Putting pharmacogenetics into practice

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Genetics is slowly explaining variations in drug response, but applying this knowledge depends on implementation of a host of policies that provide long-term support to the field, from translational research and regulation to professional education.

Pharmacogenetics, the study of variation in patient responses to drugs due to hereditary traits, has been suggested as the area of genetics with the most potential to rapidly provide public health benefits[1]. Although early expectations of 'tailor-made' or 'personalized' medicines may have been inflated, and although they remain mostly unfulfilled, more modest benefits are still widely anticipated[2–4]. Here we present the results of a study assessing the progress in exploiting pharmacogenetics and current challenges for those attempting to apply this new knowledge. This study is based on a comprehensive review of the science base and industry in the United States, Europe and Japan as well as the institutional support frameworks needed for the development and use of genetic predictors of drug response. The findings are derived from a recently completed European Science and Technology Observatory (ESTO) study. A summary report and more detailed data reports will be available in April 2006 (http://www.jrc.es/).

We find that a growing number of pharmacogenetics and pharmacogenomics products and services are now available, from drugs that target specific disease subtypes, such as ImClone Systems' (Branchburg, NJ, USA) Erbitux (cetuximab), to stand-alone diagnostic tests, such as Roche's (Basel) AmpliChip Cytochrome P450 (CYP450) test that detects polymorphisms associated with severe adverse drug reactions (ADRs), and genotyping services to support clinical trials offered by companies such as DxS (Manchester, UK). Whereas much of this activity centers on well-characterized drug-metabolizing enzymes, many new targets are emerging. Yet even where the evidence base is relatively established and interest in product development is strong, validation, approval, clinical utility and widespread clinical demand is taking much longer to establish.

Defining pharmacogenetics and pharmacogenomics

The field of pharmacogenetics has a history dating back to the 1950s, when Arno Motulsky first proposed that the inheritance of acquired traits might explain individual difference in the efficacy of drugs and in the occurrence of adverse drug reactions[5,6]. The term pharmacogenomics emerged in the late 1990s and is often associated with the application of genomics in drug discovery. Although many have struggled to find agreement on the precise meaning of the terms pharmacogenetics and pharmacogenomics[7–9], here we use the term PGx to refer collectively to the science and technologies associated with dividing patients or populations into groups on the basis of their biological response to drug treatment using a genetic test. We therefore include activities related to classical pharmacogenetics as well as studies of gene expression or methods of disease stratification related to predicting drug response. Although more recently PGx has become associated with molecular genetics, we do not limit our definition of a genetic test to methods that rely on direct DNA analysis, but also include phenotypic tests (such as those operating at the protein, metabolite or other biomarker level) where these may be used to reveal an underlying genetic change relevant during the therapeutic decision-making process.

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Box 1 Overview of project methodology and focus

We used diverse methods including a range of publication and commercial database search strategies, online surveys, policy literature reviews and in-depth interviews as the basis for our findings. The project consisted of three streams of research and relied on a range of methods to gain quantitative and qualitative data. In particular a large number of semi-structured interviews were conducted with representatives of prominent institutions involved in PGx in the countries studied. Please note many interviewees contributed to more than one stream.

Mapping R&D activity in pharmacogenetics and pharmacogenomics. A key aim was the identification of noncommercial research institutions (e.g., hospitals, charities, universities) in the United States, Europe and Japan. Results are based on manual and keyword searches of academic literature in conference proceedings, journals, online databases and the web. This search revealed 264 relevant institutions.

The 264 institutions were surveyed using an online questionnaire to explore issues such as areas of research interest, funding and collaborative activities. Sixty responses were received overall (23% response rate).

Identifying commercial groups with significant R&D programs relating to PGx was another key aim. Using industry databases (http://www.gendatabaseonline.com/, http://www.marketresearch.com/, http://www.newsanalyzer.com/, http://www.recap.com/) a universe of over 1,000 companies was searched to identify companies with a focus on PGx. Companies were profiled on the basis of public documents such as press releases and SEC filings.

Interviews with 20 prominent academic departments and companies were conducted to provide more detailed insights into the themes emerging from the survey. Interviewee selection was guided by information from the literature and website searches to capture a broad range of experience–for example, United States versus EU, diagnostic development versus drug development.

Case studies on the application of PGx tests in the clinic in four EU countries. Using a common research design, qualitative case studies were undertaken by researchers in Germany, Ireland, the Netherlands and the UK. Case studies were based on a review of academic literature and policy documents, as well as interviews with clinicians, laboratory staff, industry, government healthcare policy makers and health insurers. Interview themes were guided in part by a pilot survey sent to 407 physicians in four countries, the results of which are reported elsewhere[16]. Two PGx applications were chosen: testing to improve drug efficacy (HER2 testing) and testing to improve drug safety (TPMT testing).

HER2 expression testing before prescription of Herceptin in treatment of late-stage breast cancer. The number of interviews conducted in each country was as follows: Germany, 18; Ireland, 11; the Netherlands, 11; the United Kingdom, 36. Note: The UK case study is based on an update of published work[19].

TPMT activity testing before prescription of 6-mecaptopurine in treatment of acute lymphatic leukemia. The number of interviews conducted in each country was as follows: Germany, 21; Ireland, 11; the Netherlands, 7; the United Kingdom, 11.

Case studies on regulatory frameworks influencing PGx use. Using a common research design, qualitative case studies were undertaken to describe the regulatory environments for PGx in the United States, Germany, Ireland, The Netherlands and the UK, as well as relevant EU-wide frameworks. A broad interpretation of regulation was applied, spanning factors that shape the effective use of medical technologies from the bench to the clinic (for example, the development/licensing of drugs and diagnostic tests, oversight of testing services and availability of clinician education/guidelines). Data collection focused on reviews of the academic and policy literature, interviews with regulatory authorities (including the EMEA and FDA), quality assurance scheme administrators and laboratory staff). Interviews with 15 companies chosen as described above to provide additional insight also informed this stream of activities. The number of interviews conducted in each country was as follows: US, 11; Germany, 21; Ireland, 16; the Netherlands, 5; the United Kingdom, 9.

PGx is emerging as an interdisciplinary area comprising different specialties such as medicine, informatics, cell and molecular biology, genomics, epidemiology and pharmacology. In broad terms the potential applications of PGx are:

1. Research. Discovery of better drugs and the determination of disease mechanisms.
2. Development. Improvement of drug safety and efficacy.
3. Clinical application. Improved drug safety and efficacy.

Tapping the research base

We undertook a survey of international noncommercial organizations—government research institutions, universities and hospitals—engaged in PGx-related research to identify opportunities and barriers to the exploitation of PGx (**Box 1**). Relevant institutions were identified through data mining of academic literature, conference proceedings and individual institutions' websites. Focusing on Europe (excluding the 10 countries admitted to the EU in 2004), the United States and Japan, our search revealed 264 noncommercial research groups involved with PGx research in Europe, Japan and the United States (**Fig. 1**).

An in-depth questionnaire to which 60 centers located in Europe, Japan and the United States responded indicated that, in general, US groups are larger and better funded than European groups, although fewer in number. This is attributed in part to the Pharmacogenetics Research Network initiative established by the US National Institutes of Health, under which individual laboratories may receive generous grants of up to $10–15 million (see http://www.nigms.nih.gov/pharmacogenetics/). This has considerably stimulated US research efforts in this field. EU funding is currently not fully exploited, with some European research groups complaining there is no clearly earmarked European Commission funding for PGx. As a result, most research in the EU is funded by national governments.

The survey identified some global trends. PGx research focused most commonly on drug metabolism (52%), disease mechanisms (27%) and disease predisposition (27%). The elucidation of disease mechanisms and development of diagnostics were the most frequent aims of research (around 20% of respondents each) whereas pharmaceutical applications and validation/standardization was an objective of around 15% of respondents. There are clear national differences. For example, elucidation of disease mechanisms appears to be a key goal in the United Kingdom, whereas in Germany diagnostics are a major focus. The relative diversity in research objectives highlights the heterogeneity of the PGx field, suggesting the need to design similarly broad funding programs.

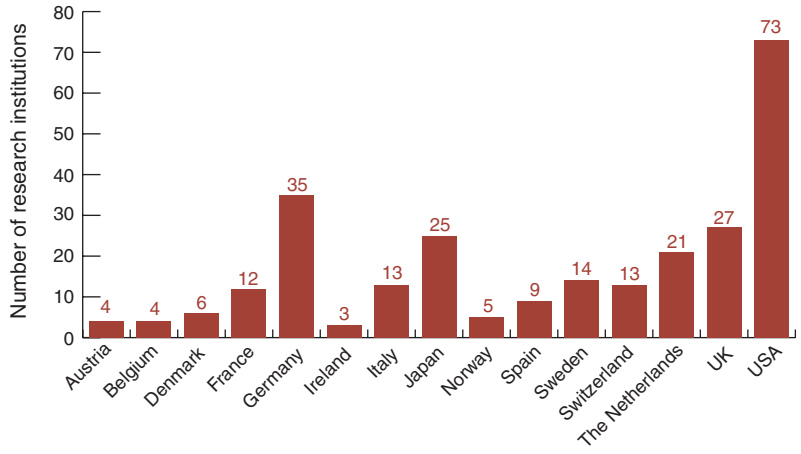

Figure 1 PGx public sector research groups in Europe, Japan and the United States.

The field is more homogeneous in its application of particular scientific methods, with almost 80% of research groups using single nucleotide polymorphism analysis and 65% using enzymatic analysis in their studies.

Given the importance of noncommercial research for commercial biotech in general, it is perhaps surprising that our survey revealed a global trend for research groups to collaborate with other noncommercial groups over four times more frequently than with small companies (66% versus 15% of all collaborations). Large companies were only marginally more favored, accounting for nearly 20% of collaborations reported. This is not to suggest that academics working in PGx do not have contact with industry— nearly half of respondents reported they sit on advisory boards, although only a handful reported having industrial members on their own advisory boards. Our survey highlights that PGx is a diverse field, where multidisciplinary research is important. Centers of excellence are found throughout the EU and the United States, but closer ties with industry might facilitate the exploitation of this research.

Interviews with 20 academic and industrial experts put some of the above findings in perspective (**Box 1**) and revealed important challenges that may limit the exploitation of the noncommercial sector's PGx research capabilities, as well as affect commercial activities. Low levels of industry-academia collaboration were attributed to underresourcing of many noncommercial groups, resulting in small studies rather than the more robust studies indicated as desirable[1,4]. Whereas industry values the opportunity to collaborate with noncommercial groups, the major EU and US federal funding agencies were seen as overly bureaucratic and barely worth the administrative effort in the view of participants on both sides of the Atlantic. A further barrier to the successful exploitation of PGx research is the small number of samples from well-characterized patient cohorts. This is related to the privacy concerns of patients arising from the lack of legal protection against genetic discrimination, and because industry cannot allow access to samples and data they collect in the context of clinical research. Industry representatives also saw the profusion of intellectual property rights in the field as a concern, with the need to seek multiple permissions being "a nuisance." The high staff and equipment costs for sampling, testing, data management and analysis all make PGx an expensive field of research in the view of industry. For companies working in several EU countries, compliance with multiple or poorly defined legal frameworks that surround PGx sampling, testing and storage was noted as a "logistical challenge." This makes the EU, and countries such as Sweden and France in particular, more difficult research environments than the United States.

Table 1 Small to medium-sized firms making up the core of commercial PGx

North American firms	European/rest of world firms
PGx drug development & diagnostics firms (5)	***PGx drug development & diagnostics firms (4)***
Curagen (Branford, CT, USA)	Astex Technology (Cambridge, UK)
Egeen (Mountain View, CA, USA)	deCODE/ Encode (Reykjavik, Iceland)
Genaissance (DNA Sciences) (New Haven, CT, USA)	Epidauros (Bernried, Germany)
Millennium (Cambridge, MA, USA)	Genset (part of Serono) (Bernried, Germany)
Myriad Genetics (Salt Lake City, UT, USA)	
Diagnostics only (11)	***Diagnostics only (8)***
Celera Diagnostics (Alameda, CA, USA)	Axis-Shield (Dundee, UK)
DNAPrint Genomics (Sarasota, FL, USA)	Dako (Glostrup, Denmark)
Genelex (Seattle, WA, USA)	Epigenomics AG (Berlin, Germany)
Genomas (Hartford, CT, USA)	Ipsogen (Marseille, France)
Genomic Health (Redwood City, CA, USA)	Jurilab (Kuopio, Finland)
Gentris (Morrisville, NC, USA)	LGC (Teddington, UK)
Interleukin Genetics (Waltham, MA, USA)	TheraStrat (Allschwil, Switzerland)
Prediction Sciences (La Jolla, CA, USA)	Vita Genomics (Taipei, Taiwan)
Prometheus Laboratories (La Jolla, CA, USA)	
Third Wave Technologies (Madison, WI, USA)	
ViroLogic (San Francisco, CA, USA)	

Table 1 (continued)

North American firms	European/rest of world firms
PGx service firms (inc samples banking) (7)	***PGx service firms (inc samples banking) (4)***
First Genetic Trust (Deerfield, IL, USA)	The Brain Resource Company (Ultimo, New South Wales, Australia)
Gene Logic (Gaithersburg, MD, USA)	CXR (Dundee, UK)
Genizon Biosciences (formely Galileo Genomics) (St. Laurent, QC, Canada)	DxS (Manchester, UK)
Genomics Collaborative (Cambridge, MA, USA)	Medigenomix (Martinsried, Germany)
Pergelen Sciences (Mountain View, CA, USA)	
Seryx (Cherry Hill, NJ, USA)	
Vybion (formally Viral Therapeutics) (Ithaca, NY, USA)	
PGx tools, kits and software (6)	***PGx tools, kits and software (2)***
Affymetrix (Santa Clara, CA, USA)	GE Healthcare Ltd. (formerly Amersham Biosciences) (Chalfont St. Giles, UK)
Golden Helix (Bozeman, MT, USA)	Biotage (Uppsala, Sweden)
Nanogen (San Diego, CA, USA)	
Sequenom (San Diego, CA, USA)	
Tm Biosciences (Toronto, Canada)	
Waban Software (Cambridge, MA, USA)	

Commercial focus

In spite of the difficulties of collaboration between the commercial and noncommercial sectors, the commercial promise of PGx has attracted many companies. Starting with a population of over 1,000 biotech companies found on industry databases (**Box 1**), our search revealed 47 small or medium-sized biotech companies that make up the core of the sector (**Table 1**), and a further 18 with less PGx focus (**Table 2**)[10]. Approximately 60% of these are based in the United States, with most of the rest in Europe. Comparison with a previous snapshot of the industry in 2003 (ref. 11) suggests a high churn rate over the last two years; around 40% of that population has ceased trading, disinvested from PGx or been acquired. Yet an influx of new companies has left the sector's size undiminished. The majority of companies see PGx as an additional instrument in the drug development toolbox. Only 19 of the 47 have business models dedicated purely to PGx and almost all of these are young (founded after 1997), relatively small (<100 employees) and have mainly established themselves as service providers to the pharmaceutical industry. Despite the apparent commercial promise of PGx, these dynamics suggest a fragile industry where diverse business models are being tested but remain unproven.

Our analysis of the business models of biotech companies offering PGx products and services illustrates that PGx provides at least 12 distinct technological options. However, as **Table 2** shows, the majority are focusing on just seven of these options, with little commercial investment in drug rescue for either safety or efficacy, market extension strategies, postmarketing surveillance or the use of efficacy data in drug marketing. Instead most investment is being made in services and products supporting preclinical and clinical drug development, such as genotyping services for absorption, distribution, metabolism and excretion (ADME) genes offered by Epidauros (Bernried, Germany) and DxS or products such as the Tag-It mutation detection kits for CYP450 alleles offered by Tm Biosciences (Toronto, ON, Canada). The development of diagnostic tests to aid prescribing and to enable disease stratification is another area where interest appears relatively high. For example the Oncotype DX developed by Genomic Health (Redwood City, CA, USA) can determine prognosis/therapeutic response to different chemotherapies in breast cancer, whereas Celera Diagnostic's (Alameda, CA, USA)ViroSeq HIV-1 Genotyping test can aid therapeutic regime choice for physicians treating AIDS patients.

A smaller number of companies also provide services to support drug discovery. Companies applying PGx to clinical drug development are focused on both safety and efficacy. They offer a range of services including ADME testing, toxicity screening, genotyping and association studies, and products such as genetic tests for ADRs, ADME/CYP450 assays and chips,

Table 2 Small to medium-sized companies with a minor interest in PGx

North American firms	European/ rest of world firms
Amgen (Thousand Oaks, CA, USA)	AdnaGen (Langenhagen, Germany)
ARCA Discovery (Denver, CO, USA)	Exon Hit (Paris, France)
Cardinal Health (Dublin, Ohio, USA)	GeneScan Europe (cyp chip) (Freiburg, Germany)
Ellipsis Biotherapeutics (Toronto, ON, Canada)	Iqur (formerly HepCgen viral genotyping) (Southampton, UK)
GeneOhm Sciences (San Diego, CA, USA)	IntegraGen (Evry, France)
InSite Vision (Alameda, CA, USA)	Memorec Biotec (Köln, Germany)
NeoPharm (Waukega, IL, USA)	PharmaMar (Madrid, Spain)
Panacea Pharmaceuticals (Gaithersburg, MD, USA)	Solvo Biotechnology (Budapest, Hungary)
PolyGenyx (Worcester, MA, USA)	
TriPath Imaging (Burlington, NC, USA)	

databases of ADRs and software tools. These are largely sold to integrated pharmaceutical companies.

Companies developing technologies to support prepresciption 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 companies are dedicated diagnostic companies, with only a few also working on drug development (Genaissance, New Haven, CT, USA; Egeen, Mountain View, CA, USA; deCODE, Reykjavik, Iceland).

With previously licensed drugs, most interest is being shown in developing tests for efficacy (16 companies), with slightly less support for safety testing (11 companies) and disease stratification (10 companies). For drugs currently in development, a similar interest is being expressed for safety and efficacy issues. The smaller group of companies supporting drug discovery mainly provide services for large pharmaceutical companies with the emphasis on ADME, CYP450 and toxicity analysis and testing.

Interviews with biotech and pharmaceutical companies suggest the majority of large pharma now have internal PGx programs. One indicator of pharma's appetite to integrate PGx knowledge into their R&D processes is the number of external collaborations with other companies (**Table 4**). The extent to which PGx is achieving its stated benefits in drug R&D is unclear. However, pharma expects reduced failure rates of clinical programs to be a benefit of PGx. This can be achieved by early weeding out of poor candidates, although this may not result in products readily identifiable as the fruits of PGx. In other words, the primary use of PGx by pharma is for internal decision-making with regard to drug development. Furthermore the demonstration of greater efficacy through definition of responder subgroups is likely to generate new products that may require diagnostic tests to accompany their clinical use.

Only a few new drugs have been launched that require diagnostic kits at present such as Genentech (S. San Francisco, CA, USA)/Roche's (Basel) Herceptin (trastuzumab) for breast cancer and ImClone/Bristol-Myers Squibb's Erbitux for colon cancer. Within large pharmaceutical companies, some executives expressed concerns that the technology remains largely unproven, expensive and potentially disruptive to the blockbuster culture that most large pharmas are accustomed to—although the

Table 3 Commercial interest in a range of PGx technological options

Drug discovery	No. of companies interested in the field	Applying internally only	Companies offering services	Companies offering products
Discovering new drugs that work well in entire population by excluding candidates metabolized by enzymes with known ADR-associated heterozygosity	8	Millennium	Gene Logic, Astex, Brain Resource, CXR, DxS	ViroLogic, Epidauros, CXR
Discovering new drugs aimed at genomic subpopulations	9	Millennium, Perlegen	Curagen, Gene Logic, Genizon, Genomics Collaborative, Sequenom, Brain Resource	ViroLogic
Safety of drugs in development				
Preclinical testing and early-stage trial design/monitoring	24		Curagen, Genaissance, Gentris, Prediction Sciences, Gene Logic, Genizon, Genomics Collaborative, Viral Therapeutics, Sequenom, Epidauros, Brain Resource, CXR, DxS, Medigenomix	Genaissance, Gentris, Viral Therapeutics, Affymetrix, Golden Helix, Nanogen Tm Biosciences, Waban, Epidauros, Jurilab, LGC, TheraStrat, CXR, Amersham, Biotage
'Rescue' of products in late-stage trials (ADRs)	6		Gene Logic, Perlegen, Astex, Epidauros, CXR	Epidauros, TheraStrat
Efficacy of drugs in development				
Later stage trial design and monitoring to target 'good responders'	23	Millennium	Egeen, Genaissance, Genomic Health, Gentris, Prediction Sciences, Gene Logic, Genizon, Perlegen, Viral Therapeutics, Sequenom, deCODE, Epidauros, Ipsogen, Brain Resource, DxS, Medigenomix	Genaissance, ViroLogic, Viral Therapeutics, Affymetrix, Golden Helix, Nanogen, Waban, Axis-Shield, Vita Genomics
Drug rescue (efficacy)	4		Gene Logic, Perlegen, Epidauros	Affymetrix, Epidauros
Safety of licensed drugs				
Market (label) extension of products restricted by ADRs	1		Perlegen	
Preprescription screening to identify patients at risk of ADRs	11		Genelex, Perlegen, Seryx	Genaissance, DNAPrint, Genomas, Gentris, Prediction Sciences, Prometheus, Third Wave, Tm Biosciences
Postmarketing surveillance	2		Perlegen	TheraStrat
Efficacy of licensed drugs				
Preprescription screening to identify 'good responders'	16		Seryx	Egeen, Genaissance, Celera, DNAPrint, Genomas, Gentris, Interleukin, Prediction Sciences, deCODE, Axis-Shield, Epigenomics, Jurilab, LGC, Vita Genomics, DxS
Use of efficacy data in drug marketing and in extending patent life	3			Egeen (patent), Genaissance, Axis-Shield (patent)
Stratification of diseases and infectious agents into subtypes				
Stratification of diseases and infectious agents into subtypes	10	Millennium	Perlegen, Epigenomics, Vita Genomics	Myriad, Celera, Genomic Health, Third Wave, ViroLogic, Dakocytomation, Epigenomics, Ipsogen, Vita Genomics

commercial success of Herceptin and Gleevec (imatinib mesylate; Novartis, Basel) for chronic myeloid leukemia may be slowly changing such views in some companies. At the moment, the most obvious fruits of PGx are the diagnostic tests that are emerging. Although a few prominent exemplars such as Roche's amplichip have gained regulatory approval, many more tests remain in development or are yet to seek regulatory approval.

When we compare the therapeutic fields rich in targets with the focus of academic research and industrial development of diagnostics, there is a significant disparity between opportunity and commercial interest (**Table 5**). Top priorities for commercial test producers are the metabolism of drugs and therapeutic response of cancers and infections. However, central nervous system (CNS) and cardiovascular targets in particular appear relatively neglected despite being the largest therapeutic revenue generators for pharmaceutical companies. This indicates CNS and cardiovascular diseases have the potential to be important fields for PGx in the future, pending resolution of technical or commercial challenges.

Licensing of PGx drugs and diagnostics

After prompting by the biotech and pharmaceutical industries, the US Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA) responded in different ways to the challenge of PGx, although both now encourage use of PGx data in clinical trials. The FDA published final guidance documents on such use in March 2005 (see http://www.fda.gov/cber/gdlns/pharmdtasub.pdf). The EMEA's approach is based on briefing meetings with the sponsors of therapeutic candidates. Although these meetings may now be held jointly with the FDA, some companies expressed concern that the EMEA was less engaged with industry and lagging behind the FDA in its preparations to receive PGx-based drug submissions. Meanwhile, there are no definite plans for compulsory submission of PGx data by the EMEA or national agencies including the FDA (see **Supplementary Table 1** for comparisons between key aspects of the regulatory frameworks in the United States and selected EU countries that affect diffusion of PGx technology).

PGx data are already being used by drug producers to stratify patients according to therapeutic efficacy in fields such as cancer, where drugs such as Herceptin work on breast cancer tumors overexpressing human epidermal growth factor receptor 2 (HER2). However, the EMEA stresses that they have yet to grant an approval where the sponsor wishes to apply stratification in relation to drug safety. Such approval would be considered only if this was the one viable option.

Where robust clinical data emerge linking genetic factors to drug response for a licensed drug, there is a legal mechanism (known as Article 31) allowing the EMEA to recommend a change of drug label in European member states. This has not been invoked for PGx as yet. The FDA has, however, revised drug labels on the basis of PGx data; for example, in July 2005 the FDA advised of the risk of hepatic dysfunction and pancreatitis in patients with mutations in *UGT1A1* taking Pfizer's (New York, NY, USA) cancer treatment Camptosar (irinotecan). Subsequently, Third Wave Technologies (Madison, WI, USA) received FDA approval in 2005 for their Invader *UGT1A1* assay that detects mutations in *UGT1A1*, which codes for UDP- glucuronosyltransferase —the enzyme that metabolizes drugs such as Camptosar, and is associated with increased risk of ADRs.

The procedures for the approval of new diagnostic and therapeutic combinations in PGx also remain untested. In the EU, the EMEA cannot approve diagnostic and therapeutic combinations, as its remit is limited to approval of therapeutics. However, it can require that a drug be used with an appropriate diagnostic test, as in its approval of Herceptin in 2000. Separate application for diagnostic PGx products in the EU must be made to the national agencies and this is set to continue. Cumbersome though this may seem, there is little evidence of this being viewed as problematic for the national authorities. Improved channels of communication with the EMEA are a likely priority to ensure this remains the case.

In vitro diagnostic (IVD) devices have a common regulatory process in the EU, based on Directive 98/79/EC (the IVD directive). Compliant tests, such as Celera's Viroseq display the 'Conformité Européene' or European Conformity Mark (CE mark), a manufacturer's declaration that a product conforms to all relevant directives (enforced by national regulatory authorities for diagnostics). In the case of Viroseq, the product can therefore be sold in 18 EU countries at present. However, the EMEA is concerned that the IVD directive requires only technical accuracy and not clinical validity—that is, validity of the disease association in the biomarker being assayed by those tests seeking the CE mark.

The FDA sees serious challenges with the validation of biomarkers. The FDA favors a more conservative view of what constitutes a 'probable' as opposed to an 'exploratory' biomarker than industry. Indeed up to 2004, the FDA had only accepted two sets of biomarkers as valid in relation to drug metabolism. These relate to the activity rates of thiopurine *S*-methyltransferase (TPMT) and the cytochrome P-450 isoenzymes (CYP450), both with an evidence base that is over two decades old. The difficulties in validating biomarkers in other fields of medicine are well known, with large-scale clinical trials often necessary, but even with such studies, few biomarkers are proven and fewer still find application in the clinic[12] . The FDA has an established office for the consideration of combination products, and recently released a concept paper on codevelopment of drug/device

Table 4 Large firms with multiple alliances to access PGx technologies

Firm	Total PGx alliances 1997–2004
Glaxo SmithKline (Brentford, UK)	16
Pfizer (with Pharmacia/ Parke-Davis/ Warner Lambert)	15
Bristol-Myers Squibb (New York, NY, USA)	8
AstraZeneca (London, UK)	8
Bayer (Leverkusen, Germany)	7
Roche (with Roche Diagnostics) (Basel, Switzerland)	7
Aventis[a] (Berlin)	6
Biogen IDEC (Cambridge, MA, USA)	4
Merck (Whitehouse Station, NJ, USA)	4
Abbott Laboratories	3
Eli Lilly (Indianapolis, IN, USA)	3
Wyeth (Madison, NJ, USA)	3
Boehringer Ingelheim (Ingelheim, Germany)	2
Novartis	2
Ono Pharmaceuticals (Osaka, Japan)	2

Source: http://www.Recap.com/

[a]Data for Aventis excludes Sanofi but includes Rhone-Poulenc Rorer.

Table 5 The top five therapeutic fields of opportunity and priority

Rank	Number of loci[a]	Active interest of noncommercial research groups in survey sample (% of respondents /number of groups)	Number of commercial tests available or in development[b]
1	CNS (13)	Drug metabolism/ toxicity (55%/33)	Drug metabolism/ toxicity (14)
2	Drug metabolism/toxicity (9)	CNS (33%/20)	Cancer (11)
3	Cardiovascular (8)	Cancer/Cardiovascular (27% each/16 each)	Infection (7)
4	Cancer (7)		CNS/respiratory disease (3 each)
5	Infection (4)	Gastrointestinal (10%/6)	

In our classification the category drug metabolism/toxicity cuts across therapeutic areas. The remaining targets concern prediction of therapeutic response, although some loci are applicable to both. [a]Loci were significantly associated with drug response in at least two studies[1]. [b]The focus here on commercial products excludes the activities of noncommercial laboratories that develop services. Exclusion of this important area of activity is a limitation of our approach.

products such as therapeutics used in conjunction with a diagnostic test (see http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf). But it is too early to assess the extent to which these initiatives will assist in the approval of such products.

Frameworks for PGx appear to be broadly in place at the EMEA and FDA. Yet within Europe the German, Irish, Dutch and UK national agencies have received few requests from sponsors to consider PGx data. This is partly because key therapeutic areas such as cancer, and drug types such as recombinant proteins and monoclonal antibodies are channeled through the EMEA's centralized marketing authorization procedure. Even at the EMEA, relatively few PGx-related products have been submitted. However, regulators anticipated that there are many products in development.

Interviewees from companies (**Box 1**) showed a keen interest for greater harmonization internationally on regulatory matters surrounding the use of PGx data. However, timing is seen as crucial. If it is done too soon, suboptimal approaches may become ingrained in agreements, which then become difficult to amend.

PGx in clinical practice

There are few examples of pharmacogenetic tests being used widely in the clinic, but some insights can be gleaned from comparative case studies on the challenges of introducing a predictor of drug efficacy (HER2 testing) and a predictor of drug safety (TPMT testing). These appear to be the two most established clinical applications of PGx in the Netherlands, Germany, Ireland and UK, where a range of stakeholders (including clinicians, clinical laboratory scientists, research scientists, patient groups and government policy makers) were interviewed (**Box 1**).

Efficacy and new medicines. The monoclonal antibody, trastuzumab, was developed by Genentech and Roche to target human epidermal growth factor receptor 2 (HER2), which is overexpressed in 20–30% of metastatic breast cancers. It was approved in the United States by the FDA as Herceptin in 1998 and in 2000 through the EMEA's centralized procedure, for use in individuals who have tumors that overexpress HER2. Commercial diagnostics for HER2 have been available for several years using immunohistochemistry (HercepTest, Dako, Glostrup, Denmark) and fluorescent *in situ* hybridization (PathVysion, Abbott, Abbott Park, IL, USA) to distinguish between normal expression and overexpression of HER2. Overexpression is also associated with more aggressive tumors, so a positive test also has prognostic value.

Roche prepared the market by funding the establishment of hospital-based HER2 testing services in large European markets such as Germany and the UK. However, despite the availability of free testing for several years, UK test utilization was only boosted to 35% of potential users according to Roche's own estimate in 2005, although there was a negligible base before this initiative. Relatively low funding for cancer treatment in the UK National Health Service and a culture less inclined to order diagnostic tests were cited as possible explanations. In Germany, the Netherlands and Ireland, testing is conducted much more widely, although Roche focused far less on preparing the smaller markets. In such markets, high utilization is explained by patient groups and doctors actively encouraging use. However, there is evidence that cost limits the use of Herceptin— in three of the four countries studied, incidents were reported of the test being withheld or results of tests undertaken not being discussed with patients, as a means of drug rationing.

The quality of testing services is also influenced indirectly by cost. Diagnostic quality assurance scheme managers emphasize the importance of experience, standardized procedures and reagents to maintain quality of testing[13]. However, laboratories frequently modify protocols or produce their own kits (so-called 'home brews') from other available materials owing to the cost differential between these materials and commercial kits. In some cases this reduces the quality of testing services. Quality assurance schemes in Europe and the United States for HER2 are well subscribed. Although these schemes are effective in disseminating best practice and education, they lack the teeth of a regulatory authority. Furthermore 'home brew' tests are not regulated by the FDA, or under the EU's IVD directive, as implemented by national regulatory authorities for diagnostic tests in Europe, when the test is used in the institution of origin. Furthermore, accreditation by a recognized national body for laboratories undertaking medical testing is not required in many European countries such as the UK and Ireland, although it is a legal requirement in Germany and in the United States. The case of HER2 testing illustrates that the cost of drugs and tests, as well as the quality of services, are important challenges for PGx.

Safety and generic drugs. Thiopurine drugs such as 6-mercaptopurine and azathioprine are immunosuppressants used to treat leukemia, autoimmune diseases and patients at risk of tissue rejection after transplants. However, acute toxicity leading to dangerous levels of myelosuppression is a potentially fatal adverse reaction. This may occur in patients homozygous for mutant alleles in *TPMT*. One in 300 caucasians have this genotype, although the incidence may be higher in mixed populations[14]. Several genotyping and enzymatic TPMT activity assays emerged in the 1990s and provide the means to identify patients most at risk, and allow dosage reduction. The founding of a pilot quality assurance scheme in 2004 by a UK hospital laboratory has attracted interest from over 20 clinical laboratories across the world, which might result in standardization of the diverse methodologies for detection of this genotype. Prometheus Laboratories offers kits and services in the United States but there is no commercial service provided in Europe (although at least one hospital has received the CE mark for its 'home brew').

TPMT testing is not a routine part of clinical practice in any of the four EU countries we studied. Patients in Ireland and the UK diagnosed with acute lymphatic leukemia (ALL) will be tested as part of an ongoing clinical trial supported by the UK's Medical Research

Council (London) and the Leukemia Research Fund (London) until 2007, although no funding arrangements for a service beyond this time have been secured. Even though this service is freely available to all treatment centers in the trial, compliance can still be a problem. This may be due to the mixture of nurses, junior doctors and more senior physicians involved in applying the protocol. Beyond treatment for ALL, there are great disparities in test usage between medical specialties, mainly due to the continued development of the evidence base and slow emergence of clinical guidelines. Furthermore, low uptake of TPMT testing by clinicians may be due to the addition to staff workload, the cost to individual departments even where benefits in the healthcare system as a whole might outweigh these and the lack of first-hand clinical experience by staff of serious adverse events.

In addition, because thiopurine drugs are off-patent and open to generic competition, there is little incentive for drug manufacturers to develop tests to support their safe use or otherwise intervene. Neither the genotypic test nor the enzyme assay is ideal; genotyping for specific mutations will detect only around 90% of faulty alleles (and perhaps less in non-caucasian populations) and the enzymatic assay gives misleading results for patients after blood transfusions and is difficult for laboratories to set up. Because only 29–50% of adverse reactions are linked to TPMT status, a PGx test cannot substitute for the existing practice of blood-count monitoring needed for all patients during thiopurine therapy[15] . The case of TPMT testing suggests that, aside from the cost of testing, ensuring clinical uptake may be a long and difficult process, and the technical limitations of the tests may mean the contribution of PGx is marginal rather than revolutionary, yet too important to be neglected.

A long-term policy view

PGx remains a promising field, but like any other medical technology, its exploitation is subject to bottlenecks. Policies are needed, especially in the EU, to encourage the development of the evidence base and use of products in areas where commercial incentives are weak. There is room for further harmonization and rationalization of regulatory frameworks, especially those governing clinical research in PGx. Steps need to be taken to promote the production and sharing of PGx data. Controls on the application of diagnostic tests remain a neglected area, especially those undertaken in noncommercial environments.

Although little evidence of patient resistance to PGx sampling or testing was reported by clinicians in the EU[16], consent procedures for diagnostic use are often lacking. The social and ethical impacts of PGx tests will have to be assessed on a case-by-case basis in accordance with existing recommendations[17,18]. The diffusion of medical practices is often slow, but this has only partly to do with education. Nonetheless, education efforts need to target all those involved in delivering relevant therapies including physicians, nurses, pharmacists, junior doctors, and in time those in primary care. The resources needed to undertake this training should not be underestimated. At present there are only sporadic examples of PGx training in the medical curriculum, usually close to centers of PGx research excellence. Even here, training may consist of a single session. Training sufficient new staff may take a generation. For more rapid change the onus rests with the professional bodies of individual specialties, where guidance will be tailored to practices that have the most relevance. Steps should also be taken to coordinate guidelines for drugs and associated tests that might be used by different medical specialists where possible.

In this paper we have shown that the successful integration of PGx into healthcare systems may rely on many interdependent factors. The emergence of PGx products and services will rely on the attractiveness of PGx as an investment area. In making PGx investment, product and service providers (in commercial and noncommercial sectors) will require clear regulatory frameworks and economic incentives such as drug pricing power, or cost-benefit studies, as well as demonstrable demand from clinical users. Clinical-user demand will in part depend on education as well as clinical utility. Clinical utility will depend on the availability of timely, accurate and reliable testing services. Services will be dependent on the growth of an extensive evidence base, affordable tools and trained personnel. All of these developments will take time to come together and, in the meanwhile, will require a nurturing policy environment.

Note: Supplementary information is available on the Nature Biotechnology website.

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