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Wakefield District Research Ethics Committee, UK

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

A. By better targeting of medicines, pharmacogenetics has the potential to result in more effective use of medicines with fewer side effects. This could avoid current trial and error and reduce drug wastage. Realistically, however, new medicines, and especially those that have undergone extra testing (pharmacogenetics), will be more expensive than older medicines and this will be reflected in the prescription charge This increase will need to be balanced against the advantages and the possibility of a reduction in overall treatment costs due to slower disease progression or cure. As we get our medicines very cheaply, there may be no objection to this increase in prescription charges, if it is going to improve the standard of care which these pharmacogenetics have an opportunity to achieve. Also of interest will be the economic impact on health economies through the need to test prior to treatment with the new medicines. Pharmacogenetics will potentially reduce costs by allowing marketing of drugs which have previously been shelved, and reducing the number of drugs invested in but not marketed, and there will be some cost for the investment in developing tests. Pharmacogenetics may encourage the development of a cohort of willing pre-tested volunteers who are not representative of the whole population. Is there enough information available yet to determine and describe adequately the extent of variation in wider populations?

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

A. Further regulatory measures are likely to be required, since current incentives to produce orphan drugs (e.g. reduced licensing costs and extended patent duration) are limited and there may be a larger requirement to produce treatments targeted at small proportions of the population. This has already been seen in the withdrawal from the market of the drug to treat sleeping sickness in Africa, because it is not considered to give a sufficient economic return. If economically unprofitable medicines are produced without regulatory measures, then the medicine will have a price tag that reflects its development costs.

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

A. Pharmacogenetics testing of participants in trials should be a regulatory requirement for the development of those specific medicines, but only when genetic testing becomes part of routine western life and where there is a proven and relevant pharmacogenetic test for the drug that is under

assessment. Until then, individuals should be able to refuse to be tested, but still participate in trials, and still benefit from the research.

Obviously the use of pharmacogenetic testing will add an enormous dimension to the consent form for any participant in such a trial, but that is dealt with later on in these questions.

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

A. The pharmaceutical company that is responsible for developing the medication should be responsible for providing the pharmacogenetic test. In other words, they would not accept anybody on their trial who had not had the pharmacogenetic test, but there should be mandatory pre-counselling about the implications of testing in the context of up-to-date information about the regulatory authorities' access to data - similar to the requirements before HIV testing. For individual therapy the medical practitioners should be responsible for providing a pharmacogenetic test, which should be part of their decision on treatment about using the prescribed medicine concerned, in the same way that renal or liver function tests are currently undertaken. Test results often require complex interpretation, but help the decision on choice of drug treatment. Pharmacogenetic testing should not be available over the counter or over the internet and should only be available through a medical practitioner. Need concurrent legislation specific to the protection of this data, and who is licensed to hold data - similar debates about tissue banks. Implications also for blood relatives of the patient need to be considered.

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

A. The legal liability is very complex. Future product licences (PL) are likely to advise caution or contraindication in some patients based on pharmacogenetic test results. Use outside the PL should continue to be the responsibility of the prescriber and they may be called to justify their decision. Initially the legal liability should lie with the pharmaceutical company to include only patients who had pharmacogenetic testing as participants of their trial when looking at the efficacy of a certain medicine. So they would be responsible legally for including those patients in their trial or excluding those who do not have pharmacogenetic testing. With regard to the prescription of these medicines, then the medical practitioner is undoubtedly going to be legally liable. However, the legal liability, should only go as far as discussing and strongly advising a patient to have pharmacogenetic testing to advise the degree of efficacy or potential side effects, providing all the side effects of the particular medicine have been identified to the patient and they have agreed

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to proceed on that understanding and on the understanding that fewer predictions can be made if they have refused pharmacogenetic testing If a test is available and not offered or used, the patient should be able to claim for negligence against the healthcare provider, unless the provider can demonstrate that full disclosure of risks and implications was given in a manner the patient understood (principles of informed consent).

If the patient decides not to go ahead with pharmacogenetic testing, then this all needs to be very carefully documented. There will obviously be some form of consent form to say they have consented or not consented to pharmacogenetic testing. If a patient refuses pharmacogenetic testing, he/she should not be denied the opportunity of a drug which might help him/her, even if it does not help him/her as much as those in whom pharmacogenetic testing has shown them to be in the right category. If an adverse reaction does occur, how likely is it that it can be proved to legal standards that the reaction was/was not caused by the genetic variation? This information will need to be robust. Pharmaceutical companies should supply robust information about the reliability of their tests, their availability and costs, ownership and uses of the test material and results, and clear information about probabilities to enable informed decision-making. The reliability of predicting the probability of adverse reactions will compound any lack of reliability of the test. However, details about the test will be commercially sensitive. There may be a potential for abuse if the test is owned and marketed by the company that owns and markets the drug, but the two seem inextricably linked; one company is currently offering 'free testing', available to help determine suitability for a drug that they market. The pricing of tests should be subject to scrutiny.

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

A. Poorer countries may well not be able to afford these new drugs at all. There is though no reason why medicines which have been developed for administration in conjunction with a pharmacogenetic test should not be distributed to countries in which testing facilities are not available, depending on the risks of not doing the test and the proportion of the population likely to benefit from the treatment or who may suffer ADRs. This would deny patients in those countries a treatment that would have potential benefit. However, obviously the awareness of potential side effects must be made clear both to the practitioner and the patient, and consent forms may have to be introduced for these medications and, of course, the facilities for pharmacogenetic testing should be instigated at the same time or as soon as possible. However, we not understand why testing would not be available. If this is due to economic factors in the country, again the principle of informed consent should apply. For the healthcare regulators of the country, the drug should only be marketed with a clear warning that a predictable reaction may occur, but that the test will not be available in this country. The care providers, and

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the patient should also receive this information, and be informed where the test is available and whether they can access it at their own expense.

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

A. This need not differ from current systems, where information is provided by the pharmaceutical industry, NICE, Drug & Therapeutics Bulletin, MTRAC, etc. A licensing system that took cost-effectiveness into account during the licensing process would have advantages for healthcare providers.
However, current systems such as NICE are not always trusted by the public because of suspicion of influence from lobby groups and companies. With regard to the private healthcare system, as long as such a system exists and is appropriately regulated, clinicians' professional codes and standards should suffice to ensure the patient makes an informed 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 basis of the provision of national healthcare in the UK? Will the benefits of pharmacogenetics only be affordable or available to the wealthy?

A. The application of pharmacogenetics may well exacerbate inequalities in the provision of healthcare due to the cost, which will probably be borne eventually by the PCTs through prescription charges and the cost of drugs. Therefore, to offset this perhaps the Government needs to look to some form of support for these drugs and the necessary pharmacogenetic testing so that this sort of inequality can be avoided. On the other hand it is likely to help optimise patient care, though it will probably take some time for pharmacogenetic testing to be integrated within standard practice in hospital and primary care and only if the benefits are significant. The NHS will be keen to employ pharmacogenetics to avoid wastage of limited resources. Costs may increase if development work takes place within restricted genetic pools. Need to ensure that cultural and religious views are considered. Are there any groups who would oppose genetic testing or storage of genetic data? What principle of solidarity?

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?

A. The only genetic information that should be stored is that relating to the potential adverse effects the patient might develop to the drug and the potential for a positive response, especially if treatment options are limited; however, this is probably not that different from current testing on disease

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staging, e.g. in cancer. All information stored should be subject to compliance with the Data Protection Act. So information about susceptibility of an individual to disease, which might be identified at the same time, should be destroyed.

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

A. If the genetic information received is related only to the patient's response to a drug or side effects, then all this information should be shared with the patient at the level the donor agrees to in an informed consent process. However, interpretation by the patient and probably most general practitioners at this stage may be limited. In that case they should be anonymous, since the relationship between pharmacogenetic test result and likely outcome will be uncertain until the research has been concluded.

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

A. Pharmaceutical companies should not normally be able to use samples for any purpose other than gaining information in relation to the drug that they are developing. Consent should be similar to current investigations e.g. blood tests. Clarity of information is essential at the point of sampling about the degree of linkage, ownership of the sample and data, how long and where the data will be stored, how and when the sample will be destroyed, and the purposes it will be used for. Donors may well be willing for anonymous samples to be used for further unspecified purposes. Donors should be aware at the point of sampling whether or not there will be access to information from linked samples.

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

A. See answer to question 10. If testing for a different variation becomes available at a later date, then the information should be made available for the donor to use for other purposes.

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

A. The same systems as for routine laboratory investigations and similar to the recent proposals for regulating tissue banks. Companies who collect genetic

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information should be required to register with a regulatory body. This would involve adherence to a code of conduct, and a fee to recoup the cost of random monitoring of practice by the regulators.

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?

A. Pharmacogenetic tests are generally different from tests that predict susceptibility to disease. They should be viewed more as a tool, like cholesterol levels, to optimise patient management. However, similar issues do apply for genetic and pharmacogenetic tests, as non-genetic tests can have equally wide-ranging implications and a lack of confirmation that a finding is genetic reduces the implications for family members.

Q15 What might be the psychological implications for individuals of pharmacogenetic tests? Are such tests likely to reveal information that is of relevance outside the context of testing for response to medicines?

A. This applies to absolutely anything and so is probably irrelevant. That is only, of course, if the information gained relates to the medication and not to other things, such as susceptibility to disease, which should probably not be included. Tests may have a psychological impact on patients if results indicate that available treatments are unlikely to be effective; however, this is not a reason for not doing them, if they help optimise treatment in the majority of patients. There may be a danger of a fatalistic response, as many individuals may not understand the concepts involved and the limited implications of probabilities. It will be imperative to establish and communicate other likely factors influencing reactions to medicines. Genetic information may not be the most important factor in some cases. Other information may be revealed, and this increases the importance of a fully informed consent process and a code of conduct for those handling this information.

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

A. We already know that genetics has a role in future disease and life expectancy; pharmacogenetics is just another piece of information, but with complex interpretation. As described in the text, there will be implications for the use of medicines. There may also be implications for health insurance similar to that for the individual tested. The extent of the implications will be determined by the agencies who may or may not have access to the data, e.g. police, government agencies.

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

A. This relates to cost and, yes, that could be a problem. There will be natural variations in the levels of understanding of the issues involved. There will also be natural variations in beliefs about risk-taking and cost. These suggest that consensus will sometimes be impossible to reach between individuals, prescribers and regulatory agencies. Will licensing authorities take a view about restricting the use of a new drug if there is no safety information available for their 'genetic group'? Controversies, if they occur, are, however, no different from current rationing of NHS resources, e.g. β-interferon in MS. The doctor will continue to be responsible for prescribing in the light of relevant patient factors, e.g. age, allergies, renal function. National and local guidance (e.g. from PCTs) on prescribing will continue to affect patient management.

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

A. See answer to question 5. Yes, they should be able to refuse and, yes, they should still be able to have the prescription if all the potential side effects are properly discussed with them, although this may restrict treatment options, since the doctor may not be prepared to prescribe treatment where use is contraindicated in patients with a given test result. It is essential that the patient has confidence in the testing process and trust in the company which will be processing and storing their data. If this is not achieved, then the patient should not be penalised in any way for refusing a test, especially as testing is likely only to indicate probabilities of reactions, in most cases. However, if adequate regulation is established, and reliable tests provide a very high indication of adverse reaction, and public money is involved, then there are some cases where withholding a prescription might be acceptable; for example if a reliable test would indicate a common genetic variation which means expensive drug administration is futile, or if a predictable adverse reaction will be severe enough to require extensive treatment at public expense.

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?

A. No we do not, although they will certainly want it and may well in the end get it. In that case access to information should be the subject of legislation. Insurers should not have access to information held by organisations. In the event that disclosure is permitted by legislation, individuals should be left to disclose known risks to life insurance companies; insurers should not be allowed to make their own determination of the level of risk associated with having a test performed. The question of whether (and which) healthcare providers have access to the information should also be the subject of legislation. Although the background information given in the consultation document suggests it is likely that this information will be shared, there is no indication at present that commercial companies are making this information available.

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?

A. Pharmacogenetics will group patients differently according to the test performed. So it might increase the grouping of patients according to racial and ethnic groups for medical purposes, if different racial ethnic groups have different genetics, and we already know that racial background does affect disease. But we think it is unlikely to cause a major social problem and

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would hope that there would not be any other reason for separate grouping of these patients; the cost should not be borne by the patient directly. It is likely that there will be a temptation to concentrate on the development of medicines which could be marketed to affluent groups or countries. It should be recognised that this happens already, with medicines developed for affluent markets while the treatment of some conditions in developing countries is neglected.

The whole concept of pharmacogenetics is to target medicines to specific patient groups. It would be unfair to expect pharmacogenetics to be a vehicle for social reform.