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The Genetic Interest Group

PHARMACOGENETICS: ETHICAL ISSUES
Response to the Nuffield Council on Bioethics from the Genetic Interest Group
January 2003

Q1 We have no information concerning the likely economic impact of pharmacogenetics on the development of new medicines.

Q2 If pharmacogenetics results in the fragmentation of common disorders into genetically (and clinically) distinct subsets then there will be a need to develop appropriate methods of demonstrating quality, safety and efficacy in order to obtain a marketing authorisation in the EU. Traditional large-scale clinical trials will not be appropriate if the clinical indication is tied to specific diagnostic test results.

Unlike the situation in the USA, where orphan drug designation is dependent on the size of the whole population with a given condition, the EU's Orphan Medicinal Products Committee will look at subsets based on biological plausibility and clinical rationale. This provides a possible access route for manufacturers to the incentives available as a result of achieving orphan designation in the EU that may not be available in the USA. Whether or not it provides a sufficient incentive to secure the development of clinically desirable but economically unprofitable medicines will need to be monitored over time.

Once marketing authorisation has been granted, post-marketing hurdles (for example, appraisal by NICE) need to take account of clinical effectiveness by reference to appropriate criteria, including not only a cost/benefit analysis of providing such drugs to those likely to benefit, but also the cost/benefit ratio of avoiding some adverse reactions and of prescribing to those unlikely to benefit.

Q3 Given our level of understanding of pharmacogenetic interactions it is too early to make the introduction of pharmacogenetic testing a regulatory requirement. If scientific research develops to the point where this becomes feasible and sensible then it should be considered. However, it seems possible that many useful drugs may not be sufficiently closely linked to particular genetically determined population subsets. In such situations, attempting to restrict their use of tests will increase costs and reduce patient benefit. With present technology, the cost of tests and any necessary limits to their validity and reliability may act as a disincentive to their introduction.

Q4 If the medicine with which a pharmacogenetic test is associated is available over the counter, then the test should be also. Given differing levels of awareness of the developments in genetics amongst medical and paramedical practitioners, a case can also be made for de-coupling access to pharmacogenetic tests and prescription medicine, making the former widely available for those who wish to purchase these. In practice it seems likely that the greatest demand for testing will be physician-led, and as such the NHS should be properly resourced to ensure quick and accurate delivery of results in ways that complement the clinical judgement of the prescribing physician. Pharmacogenetic tests should not be seen as a replacement for clinical judgement – it is an aid to be incorporated into clinical decision making.

Controlling access to tests available elsewhere in the world via the internet is virtually impossible. If tests are properly available for patients via the NHS, the number wishing to take this route is likely to be small, and the economic, social and human rights costs of trying to prevent them from doing so are likely to be disproportionately high.

Q5 From a non-specialists perspective we would assume that legal liability would be determined by reference to the nature of the information provided as to restrictions on the use of a particular drug imposed as a result of pharmacogenetic testing. Given that test results in most cases are likely to indicate that a patient is more or less likely to benefit from a drug, rather than give an absolute yes/no, then the issue will be tied up with, for example, the availability of alternatives, the explanation given to the patient and the extent to which consent was informed as a result, whether or not the test was offered, the results available in time to influence treatment and the severity of any adverse consequences resulting from a failure to use pharmacogenetic information. We would hope that the fear of litigation would not push manufacturers and/or healthcare providers into adopting a too-restrictive approach to accessing new drugs for patients potentially able to benefit.

Q6 Medicines normally used in conjunction with a pharmacogenetic test should be available in countries where testing facilities are not available providing information on restriction on use, and the risks of proceeding in the absence of test results are readily available to patients and providers. It should not be possible to uncouple the information from the medicine. In those cases where pharmacogenetic test results indicate a clear-cut subset very likely to experience a severe adverse reaction then in this case the product should not normally be sold independently of the test (e.g. thalidomide and pregnancy).

Q7 Efficacy and safety are established through the mechanisms for securing a marketing authorisation via the national system operated by the Medicines Control Agency, or through the EU's centralised procedure operated by the European Agency for the Evaluation of Medicines (EMEA). Cost is not a consideration in establishing these criteria, and it should not become one.

With regard to patient access in the NHS, cost is clearly a relevant factor to be considered. In determining cost/benefit issues, the cost of treatment taken in the round (including the wider family impact and the costs of not treating) need to be factored into the equation. Current calculations seem to be too focused on observable costs that are easily quantifiable, with little account taken of benefits accrued elsewhere resulting from expenditure on medicines.

For the private sector healthcare providers the issue is one of market forces, However, patients must be protected from undue pressure arising from the provision of partial or inaccurate information.

Q8 As long as the NHS remains publicly funded out of taxation and is the primary means by which UK citizens access healthcare, then pharmacogenetics will be unlikely to undermine the solidarity principle. If drug prices rise substantially and cost/benefit calculations lead the NHS to decline to purchase, then access will be restricted to those with the ability to pay. However, this inequality exists at present, and the emergence of pharmacogenetic-linked drug access seems unlikely to alter the situation significantly in the foreseeable future.

However, we should beware of the emergence of an untreatable "sub-class" of patients who cannot tolerate the usual drugs for their condition and who need expensive alternatives which drug companies may not wish to develop or which the NHS may

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decline to purchase because the cost/case would be high, and the necessary incentives would be lacking.

Q9 No

Q10 All personal medical information collected for research purposes should be protected from disclosure to unauthorised persons. Where data can permanently be anonymised without prejudice to the efficacy of the research being carried out this should be done as early as possible in the process. Where linkage back to the individual is necessary then care should be taken to ensure that appropriate consent for storage and use has been obtained. Whether the information is genetic in origin is irrelevant to the need to follow best practice in protecting the confidentiality of research subjects.

Q11 Whether research is to be undertaken by a public or a private sector organisation, we doubt that open-ended consent would be deemed to be valid by research ethics committees and regulators such as the Information Commissioner. Whilst some subjects might wish only to give consent to very specific uses, others might be happier – indeed they might actively prefer, to give a broader-based consent to classes of use without having to assimilate complex details and scientific rationale. Any system should be capable of accommodating the needs of both groups as well as those in between – with opportunities provided for those who feel they want detailed information about research proposed that are easy to access and use – such that research subjects are content that the consent they give has been sufficiently informed for them to be comfortable with the process and outcome. Again we would not distinguish between pharmacogenetic and other types of clinical information.

Q12 If findings emerge from pharmacogenetic research that are significant for individuals then such individuals should be given the opportunity to decide if they wish to receive them in the context of a clinical consultation provider as part of mainstream healthcare delivery. Ideally this should be once the reliability and validity of the information revealed has been established and they could be re-tested in a clinical setting, unless the urgency of the need to intervene would preclude this after weighing the balance of harm to be avoided. Research volunteers should be provided with general feedback on the progress of the project, emerging findings etc. by means of newsletters and other communication to keep them included and able to contribute further if they wish. It is possible that some polymorphisms may indicate predisposition to an illness (i.e. manic depressive psychosis or channelopathy) as well as drug sensitivity. In such instances counselling and confidentiality issues are likely to be complex.

Q13 Information gathered by doctors during the course of clinical practice is obtained in response to an identified medical need. It is not usually obtained as a result of "fishing expeditions". As with other forms of medical information, pharmacogenetics information will be generated in clinical practice for a particular purpose (e.g. to determine the most appropriate medication for use in a given individual with a specific condition). Outside the research context the gathering of information is clinically, not curiosity, driven. We see no reason why this should change in future. As with other types of medical data, its use is covered by legal constraints and by professional codes of practice. These should be enforced to prevent abuse, with sanctions in place for deterrence and punishment in the event of breach. Proper use of existing procedures should be sufficient to protect patient interests. To put additional procedures in place around pharmacogenetic information is to give such data an undue emphasis when other items on a patient's medical record may in fact be much more sensitive.

Q14 Pharmacogenetic test results will arise after diagnosis and be of use mainly for the selection of treatment and disease management purposes. As such they are more

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similar to other clinical/diagnostic tests than they are to tests for highly penetrant single gene disorders. If specific tests developed to aid prescribing are found to have other significant associations then there will be a need to explain the possible findings and what these might indicate at the time of obtaining consent for testing the sample. This would have to be done on a case by case basis, rather than putting all pharmacogenetic information into a separate category and treating it differently from other clinical information on a patient's records.

Q15 It seems unlikely that pharmacogenetic information per se will have significant psychological implications over and above the possible reaction that a patient might have to learning his/her diagnosis. Clearly it will be potentially stressful to find out that you are in the group for whom a given treatment is not recommended on the basis of your genotype, but arguably this is less stressful than experiencing an adverse drug reaction. Physicians will have to use their skill and judgement in explaining the purpose and scope of the pharmacogenetic tests prior to carrying them out in order to ensure informed consent and compliance.

Q16 Given that all genes are inherited in a mendelian manner, there is potential significance for family members arising from pharmacogenetic test results relating to a given individual with a disease. However in practice the importance of this is likely to be low, given the fact that drug metabolism is unlikely to be controlled by a single gene, and that family records are not generally linked in primary care (or in secondary/tertiary settings which do not have an explicitly genetic context, e.g. in regional genetics centres). Thus unless the proband communicates his/her pharmacogenetic results to other family members directly, a relative presenting with the same drug susceptibility is likely to need to be worked up from scratch, with the relevant pharmacogenetic data being established ab initio.

Q17 Greater access to accurate information about treatment options have created scope for controversy. Couple this with the change in doctor/patient relationships, and the move away from a hierarchical situation in which "doctor knows best", and the rise in patient advocacy and a greater (earlier) recourse to litigation and the potential for disagreements in any given case may be huge.

Pharmacogenetics will be an element in this – particularly as pharmacogenetic information is unlikely to be black or white, but rather more indeterminate in character. Thus a patient whose results indicate they are perhaps unlikely to benefit from a particular drug may actively demand it if the alternatives are even worse. A less than optimal result from given intervention may be better in the patient's eyes than no intervention at all. The arguments about the provision of beta-interferon for patients with MS provide a pointer to possible future controversies over who should get what and when. Fear of controversy, however, should not be used as a reason for delaying the introduction of pharmacogenetic tests when these have a clinical benefit.

Patients should always have the right to refuse an intervention so long as they are competent to do so (or have previously indicated their wishes when no longer competent). Refusal to undergo pharmacogenetic testing should be no barrier to treatment, but the possible consequences of a refusal should be explained in order to ensure that the withholding of consent if properly informed. This seems likely to arise more often in cases where "collateral information" (see Q12) is a possible outcome, than when the information is solely related to drug susceptibility.

Q19 Identifiable pharmacogenetic information is part of a patient's medical record and is confidential. As with all medical information it can only be disclosed with consent. This will remain the case.

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Anonymised information may prove useful for epidemiological research, for assessing the effectiveness of different types of intervention or perhaps for other purposes relevant to insurance. The principle of "uberimmae fides" that underpins insurance contracts might in future (after the ending of the current moratorium) suggest that pharmacogenetic information, where known, should be disclosed. Were this to be the case it should be up to the insurance company to determine what information should be disclosed, what its relevance/significance to the insurance under consideration is, and to demonstrate competence to interpret it accurately and appropriately. Disclosure may be beneficial to the applicant, in that it may reduce their apparent risk of a future adverse event and entitle them to a lower premium. Given current indications about the penetrance of genes associated with drug metabolism it seems unlikely that the information revealed by pharmacogenetic testing will be of sufficient significance to alter the risk assessment made by underwriters, bearing in mind that it will only become relevant (and in most cases available) after a diagnosis has been made and the policy activated. It is the risk of disease that is the principle determinant of insurability, at least at present. There is no indication that change is imminent. Should this prove to be the case in future then would be the time for reconsideration in the light of proven new knowledge rather than supposition and hypothesis.

Q20 Whilst it is possible that pharmacogenetic information will apply differently to people from different ethnic groups, it seems unlikely that this will operate a uniform way across the board. Within groups it is highly probable that there will be significant variation in response between individuals making the drawing of general conclusions based on ethnicity of dubious value clinically. On the balance of probability, developments in pharmacogenetics seem unlikely to lead to valid groupings of patients along ethnic lines to any significant extent. If new knowledge indicates this is not the case, then such groupings may be clinically valid, as they would be a reflection of some underlying biology rather than a socially-derived phenomenon. The challenge in this case would be to manage the introduction of this new knowledge into clinical practice in a way that did not result in unfair discrimination against those thus identified.

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