

# Science & *the Public Affairs forum*

## Genetics and the search for safer drugs

6 February 2003

Forum Sponsored by



Report prepared by Alice Bell and Submitted to the Nuffield Council on  
Bioethics working party on pharmacogenetics

## Executive Summary

On the 6th of February, the BA ran a Science and Public Affairs forum on pharmacogenetics, entitled "Genetics and the Search for Safer Drugs". Held in the evening, at the Royal College of Physicians, Regents Park, London, the audience were a mix of social and medical researchers, medical practitioners, medical and biotechnology administrators, patients and other members of the interested public. Tickets were free, although places had to be reserved in advance. The event was sponsored by the Medical Research Council (MRC) and formed part of the BA's programme of events to celebrate the 50th anniversary of the discovery of DNA. This is a report of the points raised and opinions declared.

The forum was chaired by Vivienne Parry, independent science writer and presenter, who led the discussion with reference to the questions of the consultation document (although this reference was not explicit to the audience, she aimed to cover as much of the questions as possible). The event started with four five-minute presentations from invited speakers: Sir Michael Rawlins from the National Centre for Clinical Excellence, NICE; Professor Robert Kerwin, Institute of Psychiatry; Dr Paul Martin, University of Nottingham; and Chris Friend, Genetic Interest Group.

This was followed by an hour and a half of open discussion lead by the chair. No particular group of the audience dominated the debate although, on occasion, the forum fell into somewhat of a question-answer structure, so the speakers ended up speaking more than the audience. The audience was informed that a report would be written for the Nuffield Council on Bioethics and asked to write any additional comments on the back of their event evaluation forms. Names and affiliations of audience members were occasionally given, but have been omitted from this report.

This report separately addresses each of the consultation questions, and so includes a mix of spoken and written comments, questions and arguments without reference to the order they were raised in the discussion. Inevitably, some issues were of particular interest to the audience, so some questions were not answered in as much detail as others. Similarly, due to the diverse nature of the audience there was not always consensus in their answers.

The development and regulation of medicines

*Q1. What do you think will be the likely economic impact of pharmacogenetics on the development of new medicines?*

Initially there was suggestion that the pharmaceutical industry would not be interested in pharmacogenetics at all. Personalised medicines would split up the drugs market, and are therefore economically unattractive to firms that want to sell their products to as many people as possible. It was proposed that pharmacogenetics could be an economic threat to the pharmaceutical industry. There was concern that this could lead to pharmacogenetics research only being undertaken through publicly funded research.

Following on from discussion about pharmacogenetic drugs in countries without testing facilities (see question 6), BRCA breast cancer testing was raised as an example. Such tests cost several thousand pounds because of patents on the gene. BRCA tests may not be pharmacogenetic, but the patent issue could easily crop up in the pharmacogenetics context, and so make pharmacogenetic testing a very expensive enterprise. Further, countering the idea that testing is not within the pharmaceutical industry's financial interest, Paul Martin emphasised that his research showed that some were looking to make pharmacogenetic testing a key part of their business, based on how much they could charge with the appropriate patents.

Conversely, there was also some debate as to whether pharmacogenetics might cut the costs of drugs as it might allow for cheaper trials procedure. Most of this debate was within the context of orphan medicine (see question 2).

*Q2. Do you think that further regulatory measures will be needed to encourage the development of clinically desirable but economically unprofitable medicines?*

Concerns were raised about "orphan medicines" were raised on several occasions. It is worth noting that the term "orphan patient groups" was used as often as "orphan medicines", suggesting a greater focus towards the people affected rather than the drugs themselves.

Throughout the forum there was much debate on the role of the pharmaceutical industry, and how adequately it served the interests of patients, including "orphan patient groups". As one audience member said "How can we trust research that comes from a focus on mass-markets?" However for every worry such as this, there were other voices that emphasised the aims of industry should not be counter-posed with aims of public health. As one audience member, who worked for GSK, said: GSK are trying to reduce the costs of medical R&D and cannot cope with the publicity of a drug with terrible side effects, which are aims it shares with the NHS. Yet, generally, there was a reasonable amount of concern about the pharmaceutical industry's aims, and one audience member later posed the rhetorical question of why are there so few human vaccines? However, even strong distrust tended to come with an attitude that it was to be expected considering they were, after all, businesses. Further, that for an overall positive effect of pharmacogenetic technology, regulations and the public healthcare system would simply have to play their role.

One audience member made the point that the pharmaceutical industry is not the only hurdle when it comes to patients getting hold of pharmacogenetic drugs: perhaps the

biggest problem is actually NHS regulations? He raised the question of what criteria NICE would use when examining pharmacogenetic drugs (see question 7). Similar to an earlier response on problems associated with industry led medicine, it was suggested that the aims of the NHS and the aims of the patients should not be divorced.

The “big five” biotechnology firms were characterised as reliant on mass-market drugs; “running on block-busters”. Considering this, one audience member suggested that pharmaceutical companies should be forced to spend some of their profits from popular drugs on less popular ones, a sort of “Lemsip fund” where headache pills could fund treatments for rare diseases. There appeared to be little support for the possibility of this, and some incredulity.

It was also pointed out that pharmacogenetics might decrease the cost of trialling a drug which, if true, could benefit orphan patient groups. Further to the suggestion that current regulatory frameworks were as much of a ‘hurdle’ as biotechnology share-holders, there was the suggestion that regulators are perhaps stuck in over-cautious, old fashioned points of view. Instead of insisting on pricy and lengthy trials, it was suggested that regulators could directly ask patient groups what amount of testing they would want for the drug for their very rare disease.

If a drug is only designed for a small number of people who are genetically immune to its side-effects, there would be no need to test it on a wide range of genomes. However, later on an audience member raised the problem of trusting doctors to take the precautions of a pharmacogenetic test before they prescribed a pharmacogenetic drug that might hurt all but a few patients. No matter how few people the drug is meant to be for, we have to assume it will be used on a wider range of patients, and so trial to see what the effect would be. Therefore, the cost of development of drugs would remain.

Related to this was the debate on whether pharmacogenetics might increase the number of medical treatments available. That is, research into drugs that had previously been halted could be re-continued, just for a smaller number of suitable patients. There was some discussion over whether this was feasible. Michael Rawlins disagreed that that pharmacogenetics could bring back previously withdrawn drugs, and stated that there are nearly always alternatives to withdrawn drugs. Despite this, several audience members highlighted that pharmacogenetics could have a role in increasing the productivity of the R&D process. Consequently research could continue on drugs that appeared unsuitable for large numbers of people, because pharmacogenetic tests testing could identify individuals that may benefit.

From this last point, an audience member did ask whether (despite all the potential benefits) such drugs would be ethical, considering the amount of “off-label” prescribing in the NHS. However no one could give an answer to this.

The provision of tests and medicines

*Q3. In your view, should pharmacogenetics testing of participants in trials be a regulatory requirement for the development of medicines in the future?*

At first this was highlighted by the audience as a very good idea. A trial should not put its participants in danger and such tests should give more evidence as to how safe the trialled drug was, or rather to whom it is safe. For example drugs trialled on men are not

necessarily safe for women. However, it was seen that too many regulations imposed on manufacturers could lead to patients suffering in terms of cost and availability of drugs. There was also the concern of the security of such information (see question 9).

*Q4. Who should be responsible for providing a pharmacogenetics tests on the internet? For individual therapy, should tests be available directly to patients over the counter or should they only be available through medical practitioners as part of a decision about the use of prescribed medicine?*

This was the first question raised at the forum. Initially it was characterised as a post-diagnosis issue. Therefore, considering the training of GPs, and the suggestion of their unreliability in prescribing, it was recommended by one audience member that the pharmacist would be the appropriate healthcare professional to provide pharmacogenetic tests, post-diagnosis by doctor. Michael Rawlins responded that it was a more complex issue than that, and so important not to ascribe the entire job of testing to particular trades, rather think of it as “horses for courses”. The problem of first exposure to drugs, where a large dose can set life-time intolerance, was also emphasised as a reason not to leave tests simply at the post-diagnosis stage.

Both speakers and audience emphasised that whoever it is decided should provide the tests will need to follow some form of regulations. Paul Martin suggested that, though a pharmacogenetic test would not have the impact of a Huntingtons diagnosis, it wasn't quite a pregnancy test either, and as such a pharmacogenetic-specific regulation strategy is needed.

Discussion on the potential for patients to internet-order pharmacogenetic tests prompted a technology analyst from the audience to raise the rhetorical question “how exactly can you stop it?” From his point of view, rather than asking whether it is right or wrong that patients can get tests for themselves or that doctors might prescribe “off-label” we should assume that it will happen and work to minimise the problems that might arise (e.g. have some form of kite-mark for over the counter drugs, or trial pharmacogenetic drugs regardless of who they are aimed at).

*Q5. What will be the implications of pharmacogenetics for pharmaceutical companies and providers of healthcare regarding legal liability for adverse reactions?*

It was mentioned that in the US there is already talk of court cases against doctors for not having carried out pharmacogenetic tests (although it was noted that there is a different attitude in UK). It was raised that not informing a patient of adverse reactions to a drug or not performing a possible pharmacogenetic test would be negligent of the doctor.

Little direct reference was made to the role of pharmaceutical companies in regard to legal liability. The question of whether a trial participant should know all the genetic information determined by the research, including knowledge of adverse reactions, was discussed separately (see question 12).

*Q6. Should medicines which have been developed for administration in conjunction with a pharmacogenetics test be distributed to countries in which testing facilities are not available?*

This question was answered on the practical level of availability of testing, rather than ethical issues. Robert Kerwin started the debate off by suggesting the question was really not worth asking; tests would be very cheap, everyone could have testing facilities.

One audience member questioned this by asking, 'will these tests remain cheap'? Surely if the pharmaceutical industry sees profit potential in the tests it will start charging as much as it can. Are the big biotechnology firms even interested in pharmacogenetic testing? Robert Kerwin suggested they were not, so this issue would never raise itself, and tests would remain cheap. However this contentious issue of how the economics will affect research and treatment was left uncertain (see questions 1 and 2).

Many in the audience disagreed with Robert Kerwin. For example, it is all very well to say "testing is cheap and available" whilst sitting in the UK, which has all the equipment and a well developed public health system. Not all countries are lucky enough to have the underlying (expensive) equipment and medical structures to facilitate pharmacogenetic testing. Without a pre-existing system, pharmacogenetics testing will be either unlikely or highly expensive. As one audience member summed up: "Genetic labs aren't cheap. Nor available - there's the set up costs".

Despite this line of argument the "should" element of this question was not really discussed; instead the general opinion appeared to be similar to the problems of doctors mis-prescribing or patients buying off the internet, it was going to happen anyway, so it should be worked out how to minimise the negative effects.

*Q7. How should prediction of efficacy and safety, as well as cost, be integrated in deciding whether to provide a particular treatment to patient in (a) a public healthcare system, and (b) a private healthcare system.*

Distinctions between private and public healthcare systems were not really raised. It was suggested that the NHS could be a potential "hurdle" in terms of patients receiving the benefits of pharmacogenetic tests (as referred to in question 2). A social-science researcher from the audience highlighted an example where the NICE decision process on pharmacogenetic issues was seen to have taken too long, and where the guidance given to clinicians had not been very useful. He asked whether NICE's decisions to fund a drug would be influenced by the number of people it will benefit. Michael Rawlins responded by saying it depended on what the drug would do for these people, not just how many it would help. NICE has a responsibility to all patients, and so has to consider how the spending of money on the few might affect the many.

An audience member did make the point that they, as a prescriber, would be more likely to choose a treatment that did not require a test unless the efficacy was going to be a great deal higher in the case of the pharmacogenetic drug, and so would want to be well informed about the efficacy, safety and cost in order to make a full decision.

*Q8. Do you think the application of pharmacogenetics might exacerbate inequalities in the provision of healthcare? Is it likely to challenge the principle of solidarity that lies at the bases of the provision of national healthcare in the UK? Will the benefits of pharmacogenetics only be affordable to available to the wealthy?*

Whether pharmacogenetics would only benefit the wealthy was discussed at length (mainly in terms of questions 1 and 6). Concerns were raised that the pharmaceutical

industry might exploit gene-patenting with pharmacogenetics, and pharmacogenetic drugs/tests could become very expensive. Whether this would mean the poor would not benefit was left somewhat unanswered. The idea that public health system would need to change and pay attention to pharmacogenetics was flagged up on several occasions. Current inequalities in healthcare provision were not really discussed.

The use and storage of genetic information - confidentiality, consent and feedback in clinical trials

*Q9. In your view, is the storage of genetic information for the purpose of pharmacogenetic analysis categorically distinct from storage of other kinds of genetic information, for example information about susceptibility to disease?*

Several of the audience were of the opinion that pharmacogenetic information is drug-reaction specific and therefore 'leaks' would have less implications than fuller genomic information. However any idea that we could just forget about the security of storage of pharmacogenetic information was not accepted by all.

*Q10. What level of anonymity should be accorded to genetic information stored as part of research in pharmacogenetics?*

Generally, the attitude of the audience was that there should be as much anonymity as possible, with cast iron assurances on everything, although little detail was provided by the forum. There was also awareness of the global context, and international differences of laws regarding genetic information.

*Q11. What kind of consent should be required for the collection of samples for research in pharmacogenetics? Should pharmaceutical companies be able to use such samples for any purpose, or should consent of the donor be restricted to allow usage for specific kinds of research?*

One audience member suggested that there was too much concern about this, in that the already existing regulatory system is sufficiently strict. He highlighted that it would be important to watch the outcomes of the merger of the MDA and MCA . Robert Kerwin mentioned that, although there are regulations in place, he had already been approached by firms wanting to buy the genetic information he had collected from his pharmacogenetic research, although emphasised that these firms had been turned down. From this point of view, the issue was already a concern, but decisions had already been made and there are already regulations in place.

*Q12. Do you think that researchers should provide individual feedback about genetic information obtained from the participants in research in pharmacogenetics?*

Some members of the audience believed that individuals should be told everything, others felt that they would not want to know themselves. There was no agreement about this, although there was the suggestion that clinician-patient interactions could help work through such issues.

The use and storage of genetic information - confidentiality, consent and decision-making in primary care.

*Q13. What, in your view, would be appropriate methods of regulating scope, storage and access with respect to pharmacogenetic information used in clinical practice?*

This was not looked at directly, although answers to questions 9, 10 and 11 are relevant. Michael Rawlins ended the discussions with the suggestion that information contained in NHS notes is not always entirely confidential. He stated that these notes are “as leaky as a sieve” which got quite a supportive response.

*Q14. Do you think that the ethical and legal issues raised by the use of pharmacogenetic tests in primary care differ from those raised by other forms of genetic testing? What about non-genetic tests, such as tests for cholesterol?*

This question was not directly asked of the audience, but answers to questions 4, 9, 10, 11 and 15 are relevant.

*Q15. What might be the psychological implications for individuals of pharmacogenetic tests?*

The sentiment was raised by the chair that it would be terrible if a pharmacogenetically tested patient was told no drugs were going to be of help to them, or that a drug might be of help but would have terrible side-effects. One response to this was that we should not concentrate on suggestions of small-scale individual worries when there are so many positive elements to pharmacogenetics. Surely it would be better to know this sort of information and face up to it as soon as possible, and also much better not be poisoned by drugs that are never going to help? Yet, on this point, it should be mentioned that not all members of the audience appeared to want to know any information about potentially fatal genetic diseases (e.g. the non-pharmacogenetic example of Huntington's).

*Q16. What implications do you think pharmacogenetic tests might have for family members?*

*Q17. In your view, are controversies likely to arise about who ultimately decides which treatment is prescribed in light of a pharmacogenetic test?*

These two questions were not addressed by the forum.

*Q18. Should patients be able to refuse a genetic test to determine response to medicines but still expect to receive a medicine?*

This question was asked of the audience, but having decided that it depended greatly on the context of the disease and the treatment, the forum moved on to discussing problems of prescription, such as doctors prescribing off-label.

*Q19. Do you think that the providers of health insurance should have access to pharmacogenetic information? What about other parts of the insurance industry, for example life insurance?*

The specific subject of insurance was not discussed directly, although concerns about the general security of genetic information were raised on several occasions. At one point the chair asked the audience whether they would be happy to wear “snip chips” of their personal genetic information round their necks, and a little over half the audience raised their hands. Some were worried about the idea of either knowing their own genetic

information or other people getting hold of this information, where as others were really quite unconcerned, especially in respect to pharmacogenetic information, which was seen as slightly different.

#### Race and ethnicity

*Q20. Do you think that pharmacogenetics will increase the likelihood of the grouping of patients according to racial or ethnic groups for medical purposes? If so, what might be the ethical and social implications of such an outcome?*

Although this issue was highlighted by some of the speakers in their talks, it was not really discussed in the forum. However in the evaluation forms, one of the audience members wrote that they felt it was an important issue that was missed out.