



editorial



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European attitudes to gene therapy and pharmacogenetics

Views on pharmacogenetics and gene therapy systematically differ across European countries. But despite a complex regulatory regime there is a balance of support, albeit laced with considerable uncertainty.

Introduction

Pharmacogenetics is the study of genetic variation that gives rise to differing response to drugs. Pharmacogenomics is the application

of genomic technologies to new drug discovery and the further characterization of older drugs. However, the terms tend to be used interchangeably. Given this, it is likely that the public will also draw little distinction between them. As with Hopkins et al. [1] and others, we use the term PGx to collectively refer to both technologies. Gene therapy (GT) is the insertion of genes into an individual's cells and tissues to treat a disease.

People's concerns about GT relate to both risks of mistakes and of human actions. Firstly, there are issues such as the risk of deliberate alteration in the human gene line, which may impact on the inherited nature of human beings. Secondly, as an example of what can go wrong, two children treated in France for immune disorders developed leukemia-like conditions. Genetic analysis of the malignant cells showed that the retroviral vector had activated an oncogene LMO2 that is associated with childhood leukemia [2]. In addition there are concerns about the application in the clinic. Gene medicines need to be stored separately from other drugs and at the correct temperature in a freezer. Expertise is needed in their administration. It is not clear that all the regions throughout the EU have either the appropriate facilities or the expertise.

PGx does not generate such concerns, indeed it may even increase safety in facilitating the better targeting of drugs and reducing the incidence of adverse reactions. However, it should also be emphasized that there is currently relatively little hard evidence on its net benefits [3]. But there are still issues, including the sharing of samples and biobank data for research, which have implications for donor privacy. There may also be concerns that PGx could lead to the stratification of populations based on genetic variants, with the risk that some population groups might be too small to be of interest to the pharmaceutical industry. PGx may also impact on the way insurance firms behave or indeed employment opportunities. Most European countries have introduced legislation aimed against genetic discrimination as, in 2008, has the USA. But doubts still remain as to how effective this legislation will prove [3]. There may also be concern that initially new drugs, new treatments will be expensive and only gradually become available to the population as a whole. Both technologies require expertise and mistakes are possible. For example with respect to genetic testing, there is evidence that it falls short of the desired quality with substantial numbers of errors in both the EU and the USA [4]. Throughout the EU, regulations, professional

standards and accreditation requirements can differ substantially with respect, for example, to preimplantation genetic diagnosis [5].

Regulation in the EU and the USA

In the EU, the European Medicines Agency (EMA) has responsibility for the conduct of clinical trials and pharmacovigilance activities. The Clinical Trial Directive (CTD) has led to harmonized authorization procedures, which take place at national level. The CTD is complemented by the GCP (Good Clinical Practice) directive, which requires sponsors to obtain authorization from the member state(s) in which the clinical trial is going to be conducted. The procedures for GT are more rigorous than for other drugs. Once trials are completed, applications for marketing authorization are made directly to the EMA, whose scientific committees carry out a peer review process. Based on this, the European Commission makes the final decision. A further Committee of EMA ensures that all appropriate measures are taken to avoid adverse effects on human health which might arise from the deliberate release of placing on the market genetically modified organisms (GMOs). Subsequent monitoring of the safety of authorised products is done in the member states. There are other differences across the EU, e.g. the rules on the contained use and deliberate releases of GMOs [6].

In the USA, theoretically at least, the regulatory structure is more unified, with the Department of Health and Human Services (DHHS) having considerable oversight over all aspects of drug development and safety. However, the various responsibilities are split between several offices within the DHHS and in reality the system is quite complex [7] and arguably needs both consolidating and simplifying [8]. The Office for Human Research Protections mandates that all research involving human subjects obtains approval from the Institutional Review Board at the researcher's institution. The Food and Drug Administration (FDA) regulates human gene therapies through its Center for Biologics Evaluation and Research. A manufacturer who is considering selling a GT product must first inform the FDA and then test the product, in a laboratory and research animals. Before studying the GT product in humans, they must obtain a special permission exemption, called an investigational new drug application, from the FDA. The manufacturer explains their methodology, the possible risks and what steps it will take to protect patients, and provides data in support of the application. Manufacturers of GT products must meet FDA requirements for safety, purity and potency before they can be marketed. Finally, a further DHHS agency, the National Institutes of Health (NIH) through the Recombinant DNA Advisory Committee (RAC), oversees the conduct of federally funded clinical trials. There are substantial overlaps in the regulatory roles of the RAC and the FDA and substantial differences in their approach, with the former being much more open [7].

PGx raises different regulatory problems. For example drugs and diagnostics often need to be jointly regulated. In the USA, the licensing of therapeutics in combination with a diagnostic test is undertaken jointly by the FDA Office for Combination Products. It is argued that this leads to more stringent regulation than in the EU [1], where separate application for diagnostic products must be made to the national agencies. The IVD (*In Vitro* diagnostic) direc-

tive is key to this and requires a European Conformity Mark, i.e. a manufacturer's declaration that the product complies to all relevant legislation [10]. Despite this directive, there are substantial differences in the regulation of *in vitro* diagnostics between member states [8]. European Commission directives also govern biobanking, which member states again interpret in different ways leading to substantially different biobanking systems in Europe, which the EU is trying to harmonize [9].

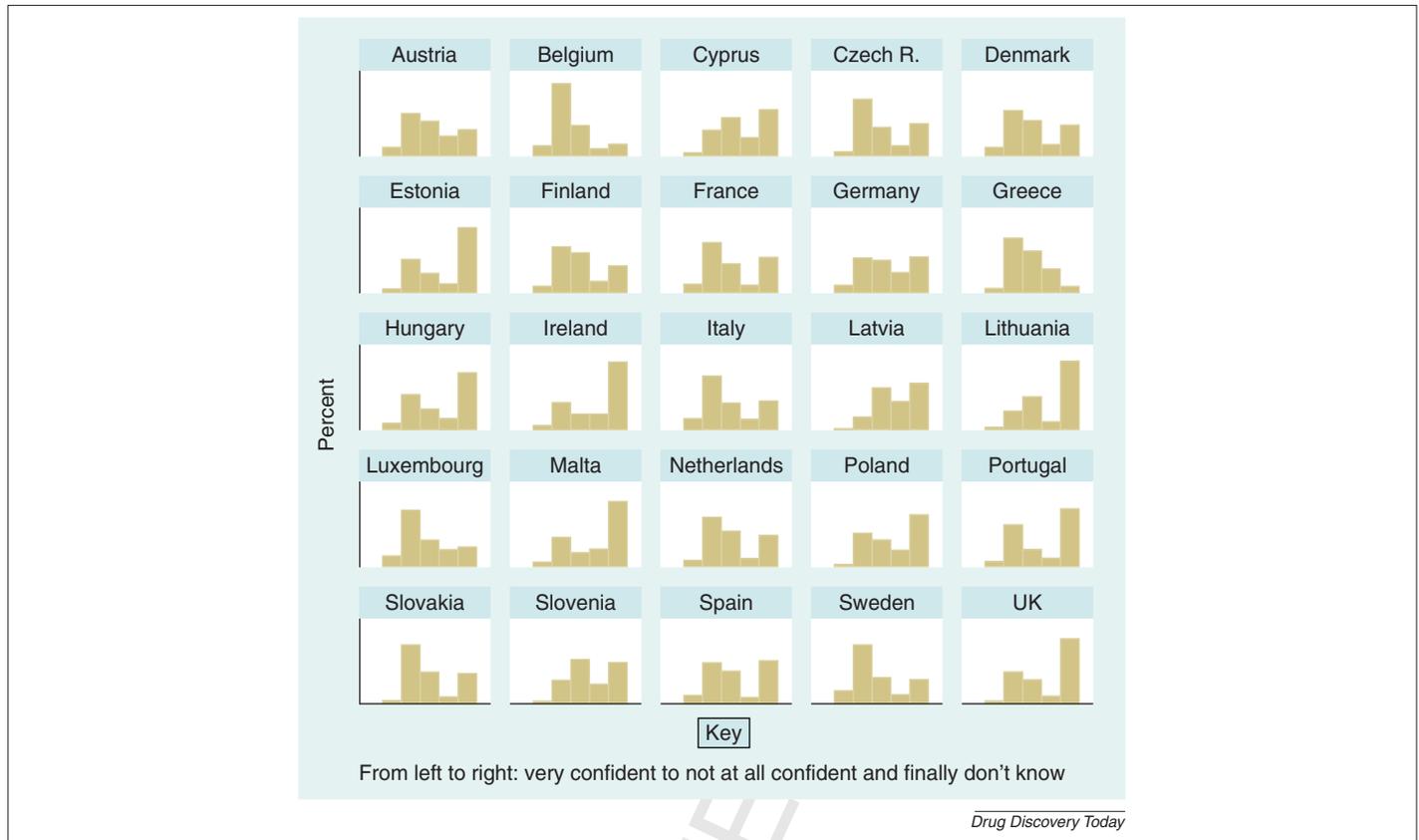
Regulation for both technologies brings potential benefits to industry as well as costs. In providing certainty it can encourage both investment and patient uptake. But there are still concerns that regulation can stifle industry innovation [11,12] and raise industry costs [13]. The CTD directive, which is currently under review, has come in for particular criticism that despite improving safety and the ethical soundness of clinical trials, it has led to a significant decline in the attractiveness of research in the EU [14,15]. The US regulatory system has evolved in something of a random way, responding piecemeal to specific events and problems [7]. The system in the EU, although still evolving, is arguably even more complex as it struggles with the need to harmonize the practices of the diverse member states. This complexity increases the regulatory burden on firms and may disadvantage industry and the development process [16]. In both areas too, as perhaps with any new technology, regulators face problems in finding people who have sufficient technical expertise [6].

Public attitudes in the EU

We use data from the November/December, 2005 Eurobarometer survey (64.3) of approximately 1000 people in each EU member country. The data on the individual responses suitable for analysis has only become available in 2009. In terms of regulatory confidence, Fig. 1 shows considerable variation between countries, which is similar to that for PGx, as well as considerable ignorance particularly in Lithuania, Estonia and Latvia.

Table 1 shows that in the EU as a whole, the public views PGx slightly more favourably than GT. A balance of opinion with respect to the regulation of both technologies was favorable, although with sizeable proportions who simply did not know, particularly for PGx. There is considerable ignorance on both these technologies and this in itself is important. Nonetheless, it is still also important to understand the determinants of views amongst those who do have definitive opinions. On balance people were slightly more confident in the regulation of PGx than GT. It is also viewed as substantially less risky, slightly more 'morally acceptable' and 'useful to society'. Indeed the majority of people with an opinion had concerns over GT with respect to risk, although a large majority also thought it useful to society. Further analysis shows a similarity of views on the two technologies. Gene therapy and pharmacogenetics have only in common the word 'gene'. They are completely different biotechnologies – one a therapy and the other a diagnostic test that, depending upon exactly which gene is studied, has the potential to provide information on therapeutic toxicity or treatment benefit. Nonetheless, amongst those who had an opinion on risk, acceptability and use to society, 47.2%, had the same opinions for both technologies.

Ordered probit regressions were used to further analyze the data. The results are summarized in Table 2. The figures relate to risk ratios and show, for example, that a man of given characteristics is

**FIGURE 1**

Regulatory confidence in gene therapy.

24.1% more likely to voice total overall approval for GT than a woman. More generally with respect to GT, men have significantly higher levels of confidence in the safety and regulatory approval system and perceptions of usefulness and moral acceptability than women. This impact is also mirrored by more educated people who also have greater knowledge about GT and perceive it as less risky. Older people tend to have the opposite pattern of significance to men, although knowledge increases with age. Those who live in rural areas tend to be less favorable on several dimensions. Finally,

the unemployed and widowers tend to have less favorable views. These figures relate to those in 'total agreement' with the various statements, but of course there will also be shifts in the numbers who 'tend to agree', and, amongst those who disagree. The results do suggest substantial variations of views across society, but that to see a substantial shift in opinion, policy makers need to work on several dimensions simultaneously, e.g. changing the attitudes of women, those in rural areas, the old and the less well educated as in the 'multiple effects row'. There are also substantial differences

TABLE 1**Summary table of attitudes**Source: derived from Eurobarometer survey (64.3).

<i>Confident in Regulation</i> ^a :	Very	Fairly	Not very	Not at all	Don't know
Gene therapy	4.3%	30.2%	29.7%	12.9%	22.9%
Pharmacogenetic	4.7%	31.5%	23.0%	10.0%	30.8%
Nanotechnology	6.0%	33.4%	20.5%	10.5%	29.6%
GM foods	3.5%	25.0%	34.7%	23.0%	13.8%
<i>Gene technology:</i>	Totally agree	Tend to agree	Tend to disagree	Totally disagree	Don't know
Is risky	12.4%	30.4%	23.8%	6.9%	26.5%
Is morally acceptable	14.4%	35.0%	17.7%	8.2%	24.7%
Useful to society	16.1%	38.1%	14.2%	6.4%	25.3%
<i>Pharmacogenetics</i>	Totally agree	Tend to agree	Tend to disagree	Totally disagree	Don't know
Is risky	6.5%	22.6%	27.6%	8.7%	34.7%
Is morally acceptable	17.3%	36.4%	10.0%	4.6%	31.7%
Useful to society	18.1%	38.3%	8.7%	3.7%	31.2%

^aSpecifically: confidence in the safety and regulatory approval system relating to the specific technology.

TABLE 2

Summary of impact of socio-economic variables on attitudes to the technologies

	Overall approval	Confident in regulation	It is morally acceptable	It is risky	It is useful	I have heard off
Gene Therapy						
Male	1.241**	1.230**	1.235**	ns	1.223**	ns
Rural area	0.917*	0.869*	0.910*	ns	0.901*	ns
Not religious	1.190**	ns	1.328**	ns	1.168**	1.051*
Manual worker	ns	0.889*	ns	ns	ns	ns
Unemployed	0.804**	0.661**	ns	ns	ns	ns
Married	1.102**	ns	1.107**	ns	ns	ns
Widow	0.867*	0.772*	ns	ns	ns	0.822**
Age 65 vs 25	0.805**	0.661**	0.840**	1.106*	0.879**	1.100**
High vs low education	1.507**	1.376**	1.403**	0.900*	1.299**	1.938**
Multiple effects	3.038	3.069	3.019	0.894	2.350	2.443
Pharmacogenetics						
Male	1.130**	ns	1.149**	ns	1.145**	1.062*
Rural area	ns	0.872*	0.897**	ns	0.916*	ns
Not religious	1.171**	ns	1.173**	ns	1.094*	1.081*
Manual worker	ns	0.831**	0.914*	1.113**	0.908*	ns
Unemployed	ns	0.706**	ns	ns	ns	ns
Married	1.105**	ns	1.132**	ns	1.113**	ns
Widow	ns	0.797*	ns	ns	ns	0.242**
Age 65 vs 25	0.792**	0.651**	0.857**	1.133*	0.836**	1.178**
High vs low education	1.346**	1.227**	1.322**	ns	1.235**	2.103**
Multiple effects	2.420	2.262	2.357	0.824	1.413	3.096

The table relates to the probability of being in total agreement with the various statements. It shows the risk ratios for the different scenarios: whether man/woman, live in rural area, aged 65, religious, high vs low education, etc. Thus a widower of given characteristics is only 82.2% as likely to have heard of GT as a non-widower. These are derived from ordered probit regressions (apart from the knowledge equation which is probit). */** denotes a significant impact at the 5%/1% levels of significance respectively, ns denotes not significant. Multiple effects compare the most and least favorable scenarios, combining age, male, rural area, education and 'not religious'. 'Not religious' are those who did not identify themselves with one of the 9 primary religions. High/low education: left school at 20+ years/by 15 years. Detailed results can be obtained from the authors.

between countries which are not simply a reflection of differing socioeconomic characteristics. Many of the countries of Central and Eastern Europe are particularly distrusting of the regulatory regime as are those in Malta and Spain. Apart from this there are also significant differences between regions within countries. These may reflect differences in the ability to utilize the technology or the likely industrial impact of GT.

The pattern of impact for the socio-economic attitudes is largely repeated for PGx, although occupation tends to be more significant than for GT. In addition, Belgium, the UK and Sweden have most faith in the regulatory regime and the countries of Central and Eastern Europe, with Malta and Greece, have least faith. For both technologies there are few systematic differences with respect to risk perceptions.

These results suggest that attitudes are linked to self-interest and the probable impact of risk on individual calculations. Younger people have longer to benefit from new biotechnologies. Rural areas often benefit from new technology later than other localities and in the context of this study may have greater problems with acquiring expertise and, for GT, storage facilities. In other research women have been shown to be more risk averse than men [17]. The impact of both education and being a manual worker suggest that people on low incomes, who are less likely to benefit from new product innovations in general, are more unfavorable to GT and PGx.

Conclusions

Public support is critical for a new technology [18]. A lack of support can delay, perhaps indefinitely, its development and diffusion, our analysis has revealed a balance of support but also widespread uncertainty, particularly with respect to PGx. It also

suggests that GT, in particular, may have more difficulty in progressing when targeted at certain sections of the population such as women and the elderly. Furthermore, diffusion is likely to be at different speeds in different countries and regions and also between cities and rural areas. This may then have an impact on commercial incentives to develop new products, biasing them to sectors of the population and areas which are more approving. The widespread uncertainty surrounding both technologies, but particularly PGx, suggests the need for greater information to be communicated to the general public and in our view this is a responsibility for the regulators. Academics too have a responsibility to write and broadcast for the media in general. However, our analysis suggests that the frequent reference to 'the public interest' in official publications, and the involvement of 'the public' in regulation [19,20] may be misplaced. We have shown that there is no such thing as 'the public interest' or indeed even 'the consumer' or 'the citizen'. There are rural consumers, old versus young consumers, wealthy versus less wealthy and each tend to want different things. Finally, for the EU, and possibly for the USA too, the substantial differences in attitudes between countries and even regions within countries make agreement on harmonized procedures more difficult.

References

- Hopkins, M.M. *et al.* Putting pharmacogenetics into practice, *Nature Biotechnology* 24, 403–410
- Cavazzana-Calvo, M. *et al.* (2004) The future of gene therapy. *Nature* 427, 779–781
- Vijvberg, S.J.H. *et al.* (2010) Ethical and social issues in pharmacogenomics testing. *Current Pharmaceutical Design* 16, 245–252
- Ibarreta, D. *et al.* (2004) Towards quality assurance and harmonization of genetic testing services in the European Union. *Nature Biotechnology* 22, 1230–1235
- Corvelyn, A. *et al.* (2008) Provision and quality assurance of preimplantation genetic diagnosis in Europe. *European Journal of Human Genetics* 16, 290–299

- 6 Gonin, P. *et al.* (2005) Gene therapy bio-safety: scientific and regulatory issues. *Gene Therapy* 12, 146–152
- 7 Wolf, S.M. *et al.* (2009) Gene therapy oversight: lessons for nanobiotechnology. *Journal of Law, Medicine and Ethics* 37, 659–684
- 8 Kuzma, J. *et al.* (2009) Evaluating oversight systems for emerging technologies: a case study of genetically engineered organisms. *Journal of Law, Medicine & Ethics* 37, 546–586
- 9 Gaisser, S. *et al.* (2007) EU policies in personalized medicine-related technologies. *Personalized Medicine* 6, 93–102
- 10 Dati, F. *et al.* (2004) European performance evaluations of the ADVIA Centaur (R) infectious disease assays: requirements for performance evaluation according to the European directive on in vitro diagnostics. *Journal of Clinical Virology* 30, S6–S10
- 11 Salerno, R.A. and Lesko, L.J. (2004) Pharmacogenomics in drug development and regulatory decision making: The Genomic Data Submission (GDS) Proposal. *Pharmacogenomics* 5, 25–30
- 12 Bates, S. (2010) Progress towards personalized medicine. *Drug Discovery Today* 15, 115–120
- 13 Lesko, L.J. *et al.* (2003) Pharmacogenetics and pharmacogenomics in drug development and regulatory decision making: report of the first FDA-PWGPhRMA-DruSafe Workshop. *Journal of Clinical Pharmacology* 43, 342–358
- 14 European Commission (2009) Assessment of the functioning of the “Clinical Trials Directive” 2001/20/EC: Public consultation paper, http://ec.europa.eu/health/files/docs/2009_10_09_public-consultation-paper.pdf
- 15 Hear, J. and Sullivan, R. (2007) The impact of the ‘Clinical Trials’ directive on the cost and conduct of non-commercial cancer trials in the UK. *European Journal of Cancer* 43, 8–13
- 16 Gurwitz, D. *et al.* (2009) Pharmacogenetics in Europe: barriers and opportunities. *Public Health Genomics* 12, 134–141
- 17 Jianakoplos, N.A. and Bernasek, A. (1998) Are women more risk averse? *Economic Inquiry* 36, 620–630
- 18 Shalala, D. (2000) Protecting research subjects – what must be done. *The New England Journal of Medicine* 343, 808–810
- 19 Chopyak, J. and Levesque, P. (2002) Public participation in science and technology decision making: trends for the future. *Technology in Society* 24, 155–166
- 20 Edwards, S.J.L. *et al.* (2004) Research ethics committees and paternalism. *Journal of Medical Ethics* 30, 88–91

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