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Cambridge Genetics Knowledge Park, UK

General Comments

Thank you for inviting our response to the Council's consultation paper. I wonder if we might make some general comments before responding to the specific questions.

First, the distinction between *pharmacogenomics* and *pharmacogenetics* is one that we believe to be of importance, the one being concerned with the impact of genetic variation in the drug development process and the other on the clinical response to pharmaceutical products. We were disturbed to note that this distinction was not made in your consultation document. We suggest that the distinction could have a moral relevance. The use of pharmacogenomics may limit drugs coming to the marketplace for certain categories of patients and place them at a disadvantage; pharmacogenetics is used to predict the response to existing drugs and do not deprive categories of patients from having drugs developed from which they might benefit.

Second, we urge that the Council attempts to distinguish issues (a) that are specific for pharmacogenetic tests from (b) those that are specific for genetic tests (including PGx) but not for medical tests in general and (c) those that relate to any type of medical test. Third, we suggest that tests that purport to have some predictive value in relation to adverse drug reactions (ADRs) may need to be treated differently to those that are concerned with efficacy or dosage. Fourth, we urge that the Council takes into account the possible impact of medico-legal drivers in this field. Fifth, we suggest that much of what might happen in the future may be consumer driven, whether or not this accords with the "rational" deliberations of policy makers or with concepts of good public health.

Our answers to the specific questions, kept deliberately brief, are as follows:

Q1.

The factors that will dictate this are complex. It is not clear whether pharmacogenomics will reduce drug development costs, and if so how that might impinge on the price of drugs, particularly if pharmacogenetic considerations lead to a reduction in the market share of individual drugs.

Q2.

The whole area of orphan drug regulation will certainly need to be reviewed. Whether further regulation is needed will depend on the findings. It is not entirely clear how the existing regulation is being applied in a pharmacogenetic setting. There are also differences between the EU's approach and that in the US. International harmonisation of regulatory frameworks would be helpful.

Q3.

It is unlikely that much will be gained by making this a mandatory requirement. The main requirement is that appropriate evidence should be produced to the regulators whenever a manufacturer asserts that responses are likely to be differentiated in accordance with genetic factors – particularly if the issue is one of adverse drug reactions (ADRs)

Q4.

The situation is no different to any other category of medical test. By and large, it should be ordered by a physician or an appropriately trained health professional. The assertion that PGx tests need to be regulated differently to other test modalities should be strongly resisted. Counselling is an issue, but only in tests for high penetrance single gene disorders. "Over the counter" testing is probably undesirable but is likely to increase. Marketing efforts by manufacturers will ensure a steady increase in the availability of such tests. It is unclear if consumers will take this up with enthusiasm. Many products of dubious efficacy are already in the health marketplace. It would be unwise to pass legislation to prevent such tests from coming on to the market just because the test technology is based on DNA. The essential requirement is for all tests to be accompanied by datasheets that accurately reflect the clinical validity of the test and written in an accessible language. Consumers would then have the means to make their own judgement. In certain instances, where patient safety is at risk, a more stringent form of regulation may be needed.

Q5.

This depends on exactly what is claimed by the manufacturer. In the case of tests that purport to predict serious ADRs, the exact nature of the evidence for this claim is a matter that both manufacturer and clinician must take very seriously. The prime responsibility will fall on the physician or health professional who orders the test, although I suspect that the manufacturer must also ensure that the claims made for the test are sound. The legal issues will be complex. Our belief is that there should be an onus on manufacturers to provide evidence of analytical and clinical sensitivity and clinical utility for any claims that they make. It should also be noted that all tests are imperfect. False positive or false negative results are inevitable. Physicians, health professionals and manufacturers have a duty to lay this out clearly in a way that may be understood by the patient.

Q6.

It depends on the issue. Where ADRs and safety is concerned the rules should be much tighter and specific regulation may be necessary to prevent a drug from being used without the test. It might also be argued that an adequate system of clinical governance would ensure that physicians do not prescribe the drug in

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those circumstances. A test that merely indicates which patients would most benefit from a drug does not necessarily mean that the drug should not be available in countries where the test is not available. The indications for use should be stated clearly. In these cases it should be for the physician to take a view on whether or not to use the drug in the absence of test information.
Q7.

There are adequate UK and European regulatory mechanisms for ensuring the safety of drugs before they are marketed. New test-drug combinations should be covered by these mechanisms. The difficult issue is to know how to regulate tests produced independently that purport to predict ADRs in drugs already in the marketplace. It is not entirely clear how these tests might be regulated in the future. Costs are not (and should perhaps not be) taken into account at the regulatory stage. These are priority setting issues for a publicly funded health care system.

Q8.

This is a possibility – but it is not specific to pharmacogenetics, nor even to genetic testing. The cost of many new technologies is such that many are not now available to patients within the NHS. Within a cash limited state funded system not everything will be available.

Q9.

No. The argument that there is something special about "genetic" information (however that is defined) requiring special regulatory treatment is not convincing. All medical information is confidential. The idea that information that derives from DNA analysis (one definition of "genetic") needs greater protection is an assertion that needs to be demonstrated. It makes no sense to give lesser protection to diagnostic information, for example, than to pharmacogenetic data that allows a physician to adjust the dosage of prescribe drugs. Both types of information need to be securely protected and kept confidential. There is no reason to treat genetic tests for disease susceptibility and PGx tests differently, not least because some of the tests may provide information about both disease susceptibility and drug response.

Q10.

In the same way as any other type of confidential medical information – securely and confidentially. The data should probably be held in a reversibly de-identified form.

Q11.

The consent should be explicit but need not be specific. The main requirement is that the research subject knows what he or she is consenting to and is prepared

to give that consent. Some subjects may require specific and detailed information about each and every research project; others may be content to give consent to a broad range of purposes. The advantages of de novo pharmacogenetic research is that the subject is in a position to give explicit consent ab initio (or to decline to give consent). So, unlike secondary research using medical records, the subject is able to take a view as to whether or not to participate given the terms set out by researchers.

Q12.

No – not in general. The research is likely to be about making appropriate statistical correlation between genotype and phenotype. Research based genetic tests are not usually subject to quality control and quality assurance demanded by clinical laboratories. The statement that individual results will not be fed back should form part of the consent procedure. There may be exceptions - such as when a genetic variant is found to predict serious ADRs.

Q13.

Guidelines from research charities, GMC based guidance about consent and confidentiality, use of existing consumer legislation, voluntary codes of practice are all legitimate forms of control that should be used in the first instance. Statutory regulation should be an exception and used only if special circumstances demand it.

Q14.

No. The purpose of any form of testing is to enable the pre-test estimate of probability of disease, complication or outcome to be replaced, as a result of the test, by a post-test estimate. PGx tests are no exception. Tests (DNA based or otherwise) for high penetrance inherited disorders place an onus on the physician to consider the implications of that diagnosis on relatives of the patient. This is not required in tests for complex disorders, unless they refer to a high penetrance monogenic subset. The material distinction is between tests for high penetrance inherited traits and tests that alter in a quantitative fashion the post-test risks of the trait.

Q15.

All tests are imperfect and run the risk of producing false positive and false negative results. These can cause unnecessary anxiety or result in inappropriate reassurance. Tests done everyday in the ordinary course of medical practice may reveal unexpected results. A chest XR in a patient suspected of having

bronchitis may, quite by chance, reveal a carcinoma. A routine cervical smear may reveal a previously suspected ovarian cyst. These issues are not specific for genetic or PGx tests.

Q16.

A PGx test that confirms that a particular patient is subject to a severe form of ADR may have significant implications for family members. It is important that the appropriate clinical management of such patients includes the taking of a family history and steps to warn and offer testing to at risk relatives.

Q17.

The physician must carry the ultimate responsibility – as he or she does for any medical test undergone by the patient.

Q18.

It depends on the circumstances but essentially yes – the patient should be able to refuse a test. This is essentially a clinical decision, and the degree of pressure that should be applied by the physician will depend on circumstances. The physician should only refuse to prescribe if there is a very high chance of a serious ADR.

Q19.

Access to PGx information by insurers should be governed by an appropriate agreement between government and the ABI. The former HGAC took the view that while there was no reason in principle to refuse access to genetic (as distinct from any other type of) information that might be relevant to risk, such information should not in practice be made available to insurers until and unless the actuarial information linking the two was sound enough to provide a reliable assessment of risk. The same principle should apply to PGx information.

Q20.

The fact is that patients are at present grouped in accordance with their racial or ethnic characteristics for certain medical purposes. Clinicians think about sickle cell disease in the black population; they are attuned to G6PD deficiency in the Chinese and the higher prevalence of BRCA in Ashkenazy Jews. These phenotypic characteristics, used as a proxy for genotypic variation are, like all tests, imperfectly sensitive or specific. It is to be hoped that PGx will in time increase the likelihood of being able to use the genotype itself in clinical practice.

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