored by regular blood tests.

Accordingly, Novartis Pharmaceuticals UK, the UK manufacturer of Clozapine, established the Clozaril Patient Monitoring Service (CPMS) in 1990. By ensuring that regular blood tests are undertaken, the service aims to prevent 'at risk' patients being prescribed clozapine. Physicians prescribing the drug must register themselves (and a pharmacist) with the CPMS. The physician must then enrol each patient into the CPMS prior to treatment. A centralised laboratory service analyses blood samples and the drug can only be prescribed on receipt of a satisfactory result. If the test results show that neutrophil levels have fallen below a defined point, the drug should be withdrawn. However, such withdrawal can result in relapse.

4.2.2 Why PGx?

With respect to drug response, studies have explored the impact of genes related to drug metabolism, drug receptors and neurotransmitter enzymes.[124] Research findings on the influence of polymorphism in neurotransmitter-receptor-related genes have been claimed to be the basis of a genetic test that could enhance prescribing.[125] However, it should be noted at the outset that such tests are focused on identifying 'good responders', not identifying those who may be at risk of the types of ADR noted above. The development of a pharmacogenetic test for good responders is not designed to replace the monitoring system that tries to ensure patient safety.

Nevertheless, a key value of a pharmacogenetic test that could identify good responders would be avoiding the potentially harmful, expensive and unnecessary treatment in poor or non-responders. A person who may be genetically predisposed to be a poor or non-responder to clozapine is unlikely to get a therapeutic benefit, while enduring an increased risk of a serious ADR, an unnecessary side effects burden and a pharmacologically untreated psychosis. Identifying good responders could also be valuable for the physician and consequently improve patient experience, and could have benefits for the health service. In particular, pharmacogenetic information could be helpful for the physician in their 'go/no-go' decision-making. This may be their initial decision to put the patient on the drug, or when to cease the therapy if the patient has had no obvious benefit (depending on the 'strength' of evidence that is available).

Furthermore, in comparison with alternative options, clozapine is an expensive drug that also incurs costs in relation to the monitoring system. Avoiding unnecessary

[124] Mancama, D., Arranz, M. J. and Kerwin, R. W. (2002), Genetic predictors of therapeutic response to clozapine - Current status of research, *CNS Drugs*, 16: 317-324.
[125] Arranz, M. J., Munro. J., Birkett, J., Bolonna, A., Mancama, D., Sodhi, M., Lesch, K.P., Meyer, J.F. W., Sham P., Collier D. A., Murray R. M. and Kerwin, R. W. (2000). Pharmacogenetic prediction of clozapine response, *Lancet*, 355: 1615-1616.

prescribing could therefore help reduce these costs. In addition, there are the opportunity costs of spending limited resources on treatments that do not work. Identifying good responders has the potential to save unnecessary cost and enable the re-direction of resources. Pharmacogenetics might also be useful to the patient in another way, by enabling their involvement in prescribing. Where it is appropriate and possible, patients are increasingly told of the different side effects burdens of drugs and asked to choose their preference. Pharmacogenetic information may therefore help inform patients' decisions about drug choice.

4.2.3 Barriers facing clinical adoption

Three main issues were reported during the interviews as the main barriers facing the clinical adoption of a pharmacogenetic test for use alongside clozapine:

The first theme was *complexity*. This included the inherent difficulties of accurately diagnosing and treating schizophrenia, and particularly treatment resistant forms of the condition. Due to the nature of schizophrenia, the scales used to define and assess the disease are clinical assessments of personal and social functioning rather than biological tests. While these scales have scientific validity and professional credibility, the lack of clear biological endpoints may prove problematic when it comes to validating a test that measures treatment response.

One respondent argued that the utility of any test would rest on its specificity, in other words its ability to give near categorical answers. However, the complexities in genetics mean that PGx tests will be unlikely to give a categorical yes or no decision for treatment. Most interview respondents in the study viewed a pharmacogenetic test as a useful 'prescribing aid' alongside the existing use of clinical factors in decision-making. [126] For example, a proponent of a planned pharmacogenetic test in development commented that, even though a test had a very high degree of accuracy[127], it was 'not accurate enough to deny someone treatment'. However, they argued that the information would be useful in decisions about when to withdraw treatment.

The second theme was *evidence*. The clinicians we talked to were unconvinced about the immediate prospect of using a pharmacogenetic test alongside clozapine. One respondent suggested that there was a 'credibility gap' between being able to identify the gene and being able to predict drug response accurately. They argued that 'every year some marker or other is associated with treatment response' and that the studies that have been done were too small and needed replication in large randomised trials. However, concerns were voiced about the practicalities and ethics of conducting such trials in mental health settings. The ethical concerns included the inclusion of a population which might unnecessarily suffer side effects and the difficulty of gaining informed consent, while the practical issues related to patient recruitment and the giving of biological samples.

The final theme related to *current practice*. On a practical note, patients deemed 'genetically suitable' for clozapine may remain unsuitable for the same reasons that currently limit those who can be given the drug, such as the lack of personal/social stability or an unwillingness on the part of the patient to have regular blood tests.

[126] As one respondent expressed it: "an addition to the armamentarium".
[127] They claimed as high as an 80-90% association between genetic markers and drug response.

Finally, there was a concern about the time burden that pharmacogenetics might add to the already cumbersome process of prescribing this drug.

4.2.4 Summary

A PGx test for good responders to clozapine might offer some clear advantages for practitioners (by informing their prescribing and treatment decisions) and the health service (by avoiding unnecessary prescribing and resource burdens related to unnecessary ADRs, and enabling the redirection of resources). If a patient is identified as a good responder, this might also translate into improved experience in a number of additional ways (by informing their decisions about drug choice and though the avoidance of unnecessary risks of ADRs, unnecessary side effects burdens and having a pharmacologically untreated psychosis). However, a number of issues were identified as barriers facing PGx in this context. There were concerns about the evidence base, the impact on working practice and resource burdens, and specific doubts about the contribution that a PGx test result might make to prescribing decisions, particularly when other clinical, personal or social factors might have a more direct impact.

4.3 Case study 2: Warfarin

4.3.1 The drug and its treatment context

Warfarin is a widely used oral anticoagulant (that is, it prevents clots from forming in blood). It is indicated for a variety of conditions, including problems that involve blood clots (such as atrial fibrillation/stroke, deep vein thrombosis and pulmonary embolus), and is given following heart attacks and some heart-valve implants.[128] Depending on the circumstances and the indication, it is a first in-line therapy. It is used both as a treatment and a prophylaxis over an extended time period. Warfarin is increasingly prescribed for atrial fibrillation through primary care. Overall, warfarin is currently prescribed to more than 600,000 patients in the UK or around 1% of the population.[129]

Warfarin's mode of action (preventing clots) means that patients are exposed to an increased risk of a potentially life threatening haemorrhage (heavy bleeding). The drug requires active management, first to establish the required dose, and then to maintain treatment at a level that ensures a therapeutic benefit without endangering the patient. This requires an extensive system of monitoring using frequent, routinised blood tests. The tests measure the time it takes for a patient's blood to clot; this 'prothrombin time' is called an INR (international normalised ratio).

[128] British Committee for Standards in Haematology (2006) Guidelines on oral anticoagulation (warfarin): third edition - 2005 update. *British Journal of Haematolog,y* 132; 277-285.

[129] Exact figures for warfarin use are hard to establish. Pirmohamed et al claim approx. 1% of the UK population or about 600,000 individuals. Some 0.5m patients receive anti-coagulation treatment each year according to Roche. http://www.rocheuk.com/html/health/Anticoagulation.asp (accessed 10/07/06). The BCSH (1998) guidelines note that patient numbers in anticoagulation clinics have more than doubled in the 5 years up to 1998. For number of prescriptions, see http://www.ic.nhs.uk/pubs/prescostanalysis2005 (accessed 10/07/06).

Given the serious nature of the conditions for which anticoagulation therapy is used, it will usually begin in secondary care.[130] Normally patients are given a three-day 'loading dose' of warfarin, preferably after a 'baseline INR' has been established. Ideally, on the fourth day a patient's INR levels are checked and adjustments made to their dose. Once patients are stable, it may be possible to pass them onto their GP. Subsequent tests allow dosages to be adjusted or stopped in order to maintain therapeutic benefits. Treatment stops after patients have been taking the drug for the prescribed period.

It is important to note that a number of interview respondents in the case study reported that warfarin is a difficult drug to manage. Firstly, achieving and maintaining a stable, effective dose can be difficult because INRs can be affected by a host of 'environmental' factors including diet (e.g. foods with high levels of vitamin K, alcohol consumption), the co-administration of other drugs (e.g. antibiotics) and the patient's age. Secondly, the dose adjustments can present difficulties with respect to patient compliance/understanding. Thirdly, prescribing and monitoring regimes are not standardised across the UK (although there are commonalties, especially in prescribing). Finally, warfarin prescribing and monitoring is a major undertaking that requires interaction between a host of professionals, such as clinicians (including haematologists, cardiologists, surgeons and general practitioners), nurses (including specialist anticoagulant and DVT nurses) and laboratory staff.

4.3.2 Why PGx?

The Cytochrome P450 system, a complex of enzymes mainly found in the liver, is involved in the processing of drugs through the body. In particular, the CYP2C9 enzyme is responsible for the metabolism of warfarin, as well as a number of commonly used medicines. There are natural genetic variations in this enzyme between individuals.[131]

Genetic variance has been 'strongly associated' with a 'low warfarin dose requirement', so that an individual requiring a low dose is six times more likely to have one or more variant alleles.[132] Furthermore, another study found that bleeding complications were about three-fold higher in carriers of these variants.[133] CYP2C9 genotyping may identify a subgroup of patients who have difficulty at induction of warfarin therapy and are potentially at a higher risk of bleeding complications.

PGx testing could have clinical benefits because it may help to avoid ADRs. Also, 'tailored' prescribing could help to minimise other problems associated with the difficult induction of warfarin therapy, such as delayed discharge from hospital, multiple visits to the anti-coagulant clinic and the need for further investigations.

The potential for introducing genotyping into clinical practice to help reduce problems associated with treatment with warfarin is now being explored by the UK Department

[130] However, it should be noted that the drug is increasingly used in primary care by practice nurses and the pattern of delivery varies across the UK with some services quite centralised through hospital clinics whilst others more localised.
[131] Known as the *2 and *3 alleles, that differ from the wild type *1.
[132] Aithal, G.P., Day C.,P., Kesteven P.J.L. and Daly, A.K. (1999), Association of polymorphisms in the cytochrome p450 CYP2C9 with warfarin dose requirement and risk of bleeding complications, *The Lancet*, 353:717-19.
[133] Margaglione et al. (2000), Genetic Modulation of Oral Anticoagulation with warfarin, *Thromb Haemost*, 84:775-8.

of Health.[134] Some interview respondents reported that pre-prescription genotyping may provide an improvement on the current 'best guess' prescribing by improving the 'standard' regime, e.g. to modify doses down for those who may be at heightened risk of a bleed, or get those who need higher doses onto them more quickly. They also reported that it might be useful in particular groups, for example, identifying a metabolism problem among patients who are not anti-coagulated despite being given high doses (to distinguish them from people who simply have poor compliance).

4.3.3 Barriers facing clinical adoption

The key question for clinicians was the value of pharmacogenetic information among the host of other influences that affect the achievement of a correct dose. There was a range of responses about the potential for pharmacogenetics to add clarity. These spanned from 'it can be worse than useless', to it can be 'a useful part of the jigsaw'. Respondents were concerned about the selection and implications of pharmacogenetic information. As one person expressed it, "it's not just getting the genetic information, it's knowing which bit to use", while another lamented that 'the test can be very specific, but what does it mean?'

Furthermore, pharmacogenetics might introduce new layers of complexity. Firstly, the possession of a particular allele does not determine a certain response in all cases, but rather increases the *chance* of having a certain response. Secondly, homozygocity/heterozygocity further blurs the relationship with clinical outcomes. Accordingly, the assignment of patients into 'categorical' levels of response might be difficult. Such difficulties could raise questions about what is a clinically acceptable level of mis-grouped patients.

Two kinds of evidence were also seen to be lacking. The first was medical, such as an RCT to prove the clinical value of using a pharmacogenetic test. The second related to health economics, such as the number of patients that would benefit from the use of pharmacogenetics. As large numbers of people are prescribed this relatively cheap drug, questions were raised about the cost/benefit of universal testing, against using more targeted tests for 'at risk' or 'difficult to treat' groups.

Even if evidence of the effectiveness and cost-effectiveness were forthcoming, widespread adoption would require the winning over of professional sceptics. The potential to use pharmacogenetics has been debated within haematology for a number of years. It was reported that some professionals felt that, given the range of factors that can affect drug metabolism, pharmacogenetic information was not as valuable as simply being an astute physician. Others, however, argued that the utility of pharmacogenetics would have to be judged in the context of a clinical examination in tandem with other information.

Utility was also questioned in respect to specific indications. A challenge was made to the view that it was necessarily urgent to establish all patients on the right dose. For example, it was argued that there is little urgency in getting patients with atrial fibrillation onto higher doses. In such cases, there might only be marginal clinical benefit to pre-prescription genotyping.

[134] Pirmohamed, M. et al. (2006), Variability in response to warfarin: a prospective analysis of pharmacogenetic and environmental factors, available at, http://www.genres.org.uk/prp/projectsliverpool2.htm.

Work practice issues that were raised included the increased time that testing and prescribing might take in an already busy clinic, the increased workload on the laboratory and the capabilities of local service provisions. A pharmacogenetic test might do little to help to reduce costs unless it could replace the current systems of blood monitoring that exist to ensure safety and efficacy. This appeared to be far from certain.

Finally, there was awareness that an alternative drug, ximelagatran, might replace warfarin in the longer term. However, it was acknowledged that some people would remain on warfarin even if this new drug does become part of clinical practice.

4.3.4 Summary

A PGx test for warfarin that leads to the prevention of ADRs could offer obvious advantages in outcomes for practitioners and patients, and potential cost savings for providers. Also, given the difficulties of managing warfarin, tailoring prescribing and distinguishing compliance problems from metabolism problems could contribute to alleviating some service delivery and patient care issues. However, an issue that was again identified as a barrier facing PGx was the relative value of PGx information and its actual usefulness in practice. In this context, the issue of value related to the multiple (biological and environmental) influences on drug metabolism. Other barriers were a lack of convincing evidence on effectiveness and cost-effectiveness, concerns about increasing time and workload burdens, the difficulties of introducing a new drug into practice, and an ethical question about the potential to 'mis-group' patients.

4.4 Case study 3: Thiopurines - 6 mercaptopurine (6-MP) and azathioprine

4.4.1 The drugs and treatment contexts

Thiopurines are immunosuppressants (i.e. they inhibit the activity of the immune system). In this case study we discuss the potential use of PGx testing in relation to two of the most commonly used of these medicines, 6-mercaptopurine (6-MP) and azathioprine.

6-MP is used to treat common childhood acute lymphoblastic leukaemia (ALL).[135] It is a component of 'maintenance treatment', an extended period of chemotherapy that usually includes a daily oral thiopurine. 6-MP is administered as part of an ongoing Medical Research Council (MRC) clinical trial, meaning that prescribing is defined by the protocols of the study. [136] 6-MP's intended therapeutic effect is to reduce the ability of bone marrow to produce blood cells (termed 'myelosuppression'), which helps to enable the elimination of any remaining cancer cells. However, patients with a compromised immune system are at risk of infection, bleeding and anaemia, which may be potentially life threatening. Treatment is thus a process of clinically managing risks and benefits. Thiopurine therapy is given at the highest tolerable dose until it approaches the threshold of being potentially problematic, when treatment is stopped for a short time. Regular blood tests are used to monitor the degree of

[135] This is a disease that is primarily suffered by children (~85%). 75% of children with ALL enjoy disease-free survival.
[136] This trial is comparing two types of treatment for ALL, one using 6-MP and another using 6-thioguanine.

myelosuppression, allowing the consultant to manipulate dosage to gain the best possible effect while avoiding adverse drug reactions.

Azathioprine is a pro-drug of 6-MP. Its action as an immuno-suppressant has proved useful to physicians who want to manipulate the dosage of potentially harmful corticosteroids that are used to treat a number of conditions. It is usually used when corticosteroid therapy alone provides inadequate control. Azathioprine is used in a range of disease areas and treatments, some of which are unlicensed. For example it may be given to patients with auto-immune conditions, such as rheumatoid arthritis. It is used in some inflammatory diseases, for example, in gastroenterology (GE) for the treatment of inflammatory bowel diseases (IBD) such as 'unresponsive or chronically active' Crohn's Disease. In dermatology it can be prescribed to patients with eczema and psoriasis 'who have failed to respond to conventional treatment', particularly 'severe refractory eczema'. It is also used in some pulmonary disorders, such as asthma and in neurology. Finally, it is licensed for use in organ transplants, as suppression of the immune system can help with the avoidance of rejection. As with 6-MP, 'blood tests and monitoring for signs of myelosuppression are essential in long-term treatment with azathioprine.'

4.4.2 Why PGx?

Patients have varying levels of tolerance to thiopurines, and thus variance in susceptibility to the risks associated with myelosupression. During the process of metabolism thiopurines undergo a process called S-methylation, which is catalysed by the enzyme thiopurine methyltransferase (TPMT). It is the natural genetic variability in the amount of TPMT in our bodies that affects how we react to thiopurine. Three mutations account for the majority of mutant alleles.[137] One patient in every 300 (0.3%) has a severe reaction because of low levels of TMPT. In addition, the 8% of patients who have very high TPMT levels gain little or no therapeutic benefit from thiopurines.

In the case of 6-MP, children with a low level of TMPT are at an increased risk of potentially life threatening myelosuppression and require appropriately lowered doses. Children with particularly high levels of TMPT may get no benefit from normal doses of the drug. Information about TMPT levels is useful before initially administering 6-MP (usually 4 weeks after diagnosis), and when setting the starting dose in the maintenance period.

Similarly with azathiorpine, the risk of myelosuppression is increased in those with a low activity of the enzyme, particularly in the very few individuals who are homozygous for low TPMT activity. Again, such information is useful prior to an initial prescription. While TPMT related ADRs with azathioprine are likely to be low in number, each one can be costly and time consuming. Clinical management can be aided by a pre-prescription test to establish TPMT status.[138] The TPMT enzyme itself

[137] 90% of the population are accounted for by 3 dominant alleles. The most frequently occurring variant allele is a 'double mutant' called TPMT*3A (McLeod, H. L., et. al (1999), Analysis of thiopurine methyltransferase variant alleles in childhood acute lymphoblastic leukaemia, *British Journal of Haematology*, 105(3):696-700.). It should be noted that this relates to TPMT activity 'in white populations' or among 'white Caucasians' (L&L, 409).

[138] It should be noted that TPMT genotype does not predict hepatic toxicity, another possible problem experienced by children treated with 6-MP. There is also debate about secondary malignancies and some suggest that TPMT genotype cannot predict other possible thiopurine related problems. Others claim 'delayed toxicity' (e.g. acute myelogenous leukemia or brain tumors) may in fact be related to TMPT

can be measured using a biochemical test, or a genetic test can be performed.[139] With respect to the use of 6-MP in ALL it has been estimated that around 2,000 tests occur each year in the UK, 6-700 of which could be considered as genetic.

In terms of the genetic test, rapid and inexpensive assays have been developed and the levels of confidence in the genotyping test are relatively high. People who are TMPT deficient can be identified, and thus treatment would be adjusted to avoid life-threatening ADRs. Those with high levels of TPMT, however, are presently not identifiable by genotype.

4.4.3 Barriers facing clinical adoption

A key question has become: what to test in order to get the best clinical information? The gene, the enzyme or even the drug metabolite? Each has benefits and drawbacks. Measuring the metabolite is beneficial because the clinician knows that the drug has actually been taken (poor compliance can confuse the clinical picture of drug response). However, this cannot prevent TMPT related ADRs as measurement occurs after the drug is administered. The gene and enzyme tests can both be undertaken prospectively. Measuring the enzyme may give a clearer indicator of drug response than the gene test, as the latter is an 'in theory' measurement (meaning that there may be a range of factors that intervene between the genotype and phenotype). However, it was argued by one interview respondent that biochemical tests were difficult and time consuming. In this respect genetic tests have an advantage, as they may be open to greater standardisation, technically easier to perform and subject to better quality control. It was reported that evidence was needed about the relative benefits of genotype versus biochemical test.

Also, evidence was needed about the benefits (in terms of patient outcomes) of predicting drug response prior to treatment. Genetic information was described as being one or two steps from the clinical outcome, i.e. drug response. There remain questions about how the links between the genetics and the clinical outcome might translate into information for prescribing decisions. How does genetic variance correlate with levels of drug response in the patient? What is the relationship between different allelic variants and dose requirement? It was also suggested that there are differences in the frequencies of alleles between 'population' groups (described in using racial or ethnic categories) that may affect the accuracy of gene testing.

The drug, the indication and treatment risk-benefit ratio will affect the likely demand for TPMT testing.[140] TPMT testing may be a necessity for every ALL patient, as 6-MP is a first in line therapy. In contrast, azathioprine may not be an essential component of (for example) dermatology therapy, so the drawbacks of its use (including any subsequent need for TPMT testing) will be weighed in the balance against its potential benefits. In other words, with 6MP a TPMT test may be essential despite any costs or

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(McLeod, H.L., Krynetski, E.Y., Relling, M.V. and Evans, W.E. (2000), Genetic polymorphism of thiopurine methyltransferase and its clinical relevance for childhood acute lymphoblastic leukaemia, *Leukemia*, 14(4):567-72.).

[139] In the UK and USA TMPT enzymes tests are already undertaken in public and private laboratories (the Thiopurine Laboratory at Guys is available through NHS charging system, while TMPT testing is routinely used in a number of US hospitals and Prometheus Laboratories in the USA offer commercial test for both enzymes and genes).

[140] "Is 1 in 300 important? […] the answer will be different for different drugs and for different indications" (Dick Weinshilboum speaking at FDA Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Science, October 23, 2002).

uncertainties, but with azathioprine the costs or uncertainties of the TPMT test may count against the drug even being used.

With respect to work practice issues, one respondent suggested that, if it was decided that pharmacogenetic information was socially and ethically sensitive, the concomitant need to get informed consent, and the provision of counselling and interpretation, could place an unreasonable burden on clinicians and clinics. It was also reported that finance had become 'a stumbling block' for clinicians who might otherwise have started using the test. Some respondents questioned the extent to which TPMT testing might be adopted in hospital or NHS clinical genetics laboratories because of financial constraints. It was argued that if pharmacogenetic testing was going to be adopted for TMPT, a strategic decision would be needed to balance the competing interests that exist between and within NHS Trusts. The fact that more than one group of clinicians might find it useful (i.e. all those using azathiorpine and 6MP) was considered to strengthen to argument for the NHS adoption of TPMT tests.

4.4.4 Summary

The PGx test that currently identifies those who have low TPMT levels offers the potential for preventing life-threatening ADRs, a clear benefit for patients and practitioners, and a potential cost savings for providers. If information were forthcoming on the relationship between genotype and dosing, this might also have treatment and resource benefits. However, a key debate exists on whether genotyping is in fact the best method of predictive testing. There were also a number of uncertainties with respect to questions of evidence of the benefits of PGx testing and how these might translate into actual prescribing advice. Finally there were practical factors relating to workload and the logistics of a testing process, and concerns about resources at the level of the clinic and the health service as a whole.

4.5 Case study 4: Isoniazid

4.5.1 The drug and its treatment context

Isoniazid is an antibacterial that is a 'first in line' therapy for tuberculosis (TB). In the UK it is prescribed in hospital and community settings under the supervision of specialist physicians and health professionals (nurse specialists or health visitors).[141] TB persists as a major cause of illness[142] and a threat to public health. After years of decline, the number of cases has recently increased, particularly in some population subgroups.[143] The bacillus, *Mycobacterium tuberculosis*, is transmitted though the air. However, many 'infected' people do not contract the active disease; other factors that contribute to the disease becoming active include immunosuppression and poor living standards. Active TB can be contracted by people of all ages; it usually affects the

[141] UK prescribing procedures are guided by the British Thoracic Society: Joint Tuberculosis Committiee of the British Thoracic Society (1998) Chemotherapy and Management of tuberculosis in the United Kingdom: recommendations ,*Thorax, 54: 536-548*.

[142] In 1998 there were almost 6000 cases in England and Wales.

[143] Rates of the disease in the 'white' classification continue to decline. Rates of the disease in the classifications 'Indian sub-continent' and 'Black Caribbean' are relatively higher, but also show slight decreases. The highest rates are among people in the classification 'Black African', and in people who have arrived in the UK within 5 years prior to 1998, particularly in the classifications 'Black African' and 'Indian sub-continent' (National TB Survey in England and Wales, 1999). The global movement of people is a crucial issue in TB, as between 2002-20, approximately 1000 million people worldwide will be newly infected, 150 million will get sick and 36 million will die (www.who.int).

pulmonary system (lungs), but may also affect other parts of the body. For patients with active TB, isoniazid is often used as one drug in a multi-drug therapy, which is given for at least six months and sometimes longer. Isoniazid may also be used as a prophylaxis. If the regimen is followed, TB treatment is often cheap and effective.

One of isoniazid's potential side effects is the rare, but serious problem of peripheral neuropathy (nerve damage), which can be irreversible. This can be treated, or preventatively addressed, with vitamin B6 (pyridoxine). In the UK, preventative vitamin B6 prescriptions are only advised for those at increased risk. Problems with hepatitis are more common and in rare instances can be fatal; patients are regularly monitored and are asked to report symptoms that may indicate the onset of hepatic toxicity. Patients who suffer isoniazid-related adverse events can have the drug withdrawn and a new treatment regimen introduced.

4.5.2 Why PGx?

The N-Acetylation (NAT) enzyme is involved in the metabolism of isoniazid and genetic variability in NAT can affect the acetylation process.[144] People can be classed as fast or slow acetylators, with slow acetylators being more susceptible to ADRs (as they have higher levels of drugs in the circulation).[145] When given isoniazid, slow acetylators can be prone to vitamin B6 deficiency and consequently suffer peripheral neuropathy. However, susceptibility to peripheral neuropathy is recognised in certain at-risk groups (such as "diabetics, alcoholic or HIV positive patients and those with chronic renal failure or malnutrition"). Some respondents in our study agreed that PGx information might be relevant for pre-emptively identifying patients to prescribe vitamin B6 to avoid the risk of peripheral neuropathy.

4.5.3 Barriers facing clinical adoption

There was great scepticism about using PGx alongside isoniazid for a number of reasons. It was again reported that many factors impinge on prescribing decisions, including age, lifestyle, indication, disease onset, drug-resistance and co-prescribed drugs (both in the regimen and more generally). As one clinician expressed it, genetics can "only tell you so much… a SNP won't change your mind." Evidence about NAT polymorphisms and the links to clinical outcomes was argued to be either outdated, contradictory or simply absent. There were particular demands for clinical evidence to prove pre-prescription genotyping would have a significant advantage and influence health outcomes. At least one interview respondent feared that commercially produced evidence might lack credibility. Probably the greatest barrier will be the lack of perceived utility. Reportedly, an existing phenotypic test for acetylator status is rarely used. Peripheral neuropathy was argued to be uncommon in the normally well-nourished UK patient population and if the problem did occur, it could often be treated cheaply with pyridoxine.

An important practice issue that also militated against the use of pharmacogenetics was the multi-drug regime. If pharmacogenetics were used, combined therapies and protocols would have to be 'unpicked' to enable the tailoring of regimens. One respondent was concerned that PGx would require better understanding/training in

[144] Pompeo, F., Brooke, E., Kawamura, A., Mushtaq, A. and Sim, E. (2002), The pharmacogenetics of NAT: structural aspects. *Pharmacogenomics*, 3 (1):19-30; Ma, M.K., Woo, M.H. and McLeod, H.L. (2002), Genetic basis of drug metabolism, *American Journal Of Health-System Pharmacy*, 59(21): 2061-2069.
[145] Rusnak, J.M., Kisabeth, R.M. and Herbert, D.P.(2001), Pharmacogenomics: A clinician's primer on emerging technologies for improved patient care*, Mayo Clinic Proceedings* 6:299-309.

prescribing and a need for 'people to think about it more'. Finally, one interview respondent argued that commercial companies would be likely to view isoniazid as an old, low-cost product that is largely used in 'poor countries', and would thus have little incentive for researching its pharmacogenetics.

4.5.4 Summary

A PGx test that identifies those at risk of peripheral neuropathy could have a direct benefit for this patient group. However, substantial barriers were identified to the potential of PGx, aptly illustrated by the lack of demand for an existing test for acetylator status. This lack of demand related to a number of issues: the relatively low incidence of the ADR, the potential for treatment if it is identified and the lack of a clear connection between knowing acetylator status and achieving beneficial outcomes. Also there were (again) issues about the complexity of the prescribing process, which in this case included not only queries about the relative benefit of knowing acetylator status for the overall prescribing decision, but also concerns that PGx knowledge would create a burden for practitioners who would have to 'unpick' routine multi-drug prescribing.

4.6 Conclusions

Supporters of pharmacogenetics often claim it is a win-win-win innovation. Patients could have better treatment by being on the 'right drug' earlier and by avoiding ADRs; practitioners will have an aid to selecting the most useful and least harmful therapies for their patient; health service funders will have additional information from which to make decisions about cost effectiveness and resource allocation.

This part of the study explored such claims with a small sample of health practitioners, many of whom had little prior knowledge about PGx. These findings provide an insight into the factors that might influence the use of PGx in specific settings and the challenges that may face the adoption of PGx into everyday clinical practice. This conclusion therefore summarises the core themes that emerged across the different case study drugs. These have been collated and together represent the interview respondents' perspectives on the potential drivers and challenges to PGx (although it should be noted that there are significant differences between the case study drugs that we have described above). In these examples the drivers for practitioners to use pharmacogenetics were the improvement of prescribing practice or patient experience and the reduction or refocusing of health service costs. The challenges facing clinical adoption were complexity, evidence, utility in practice and finance.

4.6.1 Drivers

Practitioners saw the main potential benefits of pharmacogenetics in the case study drugs as including:

- Improving treatment (get the right dose earlier/avoid ADR) or avoid unnecessary treatment (especially where there is a side effect burden);
- Aiding clinician decision-making, in concert with other clinical information (inform go/no go);
- Improving patient experience (and perhaps empower patient choice);
- Reducing costs or re-deploy resources (avoid wasteful treatment and unnecessary ADRs);

4.6.2 Challenges

The main concerns raised by practitioners about the clinical adoption of pharmacogenetics in the case study drugs can be grouped under the following headings:

Complexity

- There are numerous factors affecting decision-making in drug prescribing, including the risk/benefit of therapy, cost-effectiveness, clinical context (e.g. governance, ease and routine), and patient context (e.g. understanding, preferences and social support).
- Drug response is affected by many factors, including numerous enzymes involved in metabolism (and their natural genetic variability), other drugs, environment (e.g. food and alcohol), lifestyle (e.g. fitness and stress), age, sex and compliance.
- Genetics is inherently complex, incorporating: heterogeniety/ homogeniety; rare allelic variations; the link between genotype, phenotype and outcome; population level genetic variation; the link between any of these and the prescribing decision (from giving the drug or not, to dosing).
- Adopting pharmacogenetics will involve making difficult, context-bound decisions about boundaries and categorisations for prescribing decisions, cost effectiveness and clinical error.

Evidence

In the case study examples, the perceived lack of evidence surrounded:

- Significant benefits of pre-prescription tests;
- Link between gene, enzyme/ metabolism and drug response;
- Link between population data, clinical evidence and outcomes;
- Relative benefits and drawbacks of phenotype versus genotype tests;
- Cost-effectiveness;
- Replication of small studies in large scale randomised control trials (RCTs);
- Current evidence was contested and there was scepticism regarding claims made from small studies and commercially sponsored trials. There was a demand for strong evidence of benefits, preferably from RCTs;
- Ethical and practical issues might arise in the running of clinical trials.

Utility in practice

- Professional acceptance is unlikely to be forthcoming where current prescribing practice is considered acceptable and the utility of pharmacogenetic information is unclear.
- Utility relates not only to evidence about the value added to the treatment outcomes and the degree of certainty offered by the test, but also to contextual issues like the severity of the condition, the cost/benefits of the treatment and the availability of other drugs.
- Utility also covers matter of work practice such as the fit between a PGx test process and existing treatment protocol, and time and workload burdens for clinic and laboratories (especially if informed consent and counselling are needed).
- There was one suggestion that PGx may require a culture shift in prescribing practice or the need for (re)education. Most clinicians, however, demanded a PGx test that would fit seamlessly into their current practice, including unequivocal guidance on the impact of a PGx test result on their prescribing practice.

Finance

- Pharmacogenetic tests that assist in the allocation of scarce resources might be well received. However, dilemmas may be associated with categorising people in/out on the basis of genetics plus economic evaluations.
- In drugs prescribed to a large number of people, testing might have to be selective rather than universal, depending on the costs.
- Costs for existing technology and new developments may be prohibitive.
- Questions surround the most effective manner to select, fund, organise and provide new pharmacogenetic testing within NHS laboratories.
- Without strategic decisions and action, clinical demand for pharmacogenetic tests may be stifled.
- Commercial interest in pharmacogenetics for existing drugs was seen to lack financial incentives (e.g. off-patent drugs or small patient numbers).

4.6.2 Final comments

This section of the report concludes with a summarised assessment of the potential contribution of PGx testing in the case studies and makes some tentative extrapolations to other contexts. It also makes recommendations for how the adoption of PGx testing might be promoted to improve public health and clinical care. However, it is important to remember the study's limited small sample size and regional bias. As such, the findings of this research should be regarded as an initial attempt to identify the key issues that may arise in the adoption of PGx. Further investigation would be required to establish if concerns we have reported are shared by other health professionals, or exist in other clinical contexts.

In one of case studies, isoniazid, the barriers to the clinical adoption of PGx appear substantial: a lack of clinical demand, no clear benefit of having the extra knowledge and a resistance to 'unpicking' well established prescribing practice. In the three other case studies (warfarin, clozapine and the thiopurines) there was at the very least *some* potential for PGx testing to have benefits to patients, practitioners or health service providers. However, what these benefits were and to whom they might accrue was dependent on the circumstance of each case study. Furthermore, potential benefits were quite specific, and often needed to be weighed against concerns about potential drawbacks such as resource burdens or impacts on working practices. In all cases practitioners demanded an improved evidence base to help them make their judgements about the potential benefits (and drawbacks) of adopting PGx testing. In the warfarin and clozapine case studies a key finding was that practitioner were interested in (but sometimes sceptical of) the *relative value* of PGx information in clinical decision-making. With respect to the thiopurines, the case in which PGx testing seemed to have the greatest short-term likelihood of being used, a key finding was that alternatives to genetic testing exist and that these might provide the information that clinicians required.

Generalisations from the case studies can only be tentative, given the limitations of our research methodology. Nevertheless, this study has revealed a number of the key themes in the thinking of practitioners that may arise in other examples of the clinical adoption of PGx testing. Firstly, the balance of benefits and drawbacks for practitioners is likely to be dependent on the case in hand. Second, as might be expected, stimulating a clinical demand would require convincing clinicians that there is clear and unequivocal evidence of the benefits, particularly how a test might improve clinical outcomes and add value to existing clinical practice (with some

interest in evidence of cost-effectiveness). As an aside, it is not PGx technology itself that clinicians demand, but rather PGx (or other) tests that may in some cases provide information that can add value to the clinical process. Third, a key concern for practitioners could be the likely impact of PGx testing on existing routine practice. Fourth, in their judgments about adoption, practitioners are likely to weigh evidence of potential benefits to clinical outcomes in relation to the potential difficulties and drawbacks that may arise from altering current practice.

The adoption of a new technology will be facilitated if there are sufficient incentives and benefits (and few barriers) and it can be accommodated into established practices. In light of our findings, certain requirements must be fulfilled to create a clinical demand for PGx. Most obviously, there is the need for a stronger evidence base in terms of patient outcomes and evaluations of economic effectiveness. In addition, studies of potential benefits should be accompanied by evaluations of the impact and feasibility of integrating novel tests into current practice. The potential introduction of PGx in specific instances must be understood within the established structure of medical practice. In particular, the nature of illness under consideration, the benefits and drawbacks of available treatment regimes and the practicalities of the current treatment process are all likely to influence the chances of a valid PGx test being widely adopted.

In conclusion, there are two observations that can be made about the potential of PGx as applied to the bulk of existing medicines. In instances where medicines are very well established (often off-patent), it seems unlikely that the drive to gather and disseminate all of the required evidence will come from the private sector. The clinical adoption of PGx for these kinds of medicines is likely to require considerable public sector support. Finally, in none of the case studies did PGx tests appear to have the potential to wholly replace the monitoring systems that exist to ensure the safe and efficacious use of these drugs. Even in the best current examples of applying PGx to existing medicines, the potential is for incremental improvements to practice rather than a wholesale revolution as implied in the idea of ‘personalised medicine’.

Chapter 5
Developing policy to promote pharmacogenetics

5.1 An emerging policy and ethics framework?

There have been a number of reports on PGx published in the last few years[146] that provide overviews of the current ethics and policy-related issues. Policy matters are of course drawn much more widely than those focused exclusively on ethics, but at the same time, it is evident that in PGx, as in many other fields of medicine, policy and ethics are co-constructed. That is to say that policy and ethics feed off each other as scientific developments and their implications are apprehended – often before the science itself has been implemented in clinical settings. Sometimes, perhaps more often than not, a 'workable' ethics and regulatory framework emerges or already exists that accommodates developments in a field, but occasionally, as in the development of research on chimera, or in regard to tissue engineering, existing regulatory provisions struggle to make sense of and manage new technoscience.[147]

When an existing regulatory framework is seen to be unable to cope with new developments, the system has to adapt.[148] Any specific ethical consideration – such as concerns over the 'stacking' of informed consent that some associate with PGx tests – requires a form of moral reasoning and negotiation across regulatory, commercial, clinical or patient interests in order to build some consensus between them. For example, in the wider context of the development of genetic technologies and key infrastructures such as biobanks, Hoeyer[149] has shown how the interplay between moral, commercial and public/legal oversight eventually enables the establishing of a "framework for social entitlements in stored human biological material…which facilitates distinction between different sources of entitlement and different adjoining rights" (p 20). In the biobank case, this has allowed a narrative to be built that separates out information about stored material, which can be explored, commercialised, or sold on, from the 'actual tissue' itself, which is deemed to be the entitlement of the depositor alone. Similarly, in PGx, boundaries have emerged that, for example, distinguish between the ethical entitlements of a patient and their test results, and wider information derived that might be of research, epidemiological or commercial value. Anonymised data are seen to make the granting of discrete entitlements – at the level of the individual and the level of others - possible.

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[146] E.g. Meltzer, D. et al. (2003), *My Very Own Medicine: What Must I know?*, The Wellcome Trust: London; Nuffield Council (2003), *Pharmacogenetics; Ethical Issues*, Bedford Square: London; Buchanan, A. et al. (2002), *Pharmacogenetics: Ethical and Regulatory Issues in Research and Clinical Practice, Report of the Consortium of Pharmacogenetics*; Findings and recommendations; The Royal Society (2005), Personalised Medicines: hopes and realities, London.

[147] Brown, N. and Michael, M. (2004) Risky Creatures: institutional species boundary change in biotechnology regulation, *Health, Risk and Society,* 6,(3):207-222

[148] Melzter, D. et al (2005), Pharmacogenetics: policy needs for personal prescribing, *Journal of Health Services Research and Policy* 10(1):40–44; Brown, N. and Michael, M. (2004), Risky Creatures: institutional species boundary change in biotechnology regulation, *Health, Risk and Society* 6(3):207-222.

[149] Hoeyer, K. (2004), The Emergence of an entitlement framework for Stored Tissue. Elements and Implications of an Escalating Conflict in Sweden, *Science Studies* 17(2):62-82.

While these developments help to establish some basic 'ground rules', policy uncertainties still characterise the regulatory oversight of PGx. This is noted in the Meltzer report[150], which observed that: "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" (p6).

At the same time, the report was prepared to make some suggestions as to where action was needed:

> "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" (p6).

Here we see how an individual's rights and other (scientific and commercial) entitlements are to be woven together in such a way as to pre-empt the 'stifling' of PGx development. In a similar fashion, The Nuffield Council report [151], in commenting on the possible discrimination against specific ethnic groups who are less responsive to PGx, recommends that:

> "those responsible for monitoring the relative access of different ethnic groups to treatment in the NHS establish procedures for assessing whether problems emerge arising from the development and application of Pharmacogenetics" (p22)

Here, it is clear that ethical (and wider citizen rights) provisions are seen to be defined and developed iteratively as the science itself is mobilised across the health delivery system.

In short, ethics frameworks are not abstract moral principles imported to guide practice, but are socially embedded forms of reasoning, which, as such, may change over time and reflect socially defined boundaries of rights, obligation, duty and risk[152]. This is not to disparage or challenge the reports cited here and the recommendations they make, but simply to emphasise that a more analytical approach to ethics enables us to explore how core issues – such as 'consent' – are defined and deployed in different ways over time[153]. Again, we can see this illustrated in a Medical Research Council statement relating to the UK Biobank's Ethics and Governance Framework (EGF), wherein it declares that "This Council, the Science Committee and others will advise on *updating* the EGF in response to scientific, legal and other developments throughout the 20-year project."[154]

In regard to PGx, therefore, we should expect to see an emerging UK policy framework that is quite heterogeneous, mutable and highly context specific. It is also driven by a focus on what we *know*, and what we do with the *information* – a

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[150] Meltzer, D. et al. (2003), *My Very Own Medicine: What Must I know?*, The Wellcome Trust: London.
[151] Nuffield Council (2003), *Pharmacogenetics; Ethical Issues*, Bedford Square:London.
[152] Haimes, E. (2002), What can Sociology contribute to the study of ethics? Theoretical, empirical and substantive considerations' *Bioethics, 16 (2):89-113.*
[153] An extremely valuable symposium that discussed this issue was *Informed consent in challenging circumstances,* 30 June 2005, St Catherine's College Oxford (see http://ssl.brookes.ac.uk/mdhrn/conference/)
[154] *Medical Research Council (2003),*'UK Biobank Takes Shape, *Medical Research Council Newsletter*, (London) Winter 2003, p 8.

perspective that fosters a quite pragmatic (some might say 'British') approach to ethics that seeks to balance the warrant of science with respect for individual rights. So, for example, as the Nuffield report recommends, "in assessing whether written consent forms are required for pharmacogenetic tests undertaken in clinical practice, each test should be judged *according to the nature of the information it provides"* (pxxi, emphasis added).

This approach tends to allow regulatory adjustment to be made along the way. But it also presumes that 'the nature of the information' in terms of both its robustness and the implications it has can be clearly determined in different settings. However, PGx tests for ADME[155] responses are compromised by the fact that the metabolism of a new drug is affected by polymorphic genetic control such that there may be considerable pharmacogenetic variability. Moreover, determining the sensitivity and specificity of the tests and both of these in relation to clinical utility can be problematic. In addition, 'the nature of the information', as these last comments suggest, tends to be restricted to the nature of the *clinical* information and the implications this has for the patient/client and third parties (other kin, insurers, regulators etc).

In parallel to this, however, we need to understand what patients/users bring to a clinical encounter that might involve PGx test/drug kits. This will have an important influence on the meaning of the information obtained, its perceived risk and the response of the patient. For example, in related work on genetic screening, Bharadwaj et al.[156] have shown how although it is possible to screen individuals with a view to predicting their personal susceptibility to developing genetic conditions, such risk prognostications are often tentative. He suggests that we can identify three forms or levels of uncertainty: uncertainty over the category of the 'disease' itself; how doctors and others draw a distinction between healthy carriers and those expressing the disorder and the gradations between these two; and the personal sense of uncertainty about the future generated by the disorder. Crucially, these three do not add up to produce a *unified* risk measure or risk algorithm that can be used by clinicians or genetic counsellors, whether in regard to PGx tests or wider genetic screening. This means that in the context of advice genetic counsellors may give in respect to PGx tests, they will have new problems to address that go beyond the conventional one of balancing "truth and hope"[157].

What this points to in broader terms is a health policy domain that will have to manage – ethically, clinically, organisationally – a heterogeneous and somewhat unstable set of circumstances within which PGx will have to be mobilised. While there will be attempts, as in any complex socio-technical system, to try to bring order and stability to the deployment of a new technology, an equilibrium point might take some time to reach. This is in part because beyond the confines of PGx itself, wider developments in pharmacogenomics, gene-disease analysis, biobanks and functional genomics will press on the PGx field and disturb any hard-won ethical stability. For example, the phenotypic information that will be crucial to the future utility of

[155] ADME is an abbreviation for Absorption, Distribution, Metabolism and Excretion of a drug.

[156] Bharadwaj, A. (2002), Uncertain risk: genetic screening for susceptibility to haemochromotosis, *Health, Risk and Society*, 4(3):227-240; Bharadwaj, A. et al (2006), The Genetic Iceberg: Risk and Uncertainty in Cancer Genetics and Haemochromatosis, in A. Webster (ed*), New Technologies in Health Care: Challenge,Change and Innovation*, Palgrave: Basingstoke.

[157] Groopman, J. (2004), *The Anatomy of Hope: How People Prevail in the Face of Illness*, Random House: New York. p220.

biobanks and the emergence of genetic epidemiology will be of greater value where it can be linked to phenotypic information relating to PGx in the clinic. Patients would thereby be asked to give consent to use of information that might eventually suggest links to genetic disease predisposition. In short, genetics will be working on a much wider range of fronts than at present (currently through specialised genetics services) and balancing competing demands and expectations will become a major task for policy-maker, counsellor, clinician and user. This may be to some extent illustrative of the claims made by the 'risk society' thesis[158], which suggests that in addressing some risks created by science – such as those of ADRs – new technologies such as PGx create new risks that require further regulatory compensation. Furthermore, it should be noted, good governance and regulation do not necessarily lead to a reduction of risk, but can generate new forms precisely because of the increased level of accountability and transparency this implies[159].

The emerging policy and ethics framework is therefore likely to be quite broadly drawn if PGx is to be effectively (i.e. socially and clinically) managed on an ongoing basis. Private corporations and clinicians will have to engage with this more complicated environment and innovation landscape, albeit at different levels and with distinct priorities; in part, it is this very complication and its commercial and professional risks that is no doubt discouraging both of these groups from embracing PGx wholeheartedly, or at least as having mixed expectations about its future. In regard to general practitioners, there may not only be concerns about the relative clinical utility of PGx [160] but also a perceived threat to their monopoly and discretion over prescribing. As Britten[161] notes, "prescribing is one of the few activities that is within doctors' almost exclusive control…[such that it] is a battleground on which the cause of clinical autonomy is defended" (p. 480). Given this the rather optimistic position adopted by Emery and Hayflick[162] should be treated with caution when they argue:

> "Pharmacogenetic information may require less understanding of genetic principles than would be necessary, for example, to provide counselling for carrier screening for cystic fibrosis. Ultimately, therefore, pharmacogenetics may be a much greater driving force for the application of genetic medicine in primary care than specific genetic screening programmes."

However, it is true that in socialised health care systems such as that of the UK, clinicians will be expected to respond to government policy, where the role of expectations is typically driven by a modernising and rational (evidence-based) policy model. A recent example of this was the UK Department of Health White Paper, which is now supporting a range of initiatives related to 'the new genetics', including PGx.

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[158] Beck, U. (1992), *Risk Society: Towards a New Modernity*. London: Sage.
[159] Rothstein, H. et al (2006), A theory of risk colonization: the spiralling regulatory logics of societal and institutional risk, *Economy and Society,* 35:91-112.
[160] Shah J. (2004), Criteria influencing the clinical take-up of pharmacogenetics strategies, *British Medical Journal*, 328:1482-6.
[161] Britten, N. (2001), Prescribing and the defence of clinical autonomy, *Sociology of Health and Illness*, 23(4): 478-96.
[162] Emery, J. and Hayflick, S. (2001), The challenge of integrating genetic medicine into primary care, *British Medical Journal* 322:1027-1030.

5.2 The UK White Paper (2003): promoting PGx

Notwithstanding the uncertainties over the ways in which PGx might be stabilised, the UK government announced via its White Paper (published in July 2003) [163] that it would both provide more support for clinical research on PGx and seek to foster initiatives through which PGx might be more extensively used in the National Health Service (NHS). The White Paper called for more research especially on generic drugs that are commonly used within the NHS whose ADRs might, via PGx, be made both more predictable and containable. This focus on safety/toxicity (rather than efficacy) with drugs that have a narrow therapeutic index makes sense from both an optimal resource-use and clinical perspective, and is likely to be welcomed by clinical researchers working in both pharmacology and medical genetics. The Paper also addressed issues of perceived or potential market failure and the need for the government to support translational research that can help bridge the gap between lab and clinic or commercial product. Following on from the funding made available by the White Paper, a number of projects (with a combined funding of £4m and due for completion during 2007/8) have been commissioned by the DH to assess the relative utility of PGx in determining ADRs through a series of RCTs.

As the focus moves in the longer term towards efficacy there may be a need for the Department and regulatory agencies, such as the MHRA, to develop new approaches toward pharmacovigilance and the oversight of chronic disease management. In part this is driven by government anxiety over growing levels of litigation as a result of iatrogenic medicine (here ADRs)[164]. The costs of post-marketing surveillance will of course increase because of the need to map results of genetic tests more systematically. Recent suggestions have been made that the NHS's National Programme for Information Technology (or 'Connecting for Health') could use the Electronic Patient Record as a means for registering ADRs and helping to improve the speed and functionality of pharmacovigilance.

One way of thinking about the mobilisation of PGx within the NHS is to draw on a pertinent analogy: how might the NHS 'metabolise' PGx *itself*? The notions of 'Absorption' and 'Distribution' (of the four ADME processes) might be especially useful here. The take-up of PGx will in part be framed by some clinicians as simply an extension of what has been available for over twenty years. This both defuses its challenge while undermining claims to its dramatic effect on prescribing. Absorption here simply equates to accommodation and limited change. Clearly such a response, though quite possible in a system that gives considerable autonomy to clinicians, will fall foul of government attempts to wrest more control over prescribing. Patterns of '(A)bsorption' relate therefore to how far the existing knowledge base and professional practices open up institutional spaces through which PGx might be introduced.

At the same time, the '(D)istribution' of PGx as a technique across the NHS will depend upon a number of wider factors at work that have to be taken into consideration. One of these relates to changing patterns of procurement of medicines especially in regard to the boundaries between clinically mediated and patient-

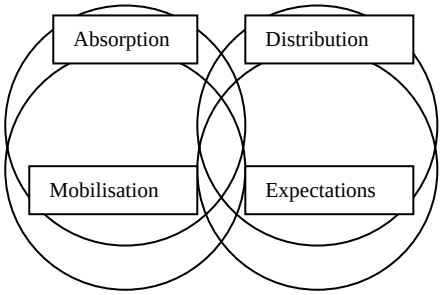
[163] Department of Health (2003), *Our Inheritance, Our Future: realising the potential of genetics in the NHS*, Stationery Office:London.

[164] UK Audit Commission (2001), A spoonful of medicine: medicines management in NHS hospitals, available at, http://www.auditcommission.gov.uk/Products/NATIONAL-REPORT/E83C8921-6CEA-4b2c-83E7-F80954A80F85/nrspoonfulsugar.pdf.

centered self-care. This involves a notable shift towards adopting self care as a *formal* policy of government (see e.g. the Wanless Report)[165] rather than such care being simply a long-standing feature of lay, personal health management. As the (OTC and web-based) market for medicines opens up, and as tests for a variety of pathologies become more readily available, PGx as a managed system of medical delivery will confront a number of challenges[166]. Other changes at work in the wider health care system that will influence the ways in which PGx is absorbed into the NHS relate to changing demographics - especially an ageing population and more diverse range of ethnic groups; the changing professional role of pharmacists with perhaps a greater responsibility for prescribing; and a wider international policy framework, especially at the European level.

We might complete the analogy with the ADME by speaking of two other processes, albeit with a change to the actual terms – the (M)obilisation of and the role of (E)xpectations about PGx. PGx will be more likely to be mobilised where commercial, professional and policy interests converge, and these in turn will reflect debate over and agreement about expectations over the utility and value of PGx. We might represent these four processes shaping the take-up of PGx as follows:

Figure 5.1 The absorption, distribution, expectation and mobilisation of PGx



A key difference from the biochemical pathways represented by the ADME model, is that the clinical take up of PGx will *not* happen in a linear way, from absorption and on through the subsequent stages. We can expect to see all four processes described above as acting together to shape the outcome within the UK (and indeed other countries too).

One of the principal objectives of the White Paper was to articulate a case for PGx as a potential solution to chronic ADRs. While ADRs are indeed a matter of concern, the Audit Commission's report (op cit.) noted that they were only partly linked to genetic response (and more about poor management of drugs for or by patients). In this sense, the degree to which PGx will actually provide a solution to a problem that lies elsewhere within health care delivery is highly arguable. Medicines (i.e. drugs) are, of course, the most common form of therapeutic intervention in the NHS: equivalent to approximately £7b in primary and £2b in secondary care sectors. PGx is to be

[165] Wanless, D (2002), *Securing our Future Health: Taking a Long-Term View. Final Report,* HM Treasury: London

[166] See Fox, N. J. et al. (2005), 'Expert Patients', Pharmaceuticals and the Medical Model of Disease: The Case of Weight Loss Drugs and the Internet,' *Social Science and Medicine*, 16(6):1299-1309.

welcomed (as we saw much earlier in this report) if it could be shown and seen to make a difference in terms of reducing ADRs, or anticipating them, working on and improving medicines with a narrow therapeutic index, and incorporating this evidence-based information into the British National Formulary: existing and off-patent drugs – warfarin, codeine, antipsychotics etc - should, it argued, be the focus of PGx research.

This approach is not unexpected as it could be seen as the least problematic from a policy perspective. It might provide the basis for building a wider more comprehensive framework for the promotion of PGx across the health service. But in doing this, new uncertainties will have to be addressed, as we now discuss.

5.3 The need for a comprehensive framework

> "At the time of writing there is no robust example of a new product that has been developed from concept to market that could be accurately labelled pharmacogenetics upon which to build a policy model." [167]

The discussion above provides a summary of commercial, regulatory and clinical challenges that will lie ahead. In the preceding section (5.2) we also argued that these need to be set in a wider context of changes in health delivery itself. However, as Raven and Ling's comment above noted, we are yet to find a single model that provides the benchmark on which a single, paradigmatic PGx strategy itself could be built. Abacavir, Herceptin and the few other cases of PGx drug development are not seen as test-beds for PGx, though perhaps the currently funded DoH projects are more suited to this given their focus on off-patent drugs with widespread use and narrow therapeutic indexes. More generally, the notion of test-bedding or piloting the application of a new technology has been questioned: evidence from innovation studies within the sociology of science and technology points to the fact that 'test beds' have to be built and cannot be predefined in their entirety. Niche spaces for innovation are first required during which new technologies might be nurtured by the state, public and private sector interests[168]. Indeed, we are likely to see a series of niche developments appear as a result of competing innovation 'narratives' and expectations which for a time will generate more, rather than less, complexity as demands for resources, claims to utility and the constraints of regulation play out in different ways.

Thus, there are a range of issues that will need to be resolved in the introduction of PGx. These include strategic institutional questions such as who is responsible for PGx tests and where would they be conducted? Would, for example, the public sector (NHS PCTs) need to secure the technical equipment to undertaken near-patient tests, or could this be offered centrally and in collaboration with not-for-profit agencies? Would genetic screening for a *predisposition* towards a PGx-related response (in regard to safety and efficacy) be too costly and too difficult to interpret, especially at the level of the GP? In the longer term, the UK White Paper hoped that there would be a step forward from questions of coping with ADRs to securing greater drug efficacy: will new institutional developments be needed to do this such as greater investment in expert systems and new ways of orchestrating pharmacovigilance, along with new

[167] Raven, A. and Ling, T. (2002), *Pharmacogenetics and uncertainty*, Working Paper, APU, Cambridge.
[168] Deuten, J. and Rip, A. (2000), The narrative shaping of a product creation process, in Brown N., Rappert, B. and Webster, A. (eds.), *Contested Futures*, Ashgate: Aldershot.

approaches to chronic disease management? Will it be likely that the very uneven and poor phenotypic information currently available will be readily improved in the future, and if so, through what mechanism – the EPR? The resolution of such issues will determine precisely what the 'absorption', 'distribution' and 'mobilisation' of PGx will mean as 'expectations' converge and stabilise.

At present, then, there is no obvious policy model given the different perceived opportunities and risks of PGx. So the problem is how to maintain strategic capacity to invest (in both a public and private sense) without getting trapped into a policy/business model that will fail. Judicious caution in policy-making is key here, as decision-making typically occurs in conditions of ignorance where, as a result, there is a need for a continued review to avoid a disastrous policy lock-in. Expertise from within the social sciences can and should be drawn on to help manage such uncertainties.

One good example of this, based on an understanding that we need to see the introduction of genetics technologies as part of wider socio-technical infrastructure, is the *Generation Scotland* initiative. This initiative is not formally linked to PGx, but focused on mapping the genetics of common medical disorders. Even so, because its focus extends beyond the science base to include social, economic and political considerations, this bodes well for its success. It has adopted a *comprehensive* framework towards genetic screening, diagnostics and tests. It has four elements, outlined in Box 5.1 below:

Box 5.1 Elements of a comprehensive framework for Generation Scotland

- A database of medical information, retained within NHS Scotland;
- A research and technology arm to conduct and interpret genetic studies;
- A communications arm to develop awareness of, engagement in, support for and understanding of the requirements for success and the outcomes from the programme;
- A commercialisation arm to develop and exploit the application of programme findings both within Scotland and elsewhere.

*Source: '*Generation Scotland': addressing the health and wealth of Scotland.[169]

What is interesting about this case, is not that it has resolved the problem of the best way to introduce genetics into the health system, but that it is highly *reflexive* about how this might be done. That is to say, there is a clear sign-up to a position that accepts the need for iteration and reflection in regard to the way its discrete elements need to be mobilised simultaneously and not sequentially. There is also a clear sense that the 'Generation Scotland' project will only succeed if it can build a presence within the main agency involved, the Scottish Executive. As its director, has observed, "My sense is that … the concept does stack up and we need to do it quickly. We need to get the public onside and we need to get in the centre of the Scottish Executive's radar screen".[170]

Such a reflexive and broadly based framework will be important in the development of PGx. But clearly, our earlier analysis suggests that a comprehensive view is one that

[169] http://www.generationscotland.org/
[170] Cited at http://www.erihost.com/gs/RSE_GS_Report.htm

needs to weigh up the alternatives to a PGx-led strategy, especially on the reduction of ADRs. An important criticism of an over-emphasis on PGx is that it distracts attention from more simple ways in which ADRs might be dealt with. As Spallone and Wilkie[171] have argued, this may not be the most sensible and cost-effective way of managing adverse effects. They point to research that estimates that up to 95% of such effects could be prevented simply on the basis of existing knowledge and a better management of drugs by prescribing clinicians. ADRs are often the result of limited understanding of drug therapy, appropriate dosage, or patient response thereto, or simply mistakes in nomenclature. Their key point is that were PGx to be implemented more fully would such mistakes be thereby less likely to happen?

A 'comprehensive framework', in other words, will require not only a reflexive and cautious approach, but one that questions the allocation and resources to be devoted to PGx itself and the opportunity costs this might involve. This will make it much more difficult for a niche narrative focusing exclusively on the pay-off from PGx to be built and legitimated. But it will perhaps ensure that any that are created, are perceived to be most likely to meet genuine need.

[171] Spallone, P. and Wilkie, T. (1999), Social, ethical, and public policy implications of advances in the biomedical sciences: The Wellcome Trust's initiative on pharmacogenetics, Paper presented to the European Workshop on Legal, Regulatory and Ethical Aspects in Pharmacogenetics, November 12, 1999, Berlin. p.13.

Chapter 6
Conclusion: Towards a comprehensive framework

6.1. Analysing the development and possible impact of PGx

The development of pharmacogenetics offers new opportunities, but also poses major challenges to the pharmaceutical industry, clinicians, healthcare providers and regulators. For industry, there remains great uncertainty about the level of market segmentation that can be commercially tolerated. For clinicians and health policy makers, PGx demands new ways of prescribing medicines and new types of service infrastructure. Similarly, regulatory agencies are faced with the tension between ensuring the safe and ethical use of PGx, whilst promoting innovation. At the same time, PGx offers the prospect of significant public health gains. These benefits relate primarily to improved safety, efficacy and cost effectiveness of both prospective and existing drugs. These potential benefits are summarised in Table 6.1 below. As we noted above, some of these benefits - such as improved targeting of existing (especially generic) drugs - may be achievable in the medium term and could thereby establish an important public health strategy in the next few years.

Unlike many other more speculative reviews, this report is based on a detailed empirical analysis of the challenge of PGx. It has examined key aspects of the contemporary development of pharmacogenetics, and has presented a state-of-the-art review of the industrial development of PGx and the regulatory framework that is emerging around the technology. In addition, Chapter 4 presented the qualitative study of factors influencing the clinical adoption of PGx in the context of existing drug products and Chapter 5 an analysis of the constraints that face policymaking. In this conclusion, the case is made for taking a systemic approach that understands the specific possibilities opened up by PGx within the wider context of genetics medicine and developing a 'comprehensive framework' within which to develop policy. Throughout our analysis we have drawn on a science and technology studies (STS) framework that sees innovation in contingent, distributed and systemic terms, emphasising the co-evolution and mutual shaping of industry, regulation, clinical practice and policy. Our analogous 'ADME' diagram (Figure 5.1) sought to illustrate this co-evolutionary process and stresses the dynamic and interactive processes that shape the early stages of a new medical technology.

The value of taking a systemic and co-evolutionary approach is that it provides a powerful analytical framework and more realistic means of assessing an emerging technology. The impact of PGx on industry, clinical practice, healthcare and ethics will depend on how the applications and designs of the technology are shaped by the different factors we have described here. By analysing the investment being made in each option and the barriers they face, it will become possible to make a more detailed assessment of which forms of PGx are most likely to be adopted in the medium term.

Table 6.1 The main potential benefits and issues raised by different applications of PGx

	Benefits to pharmaceutical companies	Benefits to Clinicians & Patients	Benefits to health care providers	Main ethical, legal and social issues	Regulatory and public policy issues
Drug discovery					
Discovering new drugs which work well in entire population	Increased chance of developing successful drug	New drugs which work well in all patients	Safer and more cost-effective therapy	-	-
Discovering new drugs aimed at genomic sub-populations	Increased chance of developing successful drug (but restricted markets)	Drugs which work well in subgroup of patients	More effective therapy for some patients	Lack of therapy for some genomic sub-populations. High cost of new drugs	Incentives to develop new drugs for genomic 'orphan' populations
Safety of drugs in development					
Pre-clinical testing and early stage trial design/ monitoring	More efficient drug development (smaller trails)	Safer new medicines	Less ADRs	-	-
'Rescue' of products in late stage trials (ADRs)	New products (but restricted markets) Ensuring return on investment	New drugs that would not be available otherwise	-	Risk of off label use	Drug labelling. Monitoring and control of off label use
Efficacy of drugs in development					
Later stage trial design and monitoring to target 'good responders'	More efficient drug development New products (but restricted markets)	Drugs which work well in subgroup of patients	More cost-effective prescribing	Risk of trial bias and undetected rare ADRs. High cost of new drugs. New 'orphan' patient groups	Tight monitoring of PGx based trials. Improved post-marketing surveillance Incentives to develop new drugs for genomic 'orphan' populations
Drug rescue (efficacy)	New products (but restricted markets) Ensuring return on investment	Drugs which work well in sub-group of patients	More cost-effective prescribing,	Risk of trial bias and undetected rare ADRs. High cost of new drugs. New 'orphan' patient groups	Tight monitoring of PGx based trials. Improved post-marketing surveillance Incentives to develop new drugs for genomic 'orphan' populations

Safety of licensed drugs					
Market (label) extension of products restricted by ADRs	Increased sales Reduced litigation arising from ADRs	Safer therapy for greater number of patients	Reduction in ADRs	-	-
Pre-prescription screening to identify patients at risk of ADRs	Reduced litigation arising from ADRs	Safer therapy for greater number of patients	Reduction in ADRs	Secondary information on poor metabolisers New 'orphan' patient groups. Prescription on basis of probabilistic test results Link to ethnicity and stigmatisation	Improved controls on genetic testing and data Incentives to develop new drugs for genomic 'orphan' populations Need for statutory clinical validation of tests
Post-marketing surveillance	Reduced litigation arising from ADRs Possibility of drug 'rescue'	Safer therapy	Reduction in ADRs	-	Improved post-marketing surveillance
Efficacy of licensed drugs					
Pre-prescription screening to identify 'good responders'	Risk of overall reduction in sales	More effective treatment Reduced use of drugs on non-responders	Reduction is number of prescriptions and costs of drugs	Secondary information on prognosis New 'orphan' patient groups Prescription on basis of probabilistic test results Link to ethnicity and stigmatisation	Improved controls on genetic testing and data Incentives to develop new drugs for genomic 'orphan' populations Need for statutory clinical validation of tests
Use of efficacy data in drug marketing	Increased sales and market penetration of premium products in segmented niche markets	More effective treatment	-	Increased cost of treatment	Need for statutory clinical validation of tests
Disease genotyping					
Stratification of diseases into sub-types	Increased sales and market penetration of premium products in segmented niche markets Risk of overall reduction in sales	Safer/ more effective therapy Reduced use of drugs on non-responders	Reduction in ADRs Reduction is number of prescriptions and costs of drugs	Secondary information on prognosis New 'orphan' patient groups Prescription on basis of probabilistic test results Link to ethnicity and stigmatisation Increased cost of treatment	Improved controls on genetic testing and data Incentives to develop new drugs for genomic 'orphan' populations Need for statutory clinical validation of tests

6.2 Analysing the factors shaping the adoption of different technical options

As outlined in the introduction, a range of factors will determine which technological options are most likely to be commercially developed and clinically adopted, and which ones may fail. In broad terms, to be successful, a technology needs commercial investment and support (especially from larger companies), a permissive regulatory environment, significant clinical demand and relatively low barriers to diffusion and adoption within healthcare systems.

The four main factors we have studied can, for purely analytical purposes, be separated out in order to capture the main findings of the project. We have shown, therefore, that in the case of ***industry****:*

- PGx technology is being developed by ~50 small biotechnology firms and ~30 large pharmaceutical companies. However, less than 20 of the small firms are dedicated to the development of this technology;

- The relatively small number of dedicated firms, the high attrition rate of companies and signs of disinvestment from incumbents highlight the lack of a well-developed market for PGx.. Despite this the field continues to attract commercial interest;

- A wide range of options is being pursued, but some appear to be much more commercially attractive than others. Which ones are successful is contingent on a range of technological, regulatory and commercial factors, most notably around the issue of market segmentation. At present it is uncertain if business models based on segmented drug markets will be commercially viable for large companies, beyond a small number of successes in the oncology field;

- Broadly speaking, there is an industrial division of labour with small firms mainly working on tests for licensed products, whilst large firms are working on new drugs. In particular, the latter are mainly applying PGx to established internal processes. However, there is some collaboration between large and small firms on the development of companion tests;

- PGx has a primary use within large firms as a technique in clinical trials to develop safer and more efficacious 'conventional' blockbuster-type drugs. Nevertheless, despite a degree of caution, there is also some interest in disease stratification;

- There is significant investment in the development of PGx tests mainly by small firms in four main areas: a) DME testing for pre-prescription genotyping and drug development; b) viral genotyping of drug response; c) cancer PGx; d) testing for drug response in a number of common diseases. Of these applications, DME testing and different forms of cancer PGx are attracting the most commercial interest. However, it is small firms, rather than large pharmaceutical companies that are developing tests for generic medicines;

- A significant number of industrial collaborations have been formed since the field started in the late 1990s, although the number of alliances created each year has decreased recently. Most collaborative efforts between small genomics and platform

companies and large pharmaceutical companies relate to internal drug development activities rather than diagnostics;

- A small number of PGx products created by large companies have already reached the market, including a number of targeted cancer therapies and technology platforms to enable PGx genotyping.

Secondly, in regard to ***regulatory agencies***:

- Regulators (most notably the FDA) have taken the lead in encouraging adoption of PGx, not least in terms of starting to institutionalise the technology in the drug assessment process. This is demonstrated by measures such as the development of industry guidelines for PGx data submission, the Voluntary Genomic Data Submission initiative for exploratory data, and work on issues around the co-development of drugs and diagnostics;

- The extent of industry commitment to the application of PGx and to data submission is largely unknown, but there is increasing evidence of PGx data being used throughout the drug development process. However, at present this is mainly in the early stages of drug development;

- PGx will not be applicable to all types of drugs and indications, but will be most likely where treatments are either non-existent or display a narrow therapeutic index;

- The broad principles behind the regulatory framework governing PGx are now starting to become established, and a number of potential benefits have been identified, including more efficient clinical trials, and improved data on patient safety and drug efficacy leading to the prospect of more targeted treatment in certain therapeutic areas.

However, industry and regulators are moving cautiously and a number of important issues remain to be to be resolved, notably:

- The type of data required by regulators and the extent to which it will be used in the drug assessment and approval process;

- The process of assessing and approving diagnostic tests to be used with both new and established medicines;

- The relationship between the oversight of the therapeutic agent and (linked) diagnostic tests, and whether such tests will be made obligatory at the level of the clinic and how their use will be enforced;

- The nature of the pharmacovigilance regimes that will become associated with PGx products;

- The governance of ‘off-label’ prescribing of medicines licensed for use with a PGx test;

- The extent to which PGx testing will be mandated for already licensed medicines, including generics, and the robustness of evidence required to make label changes. Related to this are questions about the basis for regulatory decisions on

whether available PGx data warrants mandatory testing or merely the provision of information on the drug label;

- Development of policies to tackle the possibility of 'orphan genotypes' arising, where some groups would have little access to therapy;

- A number of broader ethical issues surrounding the general use of genetic testing also remain unresolved, especially those relating to consent, confidentiality, privacy and future use of personal genetic data and the banking of DNA samples.

Within the context of ***clinical delivery*** our exploratory study among clinicians of four case study drugs with the potential to be used alongside a PGx test identified some of the key drivers and barriers shaping clinical adoption.

The main drivers behind the adoption of PGx included:

- Improving prescribing practice (including clinical decision-making) and patient experience;

- The potential to reduce health service costs or redeploy resources.

The main barriers facing the clinical adoption of PGx included:

- The relative value of PGx information and its actual usefulness in practice, especially in relation to the multiple biological and environmental influences on drug metabolism;

- The complexity of drug response, genetic markers and clinical contexts;

- A lack of evidence surrounding the benefits of testing, the genotype-phenotype relationship and cost-effectiveness;

- Concerns about increasing time and workload burdens, and the difficulties of introducing a new drug into practice;

- Financial issues, including funding and resource allocation.

It must be stressed that the incorporation of the technique into everyday, routine practice (the utility of tests and what makes them 'workable') is not simply determined by how they measure up to the evidence based requirements of sensitivity and specificity. Stimulating a clinical demand will require convincing clinicians that there is clear and unequivocal evidence of the benefits, particularly how a test might improve clinical outcomes and add value to, and be integrated into, existing clinical practice. This will be specific to a particular drug, disease and clinical context. Furthermore, practitioners are likely to weigh evidence of potential benefits regarding clinical outcomes in relation to the potential difficulties and drawbacks that may arise from altering current practice.

Certain requirements must therefore be fulfilled in order to create a clinical demand for PGx, including a strong evidence base in terms of patient outcomes and economic effectiveness, and the feasibility of integrating novel tests into current practice. The nature of the illness under consideration, the benefits and drawbacks of available treatment regimes and the practicalities of the current treatment process are all likely to influence the chances of a valid PGx test being widely adopted. Even in the best

current examples of applying PGx to existing medicines, the potential is for incremental improvements to practice, rather than a wholesale revolution as implied in the idea of 'personalised medicine'.

Finally, with respect to the development of ***policy***, we have argued that:

- An effective policy framework should see new technologies, health services, clinical practices, regulatory regimes and ethical issues as co-constructed. In particular, the adoption of PGx will be shaped by wider social and technical developments in genetics and biotechnology;

- The field of PGx is marked by high level of technical, clinical and commercial uncertainty. As a consequence, we should expect to see an emerging policy agenda that is quite heterogeneous, mutable and highly context specific. Such a framework should be flexible and allow adjustment to be made as innovation proceeds;

- The emerging policy, ethics and governance framework will therefore need to be quite broadly drawn if PGx is to be effectively managed on an ongoing basis. Private corporations and clinicians are having to work in a highly contingent innovation landscape and this may be an important reason why adoption has been slow;

- Rather than placing an emphasis on the test-bedding or piloting of PGx application in established institutional settings, policy should explore how it can foster the creation of 'innovation niche spaces' in which new technologies might be nurtured by both public and private sector interests. A series of niche developments may appear as a result of competing innovation expectations, which for a time will generate more, rather than less, complexity;

- The pattern of 'absorption' of PGx within healthcare systems will therefore critically depend on how far the existing knowledge base and professional practices open up to create institutional spaces through which PGx might be introduced;

- PGx will be more likely to be successfully mobilised where commercial, professional and policy interests converge, and these in turn will be reflected in the creation of robust expectations about the utility and value of PGx;

- At present there is no obvious policy model given the different perceived opportunities and risks of PGx; instead the key problem is how to build strategic capacity without getting trapped into a policy/business model that will fail. This requires an approach that is highly *reflexive* and accepts the need for iteration and reflection about the way discrete policy elements need to be mobilised simultaneously and not sequentially;

- Public policy will therefore need to adopt and develop a 'comprehensive framework', that not only requires a reflexive and cautious approach, but one that questions the allocation and resources to be devoted to PGx itself and the opportunity costs this might involve. This will ensure that any pay-off from PGx is perceived to meet genuine need.

The way in which these different factors are influencing the selection and development of different technological options will be considered in the next section. This will be followed by a set of proposals that may form part of a comprehensive policy framework.

6.3 Assessing the current trajectory of PGx development

The data presented in the preceding chapters and the analysis carried out above enables an assessment to be made of the different factors that are shaping the development and adoption of PGx for each of the main technological options discussed in Chapters 1 and 2. In particular, we have looked at the level of interest from large and small firms, the nature of the regulatory environment, the main barriers to clinical adoption, and the potential public health benefits and health policies issues raised for each option. This is summarised in Table 6.2. Although this can only be a broad-brush analysis, it does help to identify options that have a significant level of industrial support, a permissive regulatory environment and relatively low barriers to clinical adoption, and those that have attracted little commercial support and face significant regulatory and clinical challenges. It also highlights key areas for public policy action that may be critical in shaping the emerging field in order to maximise public health gain.

As a result, the 12 technological options for PGx can be divided into four groups as follows:

A. Applications of PGx that have a direct commercial benefit to the pharmaceutical industry and largely fit into established patterns of innovation and healthcare delivery

This group of applications includes:

- Option 1. Discovering new drugs which work well in the entire population;
- Option 3. Pre-clinical testing and early stage trial design/ monitoring of new drugs;
- Option 12. Stratification of diseases into sub-types.

These are marked by: 1) a high level of commercial interest from large firms; 2) a permissive regulatory environment; 3) the absence of major barriers to clinical adoption (but Option 12 may require diagnostic genotyping); and 4) the absence of significant issues for health policy. There is already evidence that Options 1 and 3 are becoming widely entrenched in the pharmaceutical industry and that disease stratification (Option 12) is also becoming a significant feature of drug discovery and development. In this sense, the further development of these options will be driven and shaped by large companies and do not appear to face any significant barriers to adoption. *It therefore seems likely that these applications of PGx will continue to be integrated into established internal industrial processes and that disease stratification, most notably for cancer, will become widespread.*

B. Applications of PGx that offer some commercial benefits to the pharmaceutical industry, but require new forms of innovation and the creation of new service and regulatory infrastructures.

This group of applications includes:

- Option 2. Discovering new drugs aimed at genomic sub-populations;

- Option 5. Later stage trial design and monitoring of new drugs to target 'good responders';
- Option 7. Market (label) extension of licensed products restricted by ADRs.

These are marked by: 1) some level of interest from large companies; 2) a cautious regulatory environment; 3) barriers to clinical adoption due to the need for pre-prescription genotyping; and 4) absence of significant issues for health policy. Each of these options involves the creation, or repositioning, of products based on pre-prescription genotyping. As a consequence, they require new regulatory and practice infrastructures, and are predicated on market segmentation. The potential benefits to the pharmaceutical industry are significant in terms of improving the efficiency of the drug development process and extending product sales. However, these are only likely to be realised if viable business models can be created for new products aimed at segmented markets (Options 2 and 5) or if the increased sales from market extension is greater that the cost of genotyping and the service changes associated with it. *The future development of these options is therefore uncertain and largely contingent on the commercial strategies adopted by large pharmaceutical companies*. However, two factors will be important in influencing commercial viability, namely the overall regulatory environment governing products targeting patient sub-populations and the availability of financial incentives to develop products for sub-populations, such as orphan drug legislation.

C. Applications of PGx that offer direct public health benefits, but are not commercially attractive to the pharmaceutical industry and require new forms of service infrastructure

This group of applications includes:

- Option 8. Pre-prescription screening to identify patients at risk of ADRs from licensed drugs;
- Option 9. Post-marketing surveillance of licensed drugs;
- Option 10. Pre-prescription screening to identify 'good responders' to licensed drugs.

These are marked by: 1) a low level of commercial interest from large firms, but a high level of interest from small firms developing diagnostics; 2) a permissive regulatory environment; 3) barriers to clinical adoption due to the need for pre-prescription genotyping; and 4) the potential for significant public health benefits. Each of these options aims to improve the safety or efficacy of licensed products, many of which will be generic. As has been highlighted, they offer important public health benefits in terms of improved patient care and increased cost-effectiveness, but are not commercially attractive to large companies. *Their development is therefore likely to be driven by the actions of smaller diagnostic companies and health care providers, such as the NHS, and will be heavily influenced by public policy.* Furthermore, whilst the regulatory environment appears to be generally favourable, there remains some uncertainty about the exact way in which PGx testing will be linked to already licensed products.

D. Applications of PGx that have little direct commercial or public health benefits, raise regulatory concerns and require new service infrastructures

This group of applications includes:

- Option 4. 'Rescue' of new products in late stage trials (ADRs);
- Option 6. 'Rescue' of new products based on efficacy;

- Option 11. Use of efficacy data in drug marketing.

These are marked by: 1) a low level of commercial interest; 2) a cautious regulatory environment; 3) barriers to clinical adoption in the form of pre-prescription genotyping; and 4) offering few direct public health benefits. *As a consequence, it is unclear which set of actors in the innovation system will drive their adoption.* In the future there may be commercial proof of principle for drug rescue/ repositioning or the use of PGx data in marketing, but until this is demonstrated the major regulatory barriers that face products that have failed clinical trials may prove insurmountable.

In conclusion, it can be seen that these four groups of applications of PGx will be shaped by the interaction between company strategies, regulatory regimes, the development of service infrastructures and the actions of health policy makers. The first two sets of applications appear to be largely driven by large companies, whilst the success of the third group of applications will be heavily dependent on the implementation of effective public policy.

6.4 Towards a 'comprehensive framework'

With respect to PGx, the primary aims of public policy should be to improve the health of the population by:

- Supporting the creation of safe and effective medicines that meet unmet clinical need;
- Improving the safety and efficacy of new and already licensed medicines;
- Promoting the cost-effective use of healthcare resources.

In order to achieve this, we have argued that policy makers need to adopt a broad, comprehensive framework for PGx that is responsive to the emergent technology, commercial interest and regulatory and clinical responses. We have suggested that this framework is best developed from within a public health perspective and will be guided by the following principles:

A. The development and adoption of PGx should be understood in systemic terms in which health services, clinical practices, regulatory regimes and ethical issues are seen as co-constructed;

B. The emerging policy agenda will be broadly drawn, heterogeneous, and highly context specific and will need to be flexible to allow adjustment to be made as innovation proceeds;

C. Policy should explore how it can foster the creation of 'innovation niche spaces', which will critically depend on opening up the existing knowledge base and professional practices, as well as creating robust shared expectations about the utility of PGx;

D. The focus should be on building strategic capacity, and the need for reflection about the benefits and opportunity costs of adopting PGx, and the simultaneous co-ordination of discrete policy elements.

Specifically, a comprehensive framework might have the following objectives:

6.4.1 Supporting industrial innovation

In broad terms, policy might aim to steer industry to use PGx in a way that fosters the development of new drugs that have improved safety profiles, greater efficacy, proven utility and meet clinical need. However, from the research the main issue of concern to industry is the need to:

- **Recommendation 1**: *Create greater regulatory certainty* in order to sustain long-term investment in PGx. In particular, this relates to the:
  - Type of data required by regulators and how it will be used within the assessment process;
  - Process of assessing and approving companion diagnostics;
  - Oversight of the use of companion diagnostic tests;
  - Nature of the pharmacovigilance regime associated with PGx;
  - Extent to which PGx tests will be mandated for already licensed medicines and the evidence required to make label changes;
  - Resolution of the ethical issues surrounding the more general use of genetic testing and personal genetic information in healthcare systems.

6.4.2 Preventing market failure

A major issue this study has identified is the possibility of market failure for technological options of PGx that offer considerable public health benefits, but that appear to be commercially unattractive (these include developing new drugs for so called 'orphan genotypes'; pre-prescription screening to identity patients at risk of ADRs from already licensed drugs or who will be good responders to already licensed drugs; the use of PGx in post-marketing surveillance). This problem might be addressed through the following measures:

- **Recommendation 2**: *Extend orphan drug legislation* to provide incentives for companies to develop drugs for markets and patient groups segmented by PGx tests that may not otherwise be commercially attractive.
- **Recommendation 3**: *Create public-private PGx partnerships* to develop diagnostic tests for a number of important and widely used already licensed medicines that are currently commercially unattractive.

6.4.3 Protecting the safety and rights of the public

There are a number of ways in which the introduction of PGx might be used to improve the safety of medicines (pre-prescription genotyping, improved pharmacovigilance). At the same time, PGx also raises new issues for public safety, including the risk of more widespread and potentially dangerous off-label prescribing and threats to privacy and patient confidentiality through the disclosure of personal genetic information to third parties. To realise the potential safety benefits of PGx and address these concerns public policy might aim to:

- **Recommendation 4**: *Enhance pharmacovigilance systems* to ensure that PGx technology and data are introduced into the monitoring of new medicines and already existing drugs where appropriate.
- **Recommendation 5**: *Improve drug labelling, the oversight of off-label prescribing and the transparency of decision-making* on the inclusion of PGx data on drug labels, including whether such data is made mandatory or not.
- **Recommendation 6**: *Ensure tight statutory regulation and oversight of the third party use of personal genetic information*.

6.4.4 Supporting the clinical adoption of PGx

This study has stressed that the clinical adoption of any drug is highly dependent on its clinical profile and its use in specific contexts. However, the research has identified a number of important barriers that appear to be common across case studies and might stand in the way of the widespread adoption of PGx testing in routine clinical practice. These include, the utility of the technology in practice, the lack of evidence (on the benefits of testing, the genotype-phenotype relationship, and cost effectiveness), and how testing will be funded. To overcome these barriers public policy might aim to:

- **Recommendation 7**: *Include data on proof of clinical utility in the approval process for all PGx related diagnostic products.*
- **Recommendation 8**: *Give greater public funding to help create an evidence base on the clinical utility and cost-effectiveness of using PGx testing for important already licensed drugs*. Greater effort should also be made to improve the provision of information to clinicians on test availability and clinical utility.
- **Recommendation 9**: *Support the development of PGx delivery systems* that can be integrated in established patterns of professional practice. The process of translation could be stimulated by providing clear guidance on exactly how PGx tests might be used and interpreted by clinicians. This might be included in the design of the electronic patient record and computer-based decision support systems.

6.4.5 Creating a PGx innovation platform in health delivery systems

Any systematic approach that is taken by public health agencies will establish the context within which future drug regimes based on PGx will operate. This includes the policies, practices and infrastructures that support the development, introduction, purchase, use and governance of new and existing medicines – these might collectively be called a 'medicines innovation platform'. As has been stressed throughout this report, the collection of policies and institutional arrangements that constituted such a platform would need to be flexible, foster the creation of innovation niches and reflect on its own actions and the value of new technologies such as PGx. Policies to support a PGx innovation platform might include the following:

- **Recommendation 10**: *Provide further investment in developing the overall structuring of genetic health service delivery* and especially the organisation, funding and governance of genetic testing. However, it must be stressed that it will be neither viable nor rational to adopt PGx in all therapeutic areas.
- **Recommendation 11:** *Explore alternative ways of providing PGx testing services*. It is not clear that the established structure of genetic testing laboratories in the UK either has the capacity or is best placed to carry out high volumes of routine PGx testing. Policy should explore a range of different service delivery models.
- **Recommendation 12:** *Fund ongoing and systematic evaluation* of the routine use and utility of medicines, the wider cause of ADRs, and the benefits of PGx in this context.

6.4.6 The contribution of social science in helping understand the development of pharmacogenetics

This report has adopted an explicit conceptual framework based on current research in the social sciences to describe, analyse and assess the current and future development of pharmacogenetics. By adopting a systemic comprehensive framework, that stresses the co-construction of new technologies, industries, clinical practices, health services and regulatory regimes, new insights can be provided into the process of technical change in medicine. Not only does this help better understand the drivers and barriers that shape adoption, but it also helps identify key issues for policy intervention that more traditional analytical approaches may miss.

Research on the introduction of pharmacogenetics has been supported in the UK by bodies such as the Wellcome Trust and the ESRC, with results from a number of empirical studies now available in the academic literature. This effort needs to continue, along with specific encouragement for dissemination to the wider health care policy community including clinicians. The July 2006 publication *Policy Issues in Pharmacogenetics: a Policy Briefing from the UK Pharmacogenetics Study Group* published by social scientists from several UK universities is a good example of the latter.

- **Recommendation 13:** *Continue to support multidisciplinary social science research on emerging genetic technologies, such as PGx*.

Table 6.2 Key factors shaping the development of different options for PGx

	Level of interest from large companies	Level of interest from small firms	Regulatory environment	Barriers to clinical adoption	Public health benefits & health policy initiatives
Drug discovery					
1. Discovering new drugs which work well in entire population	High	Low	Permissive	None	No significant health policy issues-
2. Discovering new drugs aimed at genomic sub-populations	Low	Low	Permissive	Need for pre-prescription genotyping	Creation of new orphan populations - Orphan drug legislation
Safety of drugs in development					
3. Pre-clinical testing and early stage trial design/ monitoring	High	High	Permissive	N/a	No significant health policy issues
4. 'Rescue' of products in late stage trials (ADRs)	Low	Low	Cautious (safety concerns)	Need for pre-prescription genotyping	No significant health policy issues
Efficacy of drugs in development					
5. Later stage trial design and monitoring to target 'good responders'	Medium	Medium	Cautious (safety concerns)	N/a	No significant health policy issues
6. Drug rescue (efficacy)	Low	Low	Cautious (safety concerns)	Need for pre-prescription genotyping	No significant health policy issues

Safety of licensed drugs					
7. Market (label) extension of products restricted by ADRs	Medium	Low	Cautious (safety concerns)	Need for pre-prescription genotyping	No significant health policy issues
8. Pre-prescription screening to identify patients at risk of ADRs	Low	High	Permissive	Need for pre-prescription genotyping	Potential public health benefit – greater investment in creating evidence base for generic products
9. Post-marketing surveillance	Low	Low	Permissive	None	Potential public health benefit - new policies to improve drug monitoring
Efficacy of licensed drugs					
10. Pre-prescription screening to identify 'good responders'	Low	High	Permissive	Need for pre-prescription genotyping	Potential public health benefit – greater investment in creating evidence base for generic products
11. Use of efficacy data in drug marketing	Low	Low	Unknown	None	No significant health policy issues
Disease genotyping					
12. Stratification of diseases into sub-types	High	High	Permissive	May require pre-prescription genotyping	No significant health policy issues

About the authors

Dr Paul Martin is Reader in Science and Technology Studies and Deputy Director of the Institute for the Study of Genetics, Biorisks and Society (IGBiS), University of Nottingham. He originally trained as a molecular biologist and subsequently worked as a health policy analyst before taking a PhD in science and technology studies at the University of Sussex. His research interests cover innovation in the biotechnology industry, the social and ethical issues raised by genetics and the regulation of new medical technologies. Other recent major grants include studies of the impact of genomics on innovation in the pharmaceutical industry (ESRC) and expectations of haematopoietic stem cell technology (ESRC). He was a major contributor to the European Commission's Institute for Prospective Technological Studies international comparative study on pharmacogenetics in 2006. Recent publications include articles in *Social Studies of Science*, *Science as Culture*, and *Nature Biotechnology.*

Dr Graham Lewis is a Research Fellow in the Science and Technology Studies Unit (SATSU), University of York and Director of the University's new Centre for Prospective Regulation. Originally trained as a chemist, he worked for many years in the pharmaceutical industry in the UK and USA before obtaining a PhD in science and technology policy at the University of Manchester. He has researched the development of pharmacogenetics for a number of years, focusing on factors shaping clinical adoption and the part played by regulatory agencies. Other interests include international harmonisation of medicines regulation and international biorepositories. On-going work includes studies on PGx, diagnostic tests and clinician acceptance, part of the ESRC Science in Society Programme, and the pharmacogenetics of warfarin (with M. Pirmohamed and others) for the UK Department of Health. He was a major contributor to the European Commission's Institute for Prospective Technological Studies international comparative study on pharmacogenetics in 2006. Recent publications include articles in *Nature Genetics Review* and *Nature Biotechnology*.

Dr Andrew Smart is a Senior Lecture in Sociology at Bath Spa University. His interest is in the social aspects of genetic health technologies, which he has empirically explored in a range of contexts including the mass media, the commercial sector, clinical medicine and research and clinical laboratories. His current research (associated with The Ethox Centre, University of Oxford and the Oxford Genetics Knowledge Park) is focused on the experiences of patients offered a clinical service that employs DNA testing and 'cascade screening' for an inherited heart condition. Along with colleagues from Nottingham, London and Oxford, he is coordinating two studies funded by The Wellcome Trust: the first is on the use of the categories of race and ethnicity in population genetic research, and the second is exploring the issues surrounding the governance of genetic databases. He has published in several journals including *Sociology of Health and Illness, Bioethics, Critical Public Health, Biosocieties, Studies in the History and Philosophy of Biological and Biomedical Sciences* and the *International Journal for Quality in Health Care.*

Professor Andrew Webster is Director of the Science and Technology Studies Unit (SATSU), University of York and Head of the Department of Sociology. He is a member of various national Boards and Committees, including the UK Department of Health's Advisory Group on Genetics Research and the MRC Stem Cell Bank Steering Committee. He was Director of the ESRC/MRC Innovative Health Technologies Programme, and is national co-ordinator of the ESRC Stem Cells initiative (2005-8). He is also a member of the Royal Society's Expert Working Group on Informatics, and recently co-ordinated and co-authored the ESRC's Research Ethics Framework. His most recent texts are *New Medical Technologies and Society: Reordering Life* (2004) (with N. Brown), *New Technologies in Healthcare: Challenge, Change and Innovation* (2006) (ed), and *Health, Technology and Society: A Sociological Critique* (forthcoming). His research interests are in the areas of the sociology of science and technology, science policy studies, innovative health technologies and their use, the sociology of innovation, the commercialisation of research, and technology foresight. He is currently undertaking research on stem cells, the implementation of pharmacogenetics, and public confidence in informatics systems. He recently won an ANU research fellowship at Canberra.