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Competing interests statement
The author declares no competing financial interests.

Online Links

DATABASES
The following terms in this article are linked online to:
Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
ADRB1 | ADRB2 | *CFTR* | *CYP1A2* | *CYP2D6* | *CYP2E1* | *CYP3A4* | *TPMT* |
OMIM: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
cystic fibrosis
Access to this interactive links box is free online.

SCIENCE AND SOCIETY

Integrating pharmacogenetics into society: in search of a model

Andrew Webster, Paul Martin, Graham Lewis and Andrew Smart

Abstract | There has been considerable scientific, corporate and policy interest in the more effective use of genetics in both drug development and delivery. Pharmacogenetics — the study of the relationship between an individual's genetic makeup and response to medicinal drugs — has attracted global interest, but will it live up to its promise? Looking beyond the hype that has accompanied much of the commentary in the area, the future of pharmacogenetics will depend on how competing interests and options are resolved.

Pharmacogenetics (PGx) is concerned with understanding and, in the clinical setting, managing the relationship between genetic variation and an individual's response to medicinal products. It provides the possibility of targeting drugs according to a person's genetic make-up — so-called 'personalized medicine' — although it will probably be used to stratify patient populations into groups determined by their genotype[1]. Stratification along these lines might significantly improve the development, testing and use of drugs. However, realizing these benefits will depend on the development of viable commercial strategies and clinical delivery in the next few years. It might also require new approaches to regulation, drug approval and PHARMACOVIGILANCE at national and international levels.

Given its potential, PGx has gained considerable interest in the pharmaceutical industry and among clinical researchers — such as in the US-based National Institutes of Health Pharmacogenetics Research Network, as well as among national health policy agencies, as indicated by the UK government's recent White Paper on the introduction of PGx (and other genetic techniques) into the health service[2].

PGx is on the threshold of making a major impact in commercial labs and in the clinic. But, despite its promise and the heavy investment made in the technology, many companies still question whether there is a coherent business, health policy or regulatory model emerging to shape the future development of PGx. Here, on the basis of detailed research conducted on the social, economic and regulatory factors shaping PGx during the past 2 years (P.M., G.L., A.S. and A.W., *False Positive? The Clinical and Commercial Development of Pharmacogenetics*, The Wellcome Trust report, also see Online links box), we aim to provide at least a partial answer to this question. After reviewing PGx in the commercial sector, and identifying the different strategies being pursued, we discuss its likely clinical role, the regulatory regime that is emerging, and the wider policy implications that it raises, especially for advanced health-care systems.

The development of PGx technology

Who is developing PGx? There are two broad groups involved in the commercial development of PGx. Firstly, about 30 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. This core group is described in TABLE 1. Most of these firms have been formed since 1997 and are mainly located in the United States. Between 1997 and 2000, there was a steady growth in the number of small to medium enterprises working with PGx. However, in 2001 this growth slowed, and in 2002 consolidation of the sector started to take place, with five mergers and acquisitions of small PGx firms between 2001 and 2002.

Secondly, there are about 30 large pharmaceutical companies who are investing in PGx, either internally or through collaborations with smaller PGx firms. The main players — primarily global firms — are listed in BOX 1. GlaxoSmithKline, Roche and Pfizer are among the larger investors in this technology. However, it should be stressed that investment by major pharmaceutical companies can be measured along a 'spectrum' of commitment, with some companies more committed to PGx than others, at this point in time. In addition to these two main groups, a number of specialist diagnostic companies (for example, Beckton Dickinson) and US health-care providers (for example, Kaiser Permanente) are also investing in the technology through the formation of collaborations with smaller firms.

Since the first collaboration on PGx between Genset and Abbott in 1997, a further 180 industrial alliances have been formed around the technology. A similar pattern to the growth of dedicated firms can be seen, with a steady increase in the number of collaborations until 2001, followed by a declining rate of growth (FIG. 1). This pattern indicates that some of the momentum behind the technology might have plateaued recently, partly because of complications in getting it to 'work' effectively, and partly as a result of a stabilizing of investment[3].

Options for the development of PGx. There is no single or principal model for adopting PGx technology. Instead, the development of the field can 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. We have identified five broad innovation options for the application of PGx (BOX 2).

The first of these is aimed at improving the discovery of new drugs. Options 2 and 3 are mostly concerned with using PGx to improve the safety and efficacy of prospective drugs through the re-design of clinical trials. Finally, PGx is also being used to improve the safety and efficacy of medicines that have already

Table 1 | **Biotechnology and genomics companies developing pharmacogenetics**

Company	Founded	Location	Focus
Acadia Pharmaceuticals	1997	US	Pharmacogenomic drug discovery in psychiatry
Affymetrix	1992	US	Gene chips for pharmacogenetic applications
Axis-Shield	1982.	UK	Clinical diagnostics
Celera Diagnostics	2000	US	Clinical PGx diagnostics
Curagen	1996	US	PGx association and toxicogenomic studies
DeCODE (Encode)	1996 (1999)	Iceland	Clinical PGx diagnostics (pharmacogenomics CRO)
DiaDexus	1997	US	Clinical PGx diagnostics
DNAPrint Genomics	2000	US	Clinical PGx diagnostics
DxS	2001	UK	PGx genetic analysis services
Epidauros	1997	Germany	PGx assays and services
Epigenomics	1998	Germany	Clinical PGx diagnostics
Exon Hit Therapeutics	1997	France	Clinical PGx diagnostics
First Genetic Trust	2000	US	Genetic banking services
Gaifar	1997	Germany	Clinical PGx diagnostics (viral genotyping)
GAG Biosciences	2000	Germany	PGx genotyping services
Genaissance	1997	US	PGx services and diagnostics
Gene Logic	1994	US	Toxicogenomic serivces
Genelex	1987	US	Direct to consumer PGx testing
Genomics Health	2000	US	PGx patient testing services
Genset (Serono)	1989	France (Switzerland)	Association studies of drug response
Gentris	2001	US	Clinical PGx diagnostics
Interleukin Genetics	1999	US	PGx diagnostics
Millennium	1993	US	Clinical PGx diagnostics/ pharmacogenomic drug discovery
Myriad Genetics	1991	US	Clinical PGx association studies
Orchid Biosciences	1995	US and UK	PGx genotyping services
Oxagen	1997	UK	PGx association studies
Perlegen	2000	US	PGx association studies
Sciona	2000	UK	PGx diagnostics
Third Wave	1993	US	Clinical PGx diagnostics
Vita Genomics	2001	Taiwan	PGx association studies

CRO, clinical research organization; PGx, pharmacogenetics; UK, United Kingdom; US, United States.

been licensed, mainly through the use of pre-prescription patient genotyping (options 4 and 5).

A detailed analysis (P.M., G.L., A.S. and A.W., The Wellcome Trust report) of PGx investments and collaborations reveals that most of the large pharmaceutical companies invest mainly in options 1–3 — aimed at improving internal processes, reducing costs and enhancing the efficiency of drug discovery and development[4]. These companies have little commercial interest in applications of PGx that are aimed at already licensed medicines, except where value can be added by extending product licences and, therefore, markets (for example, ABACAVIR (Ziagen; GlaxoSmithKline)). There has also been some limited investment in option 4, the best example being the case of alosetron hydrochloride (Lotronex; GlaxoSmithKline). This drug, which is used for the treatment of irritable bowel syndrome, was approved then quickly withdrawn voluntarily by the manufacturer because of a number of adverse drug reactions (ADRs)[5]. It was subsequently approved again in the United States under 'RESTRICTED MARKETING' TERMS as a result of doctor/patient demand[6]. Consequently, research by the manufacturer, GlaxoSmithKline, now aims to identify the relationship between ADRs and individuals' genetic profiles as part of the US Food and Drug Administration (FDA)-imposed post-marketing commitments. This PGx-based research involves the prospective collection and analysis of samples from additional trials. The aim of this research is to identify SNPs or haplotypes that can predict adverse events in patients and to determine the genotype of polymorphic cytochrome protein 450 (CYP450) enzymes that are responsible for the drug's metabolism (REF. 7, and Roses, A., unpublished data).

Specialist diagnostics firms and health-care providers show the greatest interest in the pre-prescription genotyping of patients, to improve the safety and efficacy of established products and the development of drug-test combinations. Both aims offer the prospect of new diagnostics markets and reduced health-care costs. Although this might point to a clear business model, the situation is more complicated in relation to the development of new products, as larger firms will inevitably be involved. New drugs that are developed using stratified clinical trials on the basis of PGx tests will often require a dedicated drug-test combination to be licensed. In such cases, it is in the interests of pharmaceutical companies to undertake drug-test development, either themselves or through collaboration with specialist companies.

The smaller PGx firms offer a range of products and services across all the different options, with many working on more than one approach. Options (1–5, as outlined above) for the development of PGx, and the relationships of the main groups of firms involved in each option, are shown schematically in FIG. 2.

Assessing the medium-term development of PGx. In summary, the pharmaceutical and biotechnology industries are making an important but varied investment in PGx. However, exactly which options are adopted depends on many crucial factors, including technical feasibility, commercial attractiveness, regulatory considerations and the ability to integrate the technology into routine clinical practice. So, whereas 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, and it is here that investment by smaller diagnostic firms and health-care providers will probably be important. However, even with this investment, there is the real prospect of general 'market failure'; that is, the priorities of both large and small firms might not deliver the

Box 1 | **Pharmacogenetics investors**

US-based

Abbott Laboratories, 4 | Amgen, 1 | Becton Dickinson, 2 | Biogen, 3 | Bristol-Myers Squibb, 5 | Dade Behring, 1 | Janssen, 1 | Lilly, 2 | Merck, 3 | Pfizer*, 10 | Schering Plough, 1 | Wyeth, 1

European Union-based

AstraZeneca, 5 | Aventis‡, 5 | Bayer, 4 | Biomeriux, 1 | Boehringer Ingelheim, 1 | GlaxoSmithKline§, 11 | Novartis, 2 | Novo Nordisk, 1 | Roche, 2 | Roche Diagnostics, 3 | Sanofi Syntholabo, 1

Japanese companies

Daiichi, 2 | Ono Pharmaceuticals, 1 | Sankyo, 1

*Includes Parke-Davis, Warner Lambert and Pharmacia. ‡Includes Rhone Poulenc Rorer. §Includes SmithKline Beecham. Numbers refer to number of alliances with other companies.

greatest public health benefits (for example, testing for non-responders to widely used, already licensed drugs, such as the selective serotonin-reuptake inhibitors).

Translation into clinical practice

Discussions about PGx are approaching the issue of adoption in clinical practice[8–12]. However, there is little evidence about the practical and professional issues that might help or hinder its adoption in specific clinical contexts.

We recently examined the factors that affect the adoption of PGx through case studies of four drugs in distinct clinical contexts: CLOZAPINE (Clozaril; Novartis), WARFARIN, the THIOPURINES (6-mercaptopurine and azathioprine) and ISONIAZID (P.M., G.L., A.S. and A.W., The Wellcome Trust report). These drugs were chosen because they are known produce different responses depending on genotype and require monitoring regimes to ensure patient safety. We found that, in general, improved practices in prescribing drugs or patient experience (by getting the right dose earlier and avoiding ADRs), and the chance to refocus health service costs (by avoiding wasteful treatment), were the important factors behind the introduction of PGx in these cases[13–15]. However, there were concerns about the use and practicality of PGx in specific clinical contexts and about the weakness of the current evidence on which support for its introduction was based[8,9,11,12].

To illustrate these points, we will make some brief suggestions on the basis of our analysis of clozapine, which is used as an antipsychotic drug for patients with schizophrenia who do not respond to, or cannot tolerate, other drugs. Clozapine is effective in up to 50% of patients who do not respond to other drugs and 80% of those who suffer from intolerable side effects from other drugs[16]. However, the drug itself is associated with potentially fatal blood disorders (notably AGRANULOCYTOSIS), which necessitates a laborious and time-consuming blood monitoring process. PGx testing could, in principle, be used to identify not only those who suffer this response, but also those who are likely to be 'good responders'[17,18]. By prescribing the drug only to patients who do not suffer agranulocytosis and who meet the second criteria, the overall level of ADRs could be reduced.

Our research with clinical practitioners indicates that the perceived problems associated with the adoption of PGx testing for clozapine relate to the specific context of its use. These problems include the difficulty of validating a genetic marker for drug response, given the problem of establishing measurable biological endpoints in the diagnosis and treatment of schizophrenia. Although replicating small association studies in large randomized trials might close the 'credibility gap' between a genetic marker and clinical outcomes, there are concerns about the practicalities and ethics of conducting such trials in mental-health settings. Even if a test for 'good responders' can be proven, the availability of a near categorical answer still might not justify a denial of treatment, as clozapine is often a 'last resort' drug. Furthermore, patients deemed 'genetically suitable' could remain clinically unsuitable, for the same reasons that currently limit prescription, such as a lack of personal and/or social stability, a patient's unwillingness to have regular blood monitoring, or simply patient non-compliance with the drug regime. Finally, there are also concerns that PGx might add further complexity to an already cumbersome clinical prescription process.

Whilst these barriers might not be insurmountable, they illustrate not only the type of concerns voiced by some clinicians about the adoption of PGx, but also how potential barriers are specific to clinical context. In light of this, we identify some key points, covering a range of cases, that highlight the general problems associated with establishing a clinical model for PGx.

Clinicians currently have little evidence of the utility, or even the validity, of PGx in clinical contexts[9]. Assuming that validity (analytical and clinical) can be proven, utility remains a conspicuous hurdle; this is where visions of PGx meet the reality of existing clinical practice. Generic criteria that have been suggested for judging the clinical use of PGx tests have included the value that is added to treatment objectives (such as prompt therapeutic response), the existence of other treatments, the size of the

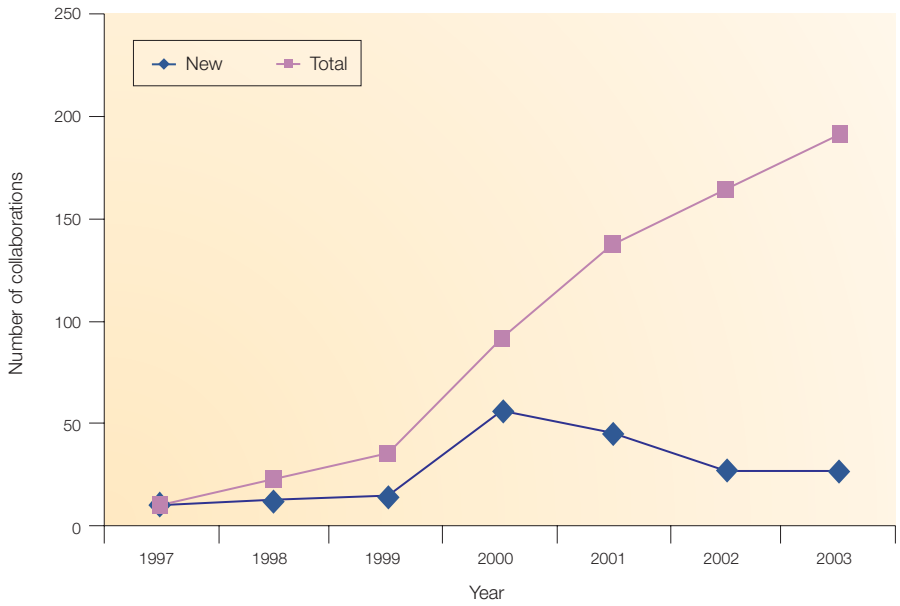

Figure 1 | **Commercial collaborations based on pharmacogenetics.** Whereas commercial collaborations have increased from 1 in 1997 to almost 200 in 2003 (pink line), there has been a decline in their rate of growth since 2001 (blue line).

Box 2 | **Potential applications of pharmacogenetics (PGx)**

Option 1: using PGx to discover better drugs
Discovering drugs for specific genomic sub-groups (allelic variants of drug target).
Discovering drugs that work in all sub-groups (ensuring leads work in all allelic variants).

Option 2: PGx to improve the safety of new drugs in development
Early stage trial design and/or monitoring (for example, ensuring balanced trial population of cytochrome P450 variants).
'Rescue' of drugs that fail clinical trials owing to safety problems.

Option 3: PGx to improve the efficacy of new drugs in development
Targeting late-stage trials as 'good responders' (prospective).
'Rescue' of drugs that fail clinical trials owing to lack of efficacy (retrospective).

Option 4: improving the safety of licensed drugs
Pre-prescription patient testing for risk of adverse drug reactions (ADRs) (for example, thiopurine methyltransferase).
Label and market extension of drugs that have been restricted by ADRs (for example, abacavir).
Improved post-marketing surveillance.

Option 5: improving the efficacy of licensed drugs
Pre-prescription patient testing to identify good responders.
The use of efficacy data in drug marketing.

patient population and the scale of negative effects that might be avoided[9,11,12,19]. It has also been recommended that PGx tests are verified, with reference to reliability, information provided, and the frequency and magnitude of the response that it predicts[11].

However, in routine clinical decision-making, information about drug response can be just one of the many influencing factors. Furthermore, because drug response is affected by several biological and environmental factors, even accurate PGx information might have limited value[12]. We found that, from the clinician's perspective, judgements about the use of a PGx test are likely to be highly context-specific, relating to the patient, their illness and the overall objectives and costs/benefits of treatment. As such, the degree of certainty that the PGx test offers was reported as a crucial factor for judging its usefulness. To encourage clinical adoption, it will be imperative for health practitioners to be in possession of clear information that links genotypes to clinical outcomes, and to have specific advice on how this might affect prescribing decisions, or alter drug dosage.

Practical barriers to the adoption of PGx might include the potential for increased time and workload burdens for laboratories and clinics, especially if informed consent and counselling are deemed necessary[9,11,12]. There are also likely to be resource implications, given the anticipated high costs of this new technology[20]. However, tests that assist in the allocation of scarce resources might be well received by health-care payers and clinicians alike. More generally, PGx might require a culture shift in prescribing practice and might generate a need for (re-) education of health professionals[10–12]. Finally, there might be ethical concerns associated with denying treatment[21,22] as a result of a person being assigned into a particular category of genotype[23]. For example, patients might be excluded from using a particular drug as a result of a PGx test that indicated that they are 'at risk' from ADR, when evidence for this might only be probabilistic; it has been argued that clinical decision-making in regard to drug therapy should not solely be on the basis of gene association, but on a detailed patient history[24]. Moreover, there are wider ethical implications, for example, if PGx led to a significant number of 'orphan patients' that had been denied access to mainstream drugs developed for the more common, most responsive genotype[21,22,24].

It therefore seems unlikely that professional acceptance will be forthcoming where current practice is considered acceptable and the use and/or practicality of PGx is unclear. Much remains to be done to verify the use and practicality of PGx in specific treatment contexts before professionals are likely to adopt it as a routine or widespread part of clinical practice. So, the gradual use of PGx testing in the context of oncology, for example, reflects both the scale and importance of this disease area. It also demonstrates the need to improve the therapeutic value of existing drugs: results from studies on gene expression profiling in the cancer field to predict drug response illustrates how PGx testing might begin to meet the twin demands of use and practicality[25,26].

The emerging regulatory regime

Current regulatory approval of any drug is given on the basis of an assessment of efficacy and safety, which is based on data generated by a series of clinical trials. Clinical trials are based on the notion that the findings from studies of trials are 'generalizable' to the whole population. By contrast, the fundamental principle of PGx is that the drug is targeted at patients according (at least in part) to their genetically determined response, whether in terms of efficacy or ADRs. What does this mean for regulation?

Given the promised precision of PGx to determine drug response, it might be

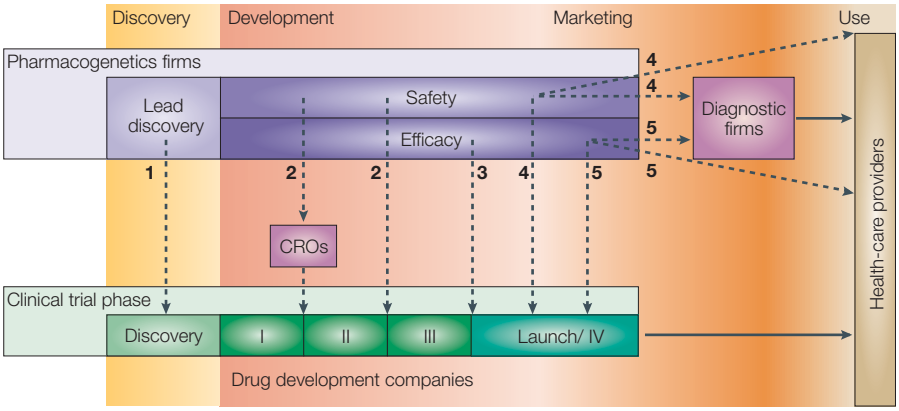

Figure 2 | **Collaborative links and strategic options for the use of pharmacogenetics (PGx).** The five options for commercially exploiting pharmacogenetics (1–5, see BOX 2) range from its use at the early stages of lead discovery (1) to its use when health care is being provided to patients (5). Different interests and needs lead to differing option priorities among actors in the PGx field. Dotted arrows in the figure indicate points of intervention in the drug development process, whereas solid arrows indicate potential PGx products. CROs, clinical research organizations; I–IV refers to the different phases of clinical development.

assumed that regulatory agencies (such as the FDA and the European Medicines Evaluation Agency (EMEA)), will demand that every drug undergo PGx testing. However, it is doubtful that this will be the case. PGx testing for a particular drug will probably be decided on the basis of the genetic factors that determine the drug's DISPOSITION, on its PHARMACODYNAMIC CHARACTERISTICS and on its THERAPEUTIC INDEX.

Regulators, at present, have the opinion that PGx will not be applicable for all types of drug, for both therapeutic and commercial reasons. The most suitable areas for the application of PGx therapy will be those in which new treatments are being developed and where existing treatments have a narrow therapeutic index[24].

The response of regulators

Over the past 18 months, the FDA (and the EMEA) has begun to collaborate with industry on PGx issues. Interventions by senior FDA staff, and statements by the recently departed FDA Commissioner, Mark McClellan, indicate that the FDA advocates the use of pharmacogenetic strategies to optimize clinical trials. The active encouragement of PGx by regulatory agencies today is in stark contrast to the position in 2001, when there was little indication of regulatory engagement with PGx.

However, the inconsistent evidence about the impact of PGx on therapy has lead to regulatory agencies adopting a number of procedures to enable a more 'united' form of regulatory review, notably the FDA's 'voluntary pharmacogenomic data submission', or 'safe harbour', proposal[27]. Initiating this proposal has required the FDA to encourage submission of pharmacogenomic data (defined data from pharmacogenomic or pharmacogenetic tests) early in the development process. This then helps discussion between the regulators and industry; provides more information on how useful such data could be, and attempts to address industry concerns about the use of such submitted data[28]. Concerns about this process focus on the possibility that data submitted might, for one reason or another, eventually form part of the formal assessment procedures. For example, corporations are concerned about how regulators might react if PGx data indicates that a potential safety issue is likely to emerge over time.

In Europe, the EMEA is developing a similar 'safe harbour' framework through its 'briefing sessions' format[29]. However, European regulators face a similar 'trust problem' to that of the FDA with regards to the status of submitted data. In the European case, care is being taken to distinguish between 'briefing sessions' and the current formal 'scientific advice' procedure, under which companies can seek advice about the type of data that regulators are likely to want included in a Marketing Authorization Application. Senior FDA staff have also stated that assessment will include what can broadly be defined as 'clinician acceptance' issues, particularly regarding the question of whether a PGx product can and will be used as specified[30].

It is possible that the important health benefits that result from PGx will come from targeted therapy using existing generic drugs, such as warfarin, the statins, 6-mercaptopurine and so on. 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 widely used to aid prescription decisions. The FDA has stated that it is considering whether PGx can provide such benefits more widely. For example, the availability of PGx data might change the risk/benefit assessment and trigger review of an already licensed drug[31]. Widespread adoption of such a policy could have important implications. Moreover, from a practical point of view, this broadening of the role of PGx (as well as its more commercially driven form) will mean that regulators will have to manage a massive increase in data, on a much wider range of treatments.

There is also the possibility of 'conflict of interest' situations developing, in which the main source of knowledge about a treatment or indication resides in industry. Regulators might become ever more reliant on company sources for expertise.

The future

At present, it is unclear how regulators might use PGx data. Indications are that gene

Glossary

ABACAVIR
An antiviral drug, used, in conjunction with other medicines, for the treatment of HIV.

AGRANULOCYTOSIS
A condition in which there is an insufficient number of white blood cells called neutrophils or granulocytes. This can be caused by a failure of the bone marrow to make sufficient neutrophils or when white blood cells are destroyed faster than they can be produced. Affected people are susceptible to infections.

BIOBANKS
Public or private tissue collections (derived from blood, DNA or other sources) comprising samples taken from specific disease groups or healthy populations. Their long-term purpose is to build biological banks that will provide new sources of (genetic) information about disease that have clinical value.

CLOZAPINE
An antipsychotic drug that works by decreasing abnormal excitement in the brain, used primarily to treat patients with schizophrenia who either fail to respond to or are unable to take other antipsychotic treatments.

DISPOSITION
Refers to all processes involved in the absorption, distribution metabolism and excretion of drugs in a living organism.

INVESTIGATIONAL NEW DRUG APPLICATION
(IND). An application that a drug sponsor must submit to FDA before beginning tests of a new drug on humans. The IND contains the plan for the study and is supposed to give a complete picture of the drug, including its structural formula, animal test results, and manufacturing information.

ISONIAZID
An antibacterial drug used to treat tuberculosis.

NEW DRUG APPLICATION
An application requesting FDA approval to market a new drug for human use in interstate commerce. The application must contain, among other things, data from specific technical viewpoints for FDA review — including chemistry, pharmacology, medical, biopharmaceutics, statistics and, for anti-infectives, microbiology.

PHARMACODYNAMIC CHARACTERISTICS
The characteristics of a drug that determine its biochemical and physiological effects and its mechanisms of action.

PHARMACOVIGILANCE
The process of monitoring medicines to identify previously unrecognised adverse effects; assessing the risks and benefits of medicines in order to determine what action, information and subsequent monitoring, if any, is necessary to improve their safe use.

THERAPEUTIC INDEX
The therapeutic index of a drug is the ratio of the toxic dose to the therapeutic (that is, 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).

'RESTRICTED MARKETING' TERMS
A drug may have such serious adverse effects that regulatory approval is given for use in a specific patient group only, for whom it can be used safely.

THIOPURINES
A family of chemotherapeutics used to treat leukaemia, as well as arthritis and inflammatory bowel disease.

WARFARIN
Used to prevent blood clots from forming or growing larger (anticoagulant). Typically used for patients with atrial fibrillation and those with a venous thromboembolism.

expression data, as well as the currently more common CYP450 data (both of which affect drug response) will feature in both 'voluntary submission' and formal INVESTIGATIONAL NEW DRUG APPLICATION (IND) and/or NEW DRUG APPLICATION (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 that are involved in drug response, but the question for both industry and regulators is how to use them. At present, the FDA does not have the understanding or expertise to interpret such data, although it is taking steps towards resolving this[32].

Regarding the underlying approach, it is unlikely that PGx testing will become part of regulatory requirements for all drugs. A drug that is highly efficacious across most of the population, has a wide therapeutic index and that shows little inter-individual variability in kinetics and dynamics should not necessarily require PGx testing. It would not be cost effective to do so. However, a drug that is efficacious in 30% of the population and that has a narrow therapeutic index, as do some current antipsychotics, should arguably be subject to PGx testing prior to prescription.

Despite uncertainty at this early stage, we can expect regulators to adopt this kind of approach when assessing PGx-based applications. In terms of drug development, constant dialogue between the industry and regulatory agencies will be important to ensure that the drug development process is as efficient as possible, whilst maintaining standards. PGx data have reportedly already been included in 70–80 NDAs and INDs submitted to the FDA[30]. Owing to confidentiality rules, it is not possible to determine in detail the type of information that these submissions contain. However, extrapolating from the picture in 2002, most are likely to refer to pharmacogenetic variability in CYP450 enzymes.

Regulatory regimes for diagnostic tests are complex and vary across countries. Historically, diagnostics have been subject to less scrutiny than medicinal products, with responsibility for approval often residing with a different agency. The harmonization of medicinal product regulation in Europe has led, in effect, to European-wide approval for innovative products[33].

Responsibility for diagnostic products, however, remains with national agencies, although adoption of the European *in vitro* diagnostics directive[34] will bring about greater coordination in the future. In the United States, tests developed by commercial labs — so-called 'home-brew' tests — are exempt from regulations that apply to marketed tests, although the FDA is expected to tighten controls on such tests in the future.

Policy implications

This paper has summarized some of the main initiators and constraints on the wider implementation and exploitation of PGx techniques in the contemporary health-care system. There are many options and competing interests involved that reflect not only the relative immaturity of the field (at least with regard to its role in drug development and clinical delivery) but also conflicting interests as to where priorities might lie (for example, between commercial and public health agendas). The five 'options' that are outlined in this paper are not all mutually exclusive, although from our evidence it is clear that the first three tend to be favoured by companies, whereas the last two are favoured by public health agencies. From a governmental perspective, where 'wealth and health' compete, this is an indication that there is no single strategy that presents itself as a self-evident candidate for setting policy priorities. The various overviews of the field that have recently emerged draw attention to these policy uncertainties characterizing the development of PGx[12,24].

Nonetheless, we can identify a number of forces that are at work, shaping the future agenda at a global level. First, as detailed above, commercial interests are actively exploring the uses of PGx, especially in the early stages of drug development, whereas regulatory agencies are moving more rapidly towards building a regulatory review process in conjunction with industry. In turn, public health systems are keen to reduce their drugs bill and derive health gains from PGx[35,36]. However, these developments are impeded by various barriers, such as clinician reluctance, ongoing commercial re-positioning (with many PGx firms shifting their focus downstream to drug development), and uncertainties within regulatory agencies about the wider implications of PGx for whole classes of drug[24].

There will be attempts, as in any complex socio-technical system, to try to bring order and stability to the deployment of this new technology, but an equilibrium point might take some time to reach. In part, this is because, beyond the confines of PGx itself, wider developments in pharmacogenomics, complex disease genetics, BIOBANKS and functional genomics put pressure on the PGx field and disturb any hard-won ethical, commercial and clinical stability[23,24]. For example, the phenotypic information that will be crucial to the future use of biobanks and the emergence of genetic epidemiology will probably aim to link to phenotypic information that relates to PGx in the clinic. In this instance, patients would be asked to give consent for this information to be used, which might eventually indicate links to a predisposition to genetic disease. In short, genetics will be applied to a wider range of projects than at present (primarily specialized genetics services). The balance between competing demands and expectations might become the main task for policy-makers, counsellors, clinicians and users. At present, there is no obvious public health policy model, owing to the different perceived opportunities and risks of PGx.

An important criticism of an over-emphasis on PGx policy is that it distracts attention from more simple and cost-effective ways in which ADRs might be dealt with. Research estimates that up to 95% of such effects could be prevented on the basis of current knowledge and a better management of drugs by prescribing clinicians[36].

So, the problem is how to maintain the strategic capacity to invest (in both a public and private sense) without getting trapped into a policy, business or clinical model that will fail and might well lead to a misuse of current knowledge and resources. We advocate an approach that emphasises public funding of research to help create a better evidence base for PGx; active steps to help stabilize some of the (regulatory and ethical) uncertainties; measures to prevent market failure; and investment in the PGx testing infrastructure, as well as in the long-term, improved strategies at national and international levels of pharmacovigilance.

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Competing interests statement

The authors declare no competing financial interests.

Online links

FURTHER INFORMATION

Encyclopedia of Life Sciences: http://www.els.net/pharmacogenetics
Institute for the Study of Genetics, Biorisks and Society: http://www.nottingham.ac.uk/igbis
Lewis' homepage: http://www.york.ac.uk/org/satsu/Staff/graham/graham.htm
Oxford Genetics Knowledge Park: http://www.oxfordgkp.org
Pharmacogenetics research at SATSU: http://www.york.ac.uk/res/pgx
University of York Science and Technology Studies Unit: www.york.ac.uk/org/satsu
Webster's homepage: http://www.york.ac.uk/depts/soci/s_webs.html
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TIMELINE

Pharmacogenetics – five decades of therapeutic lessons from genetic diversity

Urs A. Meyer

Abstract | Physicians have long been aware of the subtle differences in the responses of patients to medication. The recognition that a part of this variation is inherited, and therefore predictable, created the field of pharmacogenetics fifty years ago. Knowing the gene variants that cause differences among patients has the potential to allow 'personalized' drug therapy and to avoid therapeutic failure and serious side effects.

Pharmacogenetics (PGx) deals with genetically determined variation in how individuals respond to drugs . Observations implying that genetic variation was responsible for the diversity in some drug responses were already being made five decades ago. We now know that the therapeutic failure of drugs as well as serious adverse side effects of drugs on individuals or subpopulations of patients can both have a genetic component. The toll that such variation takes in terms of individual suffering, high healthcare costs, and even lives, is increasingly being recognized. Recent developments in genomics, and associated technological innovations, have invigorated the study of such variation. Pharmacogenetic research has seen an explosion of interest by physicians, geneticists and the pharmaceutical industry — as reflected in the rapid increase in the number of publications that contain this term (FIG. 1). PGx has the potential to identify the particular drug and the dose of drug that is most likely to be effective and safe for each patient. This has become one of the main goals of modern drug therapy, and is frequently described as 'personalized medicine'. But in spite of its importance in explaining the diversity of responses to drugs, the integration of PGx into clinical practice has met considerable challenges.

The history of PGx reflects the evolution of human genetics and genomics, of molecular pharmacology and modern drug therapy. The field has had its visionaries and godfathers, who realized its importance early in its history. These early pioneers laid the foundations for the landmark discoveries that form the basis of present concepts and approaches (TIMELINE).

The gestation of a discipline

Sir Archibald Garrod, the perceptive physician-scientist. Around the year 1898 the British physician Archibald Garrod was interested in urinary pigments and studied patients at St. Bartholomew's Hospital in London that had ALCAPTONURIA (see Glossary) and patients that had PORPHYRIA that was caused by sulphonal (a hypnotic) [1,2]. Garrod was probably the first to realize the inherited predisposition of certain individuals to alcaptonuria[1] and other conditions. In particular,