The response reproduced below was submitted further to a consultation held by the Nuffield Council on Bioethics on its Report: *Pharmacogenetics- ethical issues*, during November 2002 – February 2003. The views expressed are solely those of the respondent(s) and not those of the Council.

Integrated Medicines Consultin, UK

The following are general comments on the both the content and the issues raised by the consultation paper to help frame the specific responses to the 20 questions.

Firstly, I don't believe that acceptance of pharmacogenetics is a prerequisite for the adoption of personalised medicines, i.e., blood based diagnostic/ prognostic tests using disease or PK/PD surrogates could provide what Roses described as a Medicine Response Profile. In this sense, I think that some aspects of the consultation paper overplay the link between pharmacogenetics and the development of personalised medicines. On the contrary, although it may be beyond its scope, the consultation paper does not emphasise enough the impact of the demands for evidence-based medicines on the advent of personalised medicines.

Secondly, genetic tests are static readouts of propensity to AE or disease. Non-genetic diagnostic tests, e.g., RNA or protein profiling, could give a "real-time" objective measurement of disease status that benefits the patient by ensuring the *right* dose at the *right* time, in addition to the *right* medicine to the *right* patient. Similarly non-static tests could be used for monitoring response to determine whether a patient is benefiting and/or is developing the risk of an AE. This limitation in pharmacogenetic testing may be worth raising since laypersons may be unaware.

Finally, as I read the background information in the consultation paper, I found the response matrix in table 1 to be a helpful way of representing the issues faced by any objective testing. To its credit, the text of the paper does articulate fully the issues in the matrix.

Predicted Response	**Predicted AE**	**Treatment Decision♦**
Individual Does **Respond**	No AE	Treated
	AE	Treated*
Individual Does **not** respond	No AE	Treated*
	AE	Not treated⌂

Table 1: A benefits: risk matrix

♦ Other factors to be considered, e.g., disease severity & duration, AE severity & duration, patient QoL on & off medicine, re-imbursement.

* Alternative treatment desirable.

⌂ Alternative treatment essential.

Response to questions

Q1 What do you think will be the likely economic impact of pharmacogenetics on the development of new medicines?
I agree with a number of reports that larger Phase II studies, to segregate the responder and/or no AE genotype from the non-responer and/or AE genotype, will lead to smaller PIII regulatory studies. Even with the additional costs of post marketing surveillance to capture any rare AE's, the time & cost benefits to pharmaceutical companies should be positive, e.g., a report from Price WaterHouse Coopers suggests a potential savings of $130M/ drug on $600 – 800M development costs. A 1999 analysis by IMS Health of Pravachol sales in the crowded cholesterol lowering market suggested that sales could be more than doubled from $1.4bn to $3.2bn through greater compliance & market penetration by judicious use of pharmacogenetics. A key message is that market segmentation does not necessarily equate to reduced revenues

Q2 Do you think that further regulatory measures will be needed to encourage the development of clinically desirable but economically unprofitable medicines?
Yes, but pharmacogenetic or diagnostic testing could more objectively define disease thus overcoming the arguments around orphan status, e.g., in Herceptin development

Q3 In your view, should pharmacogenetic testing of participants in trials be a regulatory requirement for the development of medicines in the future?
I believe that personalised medicine is inevitable and evidence-based medicine is a stepping stone to this. However, if pharmacogenetic testing is demanded by regulators as an additional driver in the development of personalised medicines, then pharmaceutical companies must have the support of all other interested parties, e.g., patients, patient rights representatives, payors, re-imbursement agencies (NICE), government, health economists.

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?
Clearly, the responsibility for provision, interpretation and support counseling for pharmacogenetic testing will depend on the implications of the test outcome. Manufacture of pharmacogenetic tests, as with diagnostics tests, will be the responsibility of the "diagnostic" arms of pharmaceutical companies. However, given that the biggest obstacles to the uptake of wide-spread pharmacogenetic testing are likely to be social, ethical & political, it's important that responsibility for the actual testing and interpretation of the test is devolved from those selling the medicines. Test interpretation *may* involve only minimal counselling support and so GP's/PCP's and/or pharmacies could be the desired outlets. However, it is clear that GP's could be time-burdened by the need to provide pharmacogenetic guidance, interpretation & counselling and so support from the overall health service is essential.

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

Liability based on the performance of a pharmacogenetic test will lie with the test manufacturer, which could be the pharmaceutical company. Liability for correct interpretation of a test, which has performed within it's specifications, must lie with the healthcare provider. However, given that the frequency of adverse events suffered by patients taking a medicine that has a robust pharmacogenetic test should diminish, then there should be a consequent decrease in litigation.

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?

Investment in the development of medicines is generally based on the projected sales in G7 countries and the same will be true of a medicine prescribed on the basis of a pharmacogenetic test. The use of a such a medicine without it's pharmacogenetic test, e.g., in a non-G7 country, should be viewed simply as "off-label use" and would carry the same devolved risks as the "off-label" use of current medicines.

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?

In both cases, the societal benefits in terms of patient flow, health economics, hours lost/gained at work, impact on primary, secondary & tertiary care services should be considered in any re-imbursement strategy. In most scenarios, the provision of cost-effective medicines is desirable and so the increased price of a bespoke pharmacogenetics-based medicine should be easily offset against the attendant societal benefits.

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?

The early detection and early treatment of milder prodromal forms of severe disease are likely to be more cost-effective than the alternative costs of hospitalization and or terminal care. Therefore I think that it is unlikely that cost effective management of healthcare in the setting of pharmacogenetics will adversely impact individuals of any socio-economic class.

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?

Yes – this is quite clear to me. However, as the consultation paper correctly makes clear, the differentiation of pharmacogenetic testing is blurred in cases where a response to a medicine co-incides with a propensity to develop disease, e.g., in the case of Herceptin where high levels of Her2 not only indicate a better outcome in response to treatment but also indicate a poorer disease prognosis.

Q10 What level of anonymity should be accorded to genetic information stored as part of research in pharmacogenetics?
I am favour of a pragmatic approach to this question, in that anyone enrolling in a research study is offered the possibility of individual genetic "feedback" from the study at their own discretion. However, the default position should be sample anonymisation or anonymous donation with the subject made fully aware of the implications of this default.

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?
If the samples are anonymous or anonymised, I can see the value in pharmaceutical companies being able to mine their genetic sample base to determine the prevalence of genetic markers that influence adverse events to any medicine in their portfolio. However, any genetic analyses carried out in this respect should be included in regulatory submissions as mandatory.

Q12 Do you think that researchers should provide individual feedback about genetic information obtained from participants in research in pharmacogenetics?
As in my response to Q10, I am in favour of individual feedback if the individual has been fully counselled on the implications of the feedback.

Q13 What, in your view, would be appropriate methods of regulating scope, storage and access with respect to pharmacogenetic information used in clinical practice?
I appreciate that in some circumstances the access to stored genetic material or information may be required as part of police investigations. In these instances, the police service should have its own databases. Anonymisation of samples collected in clinical research will limit the value of pharmaceutical company databases. In clinical practice, I believe that careful and considered debate is necessary but should be clearly distinct from the debate on pharmacogenetics.

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?
As discussed in my second general comment, "static" genetic testing does not allow for monitoring of disease activity and/or response to therapy in the way that a cholestrol blood test can. Therefore, genetic information is somewhat limited and as such does

have a different legal implication and perhaps ethical impact too. However, a pharmacogenetic test that predicts a failure to respond to one therapy may be tempered by the provision of an alternative therapy and/ or the modification of lifestyle.

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?

With the right level of counselling, the implication of pharmacogenetic testing can be minimal. It is important that the benefits & purposes of pharmacogenetic testing are clearly differentiated from the emotive issues around genetics as a whole, e.g., gene therapy, human cloning & GM crops.

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

These implications are accurately & clearly illustrated in the consultation paper.

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

As I noted in response to question 4, I believe that it's important that responsibility for the actual testing and interpretation of the test is devolved from those manufacturing & selling the medicines. However, I can indeed see issues arising from the inappropriate interpretation of a test.

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

If, as is the case with Herceptin, regulators or payors limit the provision of a medicine to those testing positive, then it will not be possible for a patient to receive a precription for a re-imburseable medicine. In this case, the healthcare provider is legally & ethically able to refuse the prescription to a patient who has refused testing. Patients already know that they do not respond to certain OTC therapies, .g., Ibuprofen. Risk of AE's should also be desired information for all, e.g., penicillin rash, anaesthetics, and so proper counselling should persuade most patients of the benefits of testing.

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?

No – the information provided by pharmacogenetic testing is likely to be of limited value to health insurers, with the caveats alluded to in my response to Q9. I do not support life insurers having either prospective or retrospective access to pharmacogenetic information of (potential) insurees, not least because the information is unlikely to be of relevance.

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?

It is already known that certain ethnic groups are more disposed to disease such as diabetes, fatty liver, chronic heart disease, and the case of cyp2D6 described in the position paper indicates that race & disease have existing clear associations with AEs. This being the case, pharmacogenetic testing is merely a more objective view of these recognized racial or ethnic differences in responses to medicines. In fact, most pharmaceutical companies have existing efforts in the area of ethnopharmacology.