Fostering the process of adoption of personalised medicine: A matter of communication or a matter of cost?

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Abstract

Pharmacogenetics, along with its derived products, diagnostic tests and customised medicines, has been introduced to the market with high commercial expectations (derived from its obvious science-based benefits). Nevertheless, its commercial success is far below that is expected. Although the favourable arguments for its development are sufficiently documented in the literature, the reality of the market forces the consideration of a scenario with less optimistic elements. This work synthesises the different barriers limiting their development including the crucial factors acting on the demand side. In order to support this argument, an exploratory study was carried out. The research leads to interesting operative conclusions to be taken into account by the diagnostic industry in order to improve its further adoption by the market.

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INTRODUCTION

The study of inter-individual specific genetic variation related to drug responses (both safety and efficacy) is called pharmacogenetics, and the study of genomic and proteomic information for identifying new drug targets and their mechanisms of action is called pharmacogenomics. Together, the research areas of pharmacogenetics and pharmacogenomics are known as PGx. It is often said that advances in these disciplines could impact positively on the pharmaceutical and healthcare sectors, facilitating drug development and a system of personalised (individualised) medical care where drugs would be safer and more effective.[1]

Without doubt, one of the most important approaches towards more personalised medical care is the study of pharmacogenetics and pharmacogenomics, since these emerging sciences seek to determine how people's genetic makeup affects their responses to medicines. Personalised medicine involves the

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use of such genetic information in the design of strategies for the diagnosis, treatment and prevention of diseases.

Some of the potential benefits of these new technologies most often cited include the development of more powerful and safer drugs, the improvement of drug discovery and approval and a decrease in overall healthcare costs. It is worth mentioning that the last point is one of the most controversial potential benefits claimed by PGx.

The many expectations surrounding the clinical application of pharmacogenetics remain mostly unfulfilled since only a limited number of applications have actually reached clinical practice.

In this context, carrying out a study to better comprehend the factors influencing PGx development in the healthcare setting seems to be more than appropriate.

AN INTRODUCTION TO THE PGx MARKET

The first generation of marketed molecular diagnostics has been based on established immunoassays and nucleic acid tests (NAT technologies). Although the NAT market continues to be dominated by Roche, Abbott Laboratories and Bayer, many biotechnology companies have recently carried out significant investments. It is worth mentioning important niche suppliers, such as Chiron, Diagnostic Products, Epigenomics, Gen-Probe, Genaissance Pharmaceuticals, Innogenetics, Interleukin Genetics, Myriad Genetics, Nanogen, Nymox Pharmaceutical and Proteome Sciences.[2]

The size of the global PGx market is actually unclear. Ross and Ginsburg,[3] as shown in Table 1, estimate that the molecular diagnostics industry consists of a more than US$3bn market as at year 2000, and that it is currently growing at approximately 25 per cent per year. The expected size by year 2010 is around 12bn dollars. The worldwide pharmaceuticals annual market is estimated at more than 1.1tn dollars.[3] The updated report from the Business Communication Company[4] is, however, much less optimistic and estimates the worldwide market for molecular diagnosis at US$2.5bn and is expected to grow at an average annual growth rate of 13.7 per cent to reach $4.7bn by 2009.[4] In a recent study from the European Commission, the biotechnology-based diagnostic industry has been estimated at €6.6bn for 2004 with approximately 26 per cent of its revenue coming from Europe and 51 per cent from the USA.[5]

Table 1: Worldwide PGx market (Millions of US$)

	2000	2010
By diagnostic technique		
DNA probes	240	850
PCR based	1,450	4,350
Fish	600	2,350
Arrays	400	3,300
Others	450	1,150
Total	3,140	12,000
By clinical setting		
Infections	2,080	5,100
Cancer	337	1,900
Genetic tests	320	2,007
Food supply tests	110	400
Others	293	1,593
Total	3,140	12,000

Source: Ross and Ginsburg, 2002[3]

Currently, 94 per cent of DNA assays performed are concentrated in the developed world; however, by 2009 more affluent emerging nations are expected to be participating in this market.

The PGx industry is in a state of rapid evolution featuring continuous technical developments and new clinical opportunities for drug selection, predicting efficacy and toxicity and monitoring disease outcome. Maturation of the technology and the development of appropriate diagnostic applications will allow the increase of its market penetration. In total, some 49 tests are either in use or under development (Table 2). Of these just over half are already available for some kind of experimental or clinical application. Relatively few, however, have 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.

Table 2: Commercial PGx tests available for use or in development

Type of test	In use			In development			All
	US tests	EU/other tests	Total	US tests	EU/other tests	Total	Total
Drug metabolism	6	8	14	1	0	1	15
Anti-viral drug resistance	4	1	5	2	1	3	8
Cancer (disease stratification)	2	3	5	3	3	6	11
Other conditions	3	1	4	8	3	11	15
Total	15	13	28	14	7	21	49

Source: EU Report 22214, 2006[1]

FACTORS AFFECTING FURTHER DEVELOPMENT

Although 50 years of public PGx research and more than a decade of strategic activities from the private sector have promoted the field of PGx, a broad application of PGx in the clinical area is still lacking.

Since its discovery, benefits from personalised medicines and their capacity to modify and improve the healthcare systems have been surrounded by a favourable stream of publicity. Nevertheless, the consensus positive view ('customised medicines will revolutionise the healthcare systems'), which held for many years, has started to be questioned. Personalised medicines have been 'over-hyped' and will not be in a widespread use for at least 15 years.[6,7] Given the very limited adoption of PGx products by the market, it seems logical to approach this reality from a description of the elements that contribute to limiting their development. Drivers that theoretically influence such markets have been widely studied. The evidence, however, shows that in reality this has not taken place.

A comprehensive analysis of the current situation allows us to classify the factors affecting its further implementation in clinical practice into two different groups:

1. factors not directly related to market demand,
2. factors directly related to market demand.

Among the most cited reasons, why PGx technology has underperformed in terms of market expectations are medical, social, ethical and financial barriers.[8]

Without doubt, regulation is a key factor in determining the diffusion of new technologies. Regulatory policies can directly affect the availability and accessibility of PGx by creating incentives and disincentives.[9] There is an ongoing debate over whether governments should regulate PGx more closely. They should balance costs and benefits of their regulatory actions, since a highly regulated market might hamper PGx's wider application in clinical practice. Both Federal Drug Administration (FDA) and European Medicines Agency (EMEA) have taken a proactive approach towards PGx[1,10] and have developed a wide range of initiatives. The FDA has, however, also taken a further step further by developing guidance for genomic data submission.[1]

The direct costs of molecular-based diagnostic tests vary markedly.[11] Direct testing costs depend primarily on the method of testing, which can vary from cheap kit-based technologies to expensive sophisticated instruments.[8] The potential benefits of personalised medicine and PGx are undoubted, from a scientific point of view; however, since we are in a context of cost-containment and scarce resources, there is a need to prove that the new technology is also cost-effective. Healthcare resources should be used to maximise value for money.[12,13] The few cost-effectiveness studies carried out on PGx technology show unsatisfying results.[9] Several authors have evaluated the potential impact of PGx on healthcare concluding that pharmacogenomics will be cost-effective under certain circumstances.[14]

In addition, there is still a lack of evidence on its clinical validity and utility. Many findings on gene–disease associations have not been confirmed by subsequent studies. In this instance, it is worth mentioning the potential role of bio-banking in the near future for

carrying out trans-national studies to confirm gene–disease associations. Without doubt, the most challenging aspects of developing PGx tests will be to establish associations between genetic variation and clinically relevant outcomes.[8,15] And in spite of the need for further studies to characterise certain associations and evaluate their clinical endpoints, it seems, however, that there are already several good examples on the market.[15]

The effectiveness of PGx in clinical practice will be also determined by the accuracy of the genetic tests.[14] PGx tests for detection of variant genes are typically quite accurate, with sensitivities and specificities near 99 per cent. The issues of false-positives and false-negatives are important for almost all applications of PGx, and the fact that patients might be labelled as having a genetic variation despite not all of them having clinically relevant effects should be a matter of concern.

Narrower market sizes and issues related to coverage and reimbursement policies are of the utmost importance for an industry in bringing products to market. Since PGx technology is able to identify sub-groups of a population in which the medicine is effective, there is a risk that 'niche markets' could not provide the financial incentive for the development of appropriate therapies by the pharmaceutical industry.[15] There is, however, evidence to believe that it might not form a real barrier. Decreased market size may be offset by better market penetration, added value of the drug, decreased development costs resulting from streamlined clinical trials and regulatory incentives to develop PGx strategies and targeted drugs.[14] The 'blockbuster model' (drugs that generate more than US$1bn of revenue each year) that has dominated the industry for decades is starting to change; however, it does not necessarily mean that pharmaceutical markets have to suffer a decrease in their total revenues. It will depend on the strategy they decide to follow.

It seems that by applying the principles of personalised medicine, it is possible to significantly enhance the productivity of drug discovery and development. With the identification of the right genes, pathways to the development of the right drug will be clearer. Some authors remark that it seems that the real cost savings will come from fewer failures going into development. Estimated cost savings of more than $500m for drug launched have been predicted.[3] The firms' ability to better identify drug candidates, speed up clinical trials or decrease trial costs by screening enrolees is crucial for adding value to drugs[16] and as such, this higher value might facilitate a higher market price.

A genetic test can be performed using either a 'test kit' or a 'home brew'. Kits contain the test *per se*, instructions on test performance and information regarding which mutations are detected. Manufacturers sell these kits to laboratories. 'Home brew' are assembled in-house by the laboratory and are used to analyse patient samples. Many tests in USA and in Europe are conducted in-house by laboratories using their own components or analyte-specific reagents (ASR).[17] The absence of a regulatory system has allowed the entry into the marketplace of tests of unproven medical value, marketed directly to consumers. Nevertheless, it still remains unclear whether the existence of 'home brews' will become a real driver of or a barrier to the further development of the PGx market.[17]

There are other factors that have neither been widely studied in an explicit form nor are usually mentioned as barriers in the development of the PGx market. It seems that they might, however, play an important role in fostering its adoption:

- *Lack of integration and coordination across multiple stakeholders involved in the process of adoption*: Coordination among Government, biopharmaceuticals companies, diagnostic companies, life science companies, patients, payers and healthcare professionals has to be strengthened.
- *Education in genetics and genomics*: Experts argue that educating physicians is one of the biggest obstacles. When the majority of current doctors were in medical school, pharmacogenomics was not part of their training.[7,18]

- *Current opposition to PGx because of ethical implications*: There are high stakes in how race will be ultimately deployed in human genetic variation research as such practices may well inform how we engage with the moral project of justice in medicine.[19]
- *Lack of knowledge on the processes of relationship marketing with consumers*: Providing the personalised care that PGx enables might become a strategic asset.
- *Lack of appropriate marketing capabilities*: It seems essential for success, however that the shape of these competencies will change. A widespread access to doctors and hospitals will remain a source of competitive advantage. The sales force will need to be more focused on specific therapeutic areas.
- *The complexity inherent in the communication of the benefits to society*: Science and markets lead while society lags. Public attitudes will play a crucial role in realising the potential of scientific and technological advances.
- *The uncertainty surrounding intellectual property rights*: It is not clear what the impact of the actual patent system might be on the market since there are different agents involved with conflicting views about the potential effects. Experts argue that the patentability of single nucleotide polymorphisms (SNPs) makes it difficult if not impossible the development of more diagnostic tests.
- *Lack of appropriate trade channels for these products*: Laboratories need a distribution route to patients. The most reliable alternatives are direct sales of testing services or licensing to other laboratories or manufacturers.
- *Difficulties related to the much more complex relationships between physicians and patients while doctors' salaries remain static*: Will reimbursement match the time that the physician takes to target?
- *Lack of business models to ease biopharmaceutical companies' benefit from their innovations*: There is not any historic model for the introduction of these products onto the market. Extraordinary medicines are being introduced with ordinary processes. The current blockbuster model becomes useless for niche products.
- *The erroneous approach of not considering physicians in the process of adoption*: They have been considered passive subjects so far by the industry. A patient-centric approach needs to be built by working closely with doctors.
- *Time to market*: It just takes too long to diffuse innovation today. Between 12 and 15 years, it is needed for an idea to actually get to the bedside as standard practice.[20]
- *Lack of awareness among all agents directly involved in the process of adoption* (*hospitals, physicians, laboratories and analysts*).
- *Lack of appropriate economic incentives*: In some markets, the price negotiation is with a central government that has considerable power. Also it is difficult to change a price once the drug is on the market. The last problem is related to the reimbursement systems. These systems, in the case of diagnostic products, might be described as resource- or cost based rather than value based.[21]
- *Lack of knowledge about the potential market size and if these niches would be willing to pay more for these drugs*: Personalised medicine will generate personalised benefits, thus personalised prices seem to be appropriate.

OBJECTIVE AND METHODOLOGY

The previous literature review shows the complexity of the elements forming the current state of development of PGx technology. So far it has been argued that many of the factors that theoretically limit their adoption play a far lesser role or even have no influence in practice. Moreover, it seems rather complex if not impossible to act in the short- and mid-term to reduce such barriers. Nevertheless, other factors might play an important role on which it seems more feasible to act and obtain results.

It seems that the majority of authors are leaving aside the most important aspect of market, that is, demand. Assuming the

practical approach of this work, it is proposed to act on an element which, although is not the only one to explain the 'relative failure' in adoption, allows operative actions able to foster its further development in the short- and mid-term: market demands, for example, doctors and patients.

The exploratory research, part of a wider research project carried out by IPTS,[1] was aimed at applying a questionnaire to physicians (potential prescribers) in order to directly assess:

1. If there is any barrier among doctors and patients, which might influence the acceptance of these products, and
2. If these groups might be considered as primary objectives for marketing and communication actions, fostering the process of adoption by the market.

Certainly as more genetic tests are developed and marketed for use in public health and healthcare settings, physicians (eg hospitals, as the first link with demand) and patients will become the main factors playing a key role in the process of adoption. Empirical evidence shows the viability of the previous line of reasoning.[22]

A questionnaire was circulated among physicians with the objective of finding out the potential factors limiting the adoption of these products by the market. The questionnaire was focused on the perception and behaviour regarding the use of one breast cancer diagnostic product: the HER2 test. There are two tests in the FDA-label to determine HER2 status to select patients for treatment with Herceptin. The first approved was an immunohistochemistry (IHC) test, the HercepTest, which measures the level of expression of the HER2 protein. The most recently approved method, FISH, detects the underlying gene alteration in the patient's tumour cells. FISH makes the number of HER2/neu gene copies visible.

The product was chosen with the aim of maximising the representativeness of the results, enhancing the sample's validity. Its potential use in a great number of hospitals given its benefits in the treatment of a massive disease (cancer) reinforced our selection. In addition HER2 covers one of the two main strategic applications of PGx, namely improvement of the drugs' efficacy.

The research setting was European hospitals that incorporate this product in their portfolio of services. The unit sample is a medical doctor (MD) with the capacity to prescribe the diagnostic test. We have balanced the appropriateness of centring the collection of information on doctors instead of patients. Although it is assumed that the most important information comes from consumers, operative and legal reasons recommended us to focus only on doctors. The difficulty of forming a sociodemographically representative sample group of patients (dispersed in numerous hospitals), and the difficulties of access to personal data given data protection laws, persuaded us to not to focus our work on them. The questionnaire, however, attempts to gather specific information regarding the perceptions of patients through the physicians' eyes.

Academic and non-academic hospitals were chosen, from four different European countries (UK, Germany, Netherlands and Ireland) with Oncology Departments where the HER2 test is performed. Hospitals were contacted in order to get the names of the heads of these units and his/her email account. Two hundred and twelve hospitals were suitable for the study and the structured questionnaire was sent by electronic mail. Responses from Irish hospitals were eliminated due to the low response rate. Sixty-four questionnaires were correctly filled out and used for the analysis. Given the sample size and the exploratory objectives of this work, a 30 per cent response rate was considered sufficient for the descriptive analysis carried out.

After reviewing the different barriers that are limiting the further adoption of PGx products, reasons for carrying out an exploratory study are beyond doubt, since the problem appears not to be clearly identified yet. As 'exploratory research', results will provide new insights into the PGx market. It is, however, needless to say that results are not representative of the whole population being under study.

Table 3: Results

Variables related to physicians	Frequency	Variables related to patients	Frequency
Ease of interpretation		*Refusing of patients*	
Relatively difficult	17.2	Often	0.0
Not easy not difficult	28.1	Sometimes	1.6
Relatively easy	54.1	Never	98.4
Costs		*Patients ask for more info*	
Often a problem	12.5	Often	20.3
Sometimes a problem	37.5	Sometimes	64.1
Never a problem	50.0	Never	15.6
Communication with laboratory		*Patients fear to test*	
Often a problem	1.6	Often	0.0
Sometimes a problem	29.7	Sometimes	10.9
Never a problem	68.8	Never	89.1
Reluctance of medical staff		*Attitudes of patient organisations*	
Often a problem	0.0	Positive	71.9
Sometimes a problem	7.8	Neutral or do not know	28.1
Never a problem	92.2		
Informed consent			
Often a problem	0.0		
Sometimes a problem	4.7		
Never a problem	95.3		
Perceived clinical utility			
Very low	1.6		
Not high not low	4.7		
Quite high	51.6		
Very high	42.2		
Perceived cost benefit (CB)			
C little higher than B	12.5		
C = B	20.3		
B little higher than C	35.9		
B much higher than C	31.3		

RESULTS

As it has already been explained in the previous section, the physician who answered the questionnaire in each hospital was the head of the Oncology Department and it is assumed that the answer is representative of the whole department. Demographic data were not collected as part of this exploratory research. The average number of employees working in such departments ranged from 65 to 120 and the average number of beds in the hospitals ranged between 422 and 597.

Physicians need to understand the basis, reliability and accuracy of the PGx tests and the information they provide. The idea of improving communication with laboratories, and the training and education of MDs appears crucial for the further adoption of PGx products by the market. As it is shown in Table 3, about 45 per cent of physicians do not consider the interpretation of the tests very easy, and 32 per cent of MDs consider that communication with the laboratory might be a problem in the further adoption of such products.

Given that, it seems that neither reluctance of other medical staff to perform the diagnostic tests (more than 92 per cent of MDs had never seen reluctance of medical staff in this area) nor the perceived clinical utility (more than 93 per cent of MDs perceived its clinical value as high) might limit the further development of such a market in practice, the toolkit marketers should reinforce and transmit the idea that performing diagnostic tests is cost-effective. They also need to improve their marketing and communication interactions with prescribers in order to enhance and facilitate a better knowledge and understanding of the products.

Looking at the patients' results, the idea of reinforcing communication on the market demands becomes stronger. Although public acceptance is not the strongest determinant for the implementation of a new technology, the absence of it could certainly lead to a failure of an innovation (perfect examples are nuclear energy and genetically modified organisms). In addition, when technology involves 'genetics' or technology generates 'genetic data', public attitude could become an important barrier to PGx market. Given that patients seem either not to refuse tests (98.4 per cent never refused it) nor not to fear tests (89 per cent), and since they need and ask for much more information (almost 85 per cent of patients) it appears quite clear that strengthening communication with patients and patient organisations may be a successful way to increase market demands and, as a consequence, further adoption by the market. As soon as patients are better informed of such products, they will request them and the level of adoption by the market will increase. Thus it seems that the more well informed the patients, the better the possibilities appear to expand the PGx market. This idea may appear reinforced by the attitudes of patient organisations towards diagnostic tests, almost 72 per cent show a positive attitude to them.

Strong marketing campaigns towards clinicians, patients and patients associations should be designed in order to improve their knowledge of the technology that is already on the market. Stimulation of public and prescribers' awareness, confidence in and understanding of the tests will increase the demand for testing and consequently, will foster the process of adoption of PGx in clinical practice.

DISCUSSION AND CONCLUSIONS

Given the expected benefits assigned to these products, it seems that it has been forgotten that the timescale for their adoption still needs to be conventional.[15] Thus it appears inadequate to talk about 'failure in its introduction'. Certainly, once the agents of introduction involved consider it appropriate to reduce time to market, they will be able to do so effectively by acting with marketing and communication procedures on the agents of final demand: physicians and patients.

A number of operational conclusions can be drawn from the study carried out:

1. This study shows the need to understand and include physicians, patients and patient organisations in any planning for personalised medicine, as potential drivers of market demands.
2. Personalised medicine presents marketing challenges unlike any other field of healthcare. Formulating marketing strategies for these products involves integrating multiple aspects: the availability of marketers for interpreting complex science, the role of physicians in decision-making, the consumers' concerns about privacy and the lack of consumer awareness.
3. It seems clear that pharmaceutical companies ignore the disjuncture between their technological projections and the practicability of their products in clinical practice. Such confrontation is understandable given the lack of knowledge about the technology and its benefits among physicians and patients.
4. There is a need to review and update education in genetics at undergraduate and postgraduate levels, and in continuing medical education. Future doctors, nurses and pharmacists will require a deep knowledge of and training in the science of human genetics.
5. There is a need to carry out mass communication actions in order to get consumers beginning to think about pharmacogenetics. Consumers need access to trusted information and the capability to make informed decisions.
6. This study reveals that one of the main causes of the communication failure of these products is that the industry does not really know and understand their market and consumers. Marketers must begin to look for information to help them understand the changing market and to help them forecast. Key information should come from physicians and their patients.

The 'relative failure' in its introduction re-opens the debate about the lack of 'consumer orientation' in the pharmaceutical industry.[23]

7. To foster its further implementation in clinical practice, PGx marketers should develop strategies focused on the market's demand side, for example, patients and clinicians. As first steps, doctors, patients and even pharmacists (since it seems probable that their role and responsibilities will change in the future) need to understand the basis, reliability and accuracy of the PGx tests and the information they provide.
8. Strong marketing campaigns towards clinicians, patients and patients' organisations should be designed in order to improve their knowledge of the technology that is already on the market.

Beyond doubt the effective translation of all this new knowledge to healthcare settings will require a partnership of policy makers, PGx markers, pharmaceutical manufacturers, clinicians, educators, patients associations, researchers and public.

Disclaimer: The views expressed by the authors do not necessarily reflect those of the European Commission.

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