

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.

GlaxoSmithKline

GlaxoSmithKline is committed to pharmacogenetic research in order to understand the science and its application to medicine. This subset of genetic research is designed to identify DNA markers that can help predict patients' responses to medicines and thereby enhance the effectiveness and safety of medicines for individual patients. It is important to note that:

- Pharmacogenetics tests are intended to predict response to medicines
 - not susceptibility to disease
- Pharmacogenetic tests will not affect the intrinsic safety and efficacy characteristics of a medicine. It will enable better prediction of likely outcomes and thus influence the benefit-to-risk ratio of a medicine for patients.
- The applications of pharmacogenetics to medicine will evolve over time rather than there being a rapid revolution in medical practice.

As with any new technology it is important to discuss and debate the potential benefits and risks in order to create a research, regulatory and healthcare framework in which the patient benefits can be maximised and risks reduced. GSK therefore welcomes the Nuffield Council on Bioethics consultation. To foster discussion and debate GSK co-sponsored the Consortium on Pharmacogenetics that considered many of the same issues highlighted in the Nuffield Council on Bioethics' consultation document. The published report from those deliberations is therefore relevant to your discussions and is enclosed.

General Comments

Section 5 of the consultation document outlines several potential risks for pharmacogenetics based on a number of “what if” scenarios. GSK recommends that the Working Party reviews these scenarios based on an assessment of the potential *benefits* of pharmacogenetics balanced against the likelihood and potential impact of the risks described. This assessment of the risks and benefits can be difficult as the science and its applications are evolving and there are only a few real examples of pharmacogenetics in clinical practice. Nonetheless it is important that the working party maintain its objectivity so that potential benefits or risks are not overemphasised in the absence of substantive evidence. Furthermore GSK urges the Working Party to consider the extent to which the benefits of pharmacogenetics can be maximised and any risks minimised within the current legal, regulatory and health policy framework rather than beginning with the assumption that a new framework is needed. In this regard it would be useful for the Working Party to consider those risks which are specifically unique to the use and application of pharmacogenetic technology and are outside current medicine and test regulations. GSK suggests that the Working Party does not limit its deliberations to the potential risks of pharmacogenetics but also considers the possible constraints to realising the benefits of this technology. For example:

Regulatory engagement

For the benefits of pharmacogenetics to be realised it is important that the pharmaceutical industry and drug/device regulatory authorities work together to move the science into clinical practice and develop regulatory guidance, as appropriate. Dialogue between the pharmaceutical industry and the European Agency for the Evaluation of Medicinal Products (EMA) has begun. GSK, a member of the Pharmacogenetics and Pharmacogenomics Group established by the European Federation of Pharmaceutical Industries and Associations (EFPIA) to interface with EMA, is keen to continue this dialogue.

Healthcare professional and provider education

Over the next 10 years there is likely to be increased use of pharmacogenetic information prior to the prescription of medicines. Ongoing physician and healthcare provider education is therefore required together with an appropriate NHS infrastructure for the full value of this technology to be realised in the form of (1) improved therapeutic outcomes for patients and (2) the provision of cost-effective healthcare in the UK.

Public perceptions

It is important that there is increased public awareness, education and understanding of genetics and genetics-related technologies. For the benefits of pharmacogenetics to be realised it will be important that pharmacogenetics is not

confused with genetic testing for disease (or indeed other technologies such as GM foods that may be bundled under the term “genetics” in public perception) and that the associated risks and benefits are clearly distinguished.

Responses to Consultation Questions

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

Pharmacogenetic technology has the potential to enhance the effectiveness and safety of medicines for individual patients. **Enhanced treatment outcomes for patients and meeting medical needs are the primary drivers for GSK in researching and applying pharmacogenetic technology.**

In response to the question posed, where a medicine is developed using pharmacogenetic analyses and perhaps with a pharmacogenetic test, in the long term costs may be lower due to faster and more streamlined development. In the short term, however, costs may be higher than with conventional drug development. Any increase will likely be offset by:

- Improving the efficacy and productivity of research and development by helping to reduce compound attrition and, in particular, late stage attrition.
- The gains provided by developing more medicines that are better targeted to patients

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

This question relates to the statement on page 6 of the consultation document:

“...the pharmaceutical industry may find it unprofitable to make the investment required to develop a range of new medicines for specific sub-groups of a population that would previously have been treated with one medicine”

Reducing the target population does not necessarily mean that there will be lower return on R&D investment. In many circumstances the ability to more readily identify those patients likely to respond positively may enable safe and effective medicines to be developed and used in more patients. This benefits patients, healthcare systems and pharmaceutical companies.

Therefore before any regulatory changes (e.g., orphan drug provisions) are contemplated due to pharmacogenetics, it would be necessary to determine if and how pharmacogenetics restricts research agendas both within large pharmaceutical companies and in smaller biotechnology enterprises (what is financially attractive may vary with the scale of the company). The practice of larger companies out-licensing to smaller companies, niche compounds with lower market potentials should be a component of this evaluation.

Q3 In your view, should pharmacogenetic testing of participants in trials be a regulatory requirement for the development of new medicines? Although pharmacogenetic technology is developing rapidly, the interpretation and application of pharmacogenetic information to drug development and the provision of healthcare is still in its infancy. Therefore at this stage it is not appropriate for pharmacogenetic research to be a regulatory requirement. The time is right, however, for open dialogue amongst regulators, drug sponsors, health care providers and the research community on how to best integrate pharmacogenetics into drug development and the associated effects on the regulatory requirements for registering pharmacogenetics-based drugs and medicine response tests.

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?

GSK is conducting pharmacogenetic research to identify DNA markers that can help predict patients' responses to medicines. This research may lead to the development of pharmacogenetic tests (or medicine response tests) over the next 2-5 years to enable physicians and other healthcare providers to more accurately prescribe medicines to patients. These medicine response tests will be

linked to prescription only medicines and therefore we envisage these medicines and tests being reviewed by regulatory authorities and administered by physicians or other healthcare professionals (or by their order) rather than being available direct to the public. GSK does not anticipate that the payment and reimbursement of these tests will be appreciably different to other tests used in the medical management of patients. To ensure the accuracy and quality of the test result we support the DNA analysis being conducted by accredited laboratories. These measures should foster the appropriate use of the test, including proper:

- Consent procedures
- Sample handling and database protection procedures
- Interpretation and prescription of the most appropriate medicine
- Provision of pre and post test information

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

Pharmacogenetics will be one of a number of approaches to managing the risk:benefit of medicines. By helping physicians and other healthcare professionals to identify patients who are likely to experience serious adverse events, it is possible that the number of incidences in which legal action is taken against prescribers and pharmaceutical companies in relation to adverse drug reactions will be reduced.

It is difficult to speculate on the legal liability in futuristic scenarios as numerous variables often affect the determination of whether the care provided was appropriate and reasonable, and similarly whether the benefits and risks of the medicine and test were appropriately disclosed. With respect to the medicine and the test, product labelling will continue to be a primary mechanism for sponsors and regulatory authorities to communicate information to healthcare providers.

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?

Testing facilities are available in the majority of countries. In addition technologies and capabilities for testing are continually advancing. Furthermore it is important to note that pharmacogenetics will be one of a number of approaches to managing the risk:benefit of a particular medicine . Accordingly, the determination of whether a medicine is appropriate for a particular country may not turn exclusively on the issue of the availability of testing facilities.

For medicines that are developed specifically for use in the developing world (e.g. Lapdap for malaria) it may not be appropriate for them to be developed in conjunction with a pharmacogenetic test if these facilities are not available.

For medicines that are developed for administration in conjunction with a pharmacogenetic test the availability of the medicine in countries without such testing capabilities may largely depend on the benefit:risk profile of the medicine without the test in the country in question. Regulatory authorities would make this assessment prior to national approval.

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 a publicly funded healthcare system, payers focus on costs and efficient resource allocation. Payers (and review bodies such as NICE) use efficacy rates from clinical trials and other information (e.g. meta-analysis, sub group analysis, database studies and models) to assess the cost-effectiveness of a medicine in clinical practice. Thus predictions of effectiveness are already used in deciding whether or not to fund a particular treatment or in deciding which patients should receive a particular medicine. Pharmacogenetics may enable a greater degree of accuracy in targeting medicines to those patients who are likely to respond and therefore where cost effectiveness is greatest. Furthermore the use of a pharmacogenetic test may reduce the incidence of patients making multiple visits to their physicians in order to try several medications before one is identified that is efficacious.

As noted in the consultation document the likelihood that a medicine will be effective (30 or 50% chance) may be a key consideration. For example it could be considered that a particular medicine is cost effective only when given to patients with a greater than 50% chance of responding positively. **However such decisions should be reached on a case-by-case basis taking into account**

factors such as the degree of medical need, patient and physician views, and the values of society.

In both publicly funded and private healthcare systems pharmacogenetics will provide important information to be factored into the decision making process.

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?

Currently a medicine may not be prescribed for a patient in the National Health Service (NHS) if it is thought to provide little value for money. If considered appropriate by a physician that medicine may be prescribed privately if the patient is prepared to pay or has appropriate health insurance. There is therefore already a basis for inequality in the provision of healthcare in the UK.

Pharmacogenetics can offer better decision making regarding the allocation of resources for medicines based on clinically relevant data. Provided pharmacogenetics tests are available via the NHS, like other tests used in the medical management of patients, they will not exacerbate inequalities in the provision of healthcare. Lack of access to pharmacogenetic tests through the NHS, on the other hand, could create disparities in the quality of medical care.

In fact pharmacogenetics may reduce inequalities in the provision of effective healthcare in the NHS. Currently because it is generally not possible to predict patients' responses to medicines some patients will be effectively treated while others will not. Pharmacogenetics offers the possibility of effectively treating more patients and reducing these inequalities.

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

GSK believes that making categorical distinctions for genetic (e.g., pharmacogenetic versus disease susceptibility) or other health information is ill advised. The appropriate measures for storing information turn on a host of factors including the specifics of the information, whether it is linked to the source and who has access to the information. As a general principle, pharmacogenetic information is appropriately treated and protected in the same way as any other confidential medical information. It is imperative that people who participate in pharmacogenetic analyses are informed of how their information will be stored. Specific aspects relating to level of anonymity and consent are considered below.

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

There are different types of genetic databases according to the degree to which samples/data can be traced to an individual subject. Although this is well recognised, the use of different terminology by policy guidance groups and researchers can cause confusion and provide difficulties for potential participants, investigators, ethics review

boards and regulatory authorities. For example, the term “anonymous” can have different meanings in different publications and genetic research protocols.

A common language describing processes by which samples will be collected and handled is important for people involved in genetic analyses. With a common understanding and usage of terms, it should be possible to more readily discuss and evaluate these processes and understand their application in specific clinical genetic research programmes. To address this issue, as stated in the consultation document, the European Agency for the Evaluation of Medicinal Products (EMA) has recently presented a system for the classification of samples used in pharmacogenetics. GSK fully supports this classification.

The choice of which category is most appropriate for a particular study depends on the nature of the research, the intended use of the data, the regulatory and legal environment (which can vary from country to country) and the specific concerns of the investigator and study sponsor.

For pharmacogenetic research it is often appropriate that the samples/data are coded. That is, they are treated in the same way as any other confidential medical information used in research. This enables individuals to withdraw from the study which would not be possible if the samples were anonymised. Furthermore, drug regulators such as the Food and Drug Administration commonly require an audit trail of information used in regulatory submissions. Therefore anonymised information would not likely be acceptable.

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 for only specific kinds of research?

Research involving human subjects is conducted under stringent conditions that protect subjects from misuse of data and any biological tissues provided for research. The process of informed consent is an important component of subject

protection in this regard. It is the means by which potential participants make a judgement about the contribution that their involvement can make, relative to the risk or benefit to them as individuals. The scope of the research undertaken should be consistent with the informed consent obtained. This is relevant to academic researchers just as much as it is to pharmaceutical companies. The consent process must, however, strike a reasonable balance between sufficiently describing research purposes while not being overly restrictive so that samples are unusable in light of new scientific knowledge and technology.

It is the policy of GSK to obtain appropriate signed informed consents before any genetic research is conducted consistent with legislative requirements and international agreements on research involving human subjects.

Informed consent is obtained via clinical research staff following ethics committee approval of the protocol and the informed consent form. For pharmacogenetic research sponsored by GSK, the informed consent form includes information relating to the:

- Purpose of the study and scope of the research (primary and anticipated secondary uses)
- Procedures (e.g. taking a blood sample, medical history)
- Risks
- Benefits
- Measures to protect subject's confidentiality
- Voluntary nature of participation and the withdrawal options

In addition, the informed consent form includes statements regarding financial benefit from participation in the study, that the research results could have commercial, and intellectual property value and that GSK intends to claim ownership of the research results.

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

It is stated in the consultation document (page 13):

“In the UK there is currently no requirement to provide individuals feedback about genetic information”

GSK believes this statement is not correct. Under the provisions of the Data Protection Act there is a specific requirement to provide individuals, on request, with any personal data that is held on them. The data returned has to be intelligible. Therefore for unverified research information a summary of the current status of the research may fulfil this requirement.

It is important to recognise that research information may not meet mandated clinical laboratory standards for quality and accuracy. For example, research assays and methodologies may not be validated. Therefore even where the research produces information that may be of value to the healthcare management of the participant it must be provided in this context via the physician and may at most indicate the need for confirmation by a clinically-accepted test.

Currently because of the early stage of GSK's pharmacogenetic research results of the research are typically not provided to anyone unless legally required. Once the significance of the results

have been confirmed the group results are published and shared widely in a timely and responsible manner.

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

Absent exceptional circumstances, the methods used should be the same as those used for regulating the scope, storage and access to any other confidential medical information used in clinical practice particularly with regard to consent, sample handling and database protection procedures.

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 test for cholesterol?

It is important that any ethical and legal issues associated with genetic testing are not assumed to be equally relevant to pharmacogenetics. GSK urges the Working Party not to indulge in “genetic exceptionalism”—to assume that any test or information pertaining to DNA and genes necessarily carries particularly grave risks or raises especially profound ethical concerns.

In this regard it is useful to consider whether the information realistically derived from a pharmacogenetic test differs appreciably in legal or ethical concerns from types of non-genetic testing. For example: Is the extent to which cholesterol

testing (high cholesterol can have a genetic component) impacts family members meaningfully different than the impact from information provided by pharmacogenetic testing?

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 for response to medicines?

The defining objective of pharmacogenetic testing is neither diagnosis nor prediction of disease, but rather to determine an individual's likely response to medicines or a particular medicine, there may therefore be little psychological impact of this information on the individual.

The ability to predict that there is no effective medicine for an individual patient could impact an individual's hope for a cure. The alternative, however, is trial and error prescribing of medicines, which entails the risk of drug side effects and the expense of medicines that ultimately provide no therapeutic benefit. In the face of an unfavourable test result, a determination of whether the medicine is nevertheless the best option for the patient would need to be made by the physician and patient. Conversely, the prediction of a favourable response may have a positive psychological impact and encourage patients to complete courses of treatment.

Although pharmacogenetics tests will not be researched, developed, validated and marketed for the diagnosis or prediction of disease, there is the possibility

that in some circumstances some information relating to disease may be associated with the test. There are two ways in which this might occur. In some cases, disease-associated genotypes might be among the factors affecting drug-response. Clearly, where this is related to the disease being treated, there are few ethical issues since presumably the patient is already aware of the disease diagnosis and an effective treatment is likely to be available. There may, however, be instances where the pharmacogenetic test provides some information that may be associated with “another” disease for which there is no effective intervention. Even if this were the case it may be more beneficial to effectively treat a patient and not expose them to serious adverse events compared with the risk of identifying other predictive information. In addition there may be a number of measures that could help preserve confidentiality with regard to the possibility of pharmacogenetic tests providing collateral or unsolicited health-related information. For example:

- Pharmacogenetic tests would likely be comprised of patterns of markers. If genetic markers within these patterns provided some collateral or unsolicited information, they could be replaced with other markers as appropriate.
- Based on consent, the result of the test may not reveal the genotype at each individual marker to the prescribing physician or patient. It would merely report the likelihood of effectiveness or of a side effect.

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

The likely impact of information for family members resulting from a pharmacogenetic test (to predict response to a medicine) will be significantly reduced compared with genetic tests for disease (to predict susceptibility to disease). There may positive beneficial effects for family members resulting from a pharmacogenetic test as they may be alerted to the fact that they should question their doctors before taking certain medicines or classes of medicines.

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

A pharmacogenetic test will provide information relating the medicine or treatment course that is likely to be most appropriate for an individual patient. It is the physician in consultation with the patient who will use that information together with other medical information such as the severity of disease to decide on an appropriate course of action. Controversies may arise for example, where a particular course of treatment is not made available due to likely cost effectiveness of the treatment. However this is no different to the current evaluation of the cost effectiveness of medicines and recommendations to use (or not to use) medicines or to specify those patients in whom the medicine should be given. Pharmacogenetics will provide important additional data upon which to make such evaluations.

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

Pharmacogenetics will provide important benefits to patients as they are more likely to be prescribed an effective and well tolerated medicine. Nonetheless patients may refuse a pharmacogenetic test. In such circumstances the treatment decision will have to be made in the absence of this information and will turn on a risk-benefit assessment for that particular patient. The physician in consultation with the patient will use the available information to decide on an appropriate course of action. Where the pharmacogenetic test helps to predict a patient's susceptibility to a rare adverse event refusing the test may not preclude the patient from receiving the medicine as the adverse event is rare.

If the pharmacogenetic test is predictive of efficacy, a patient's refusal to have the test will likely evoke clinical as well as economic considerations. Whether the patient should nevertheless receive the medicine may be related to guidelines issued by "payers" and is a matter of clinical judgement and patient input.

Where a pharmacogenetic test is mandated in the product labelling and has high predictive value physicians may be reluctant to prescribe the medicine, based on the prevailing standard of care, in the absence of the test. This is analogous to patients today who refuse a diagnostic test with the consequence of limited or uncertain treatment options for the physician.

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?

This question relates to the assessment of actuarial evidence and the regulation of insurance services. These are areas where GSK does not have specific business interests or experience and, therefore, is not qualified to comment in detail. However pharmacogenetic information may have limited use in these areas as:

- In many instances insurance will be taken out before treatment and therefore before this information is available.
- The significance of this information is likely to be limited to situations in which alternate treatment is more expensive or the prognosis differs substantially
- The risk of disease, rather than predicted response to medicines, is currently the main factor considered for insurance purposes

However, the perceived potential for misuse of pharmacogenetic information by insurance companies risks undermining the benefits of pharmacogenetic science as patients may be reluctant to consent to testing either in the clinic or in research.

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?

Medicines are not effective in all patients and some patients may experience serious side effects. Patient characteristics (including phenotypes) such as racial or ethnic group can provide information on the likely efficacy or tolerability of medicines. This can lead to dose adjustment or the use of an alternative medicine.

However race and ethnicity are at best very crude, approximate markers for distinct genotypes. Therefore excluding patients based on race and ethnicity may disadvantage some individuals who would have been good responders.

Pharmacogenetics may reduce the grouping of patients according to their race or ethnic group for medical purposes as patient access would be on the basis of genotype rather than phenotype.