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Introduction

Pharmacogenetics, as part of personalised health care, is developing rapidly. For long, the need for personalized treatments, and particularly personalised medicines, has been felt among the health care professions, patients, their families and the public at large. This is so for many reasons, such as improving efficacy and perhaps effectiveness of treatments by targeting populations who may most benefit from them, reducing adverse effects by selecting out populations that are prone to such effects, and optimizing cost-benefit by investing in the development of such relatively effective and safe treatments. Pharmacogenetics is perhaps the most high-tech version to date of such personalised health care, and as such deserves ethical scrutiny, so that, following Sir Bertrand Russell's suggestion, technological development not lead our social practice but rather be regulated by the latter (which, in its turn, should be regulated by ethical reflection and discussion). This paper is an attempt at such a scrutiny of ethical issues in pharmacogenetics, formulated as comments on the recently published Nuffield Council on Bioethics Consultation Paper – Pharmacogenetics: ethical issues. At the request of the pertinent working party of the council, this response (subdivided as R1, R2, etc) is framed around 20 questions provided in the consultation paper, as well as one other important issue not directly addressed by these questions.

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

R1 – The likely economic impact of pharmacogenetics on the development of new medicines can be analyzed according to two dimensions. First, regarding the financial expenditure related to the development of new medicines, it can be expected that in the short term, pharmacogenetic development of new medicines will cost more than ordinary development of new medicines, due to pharmacogenetic knowledge and techniques being currently in a relatively under-developed state; yet, in the long term, pharmacogenetic development is expected to cost less, as it is guided by (mainly genomic) knowledge, rather than the expensive trial-and-error approach more common in non-genetic pharmacology (particularly in fields such as psychopharmacology). Second, regarding the financial intake related to the development (and, eventually, the sale) of new medicines, it can be expected that in the short term, pharmacogenetic development of new medicines will bring in less money than ordinary development of new medicines, due to there being a smaller population that can use each pharmacogenetically designed medicine and as use of such medicines will probably increase gradually; yet, in the long term, pharmacogenetic development is expected to bring in more money, as the market for pharmacogenetically designed medicines in general seems vast. Hence, the likely economic impact of pharmacogenetics on the development of new medicines is expected to be biphasic, with the short term (i.e., the next few years) expected to bring more expenditure and less intake, whereas the long term (i.e., the next few decades) expected to bring less expenditure and more intake. This implies that pharmaceutical companies and academic centers should be supported in looking at the long term in the pharmacogenetic development of new

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medicines. All this is without considering the indirect impact on general biological and biomedical knowledge, which in itself may have an economic impact in the long term.

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

R2 – Following the above (R1), it seems that some regulatory measures may be needed to encourage the development of clinically desirable but economically unprofitable medicines in the short term. Such measures may include governmental rewarding of pharmaceutical companies that allocate at least some acceptable part of their R&D budget to pharmacogenetics, particularly for the development of pharmacogenetically designed orphan medicines. Alternatively, or complementarily, sufficiently large pharmaceutical companies may be governmentally mandated to allocate at least some acceptable part of their R&D budget to the development of pharmacogenetically designed orphan medicines. And there may be other regulatory measures that may be needed to encourage the development of clinically desirable but economically unprofitable medicines, at least in the short term.

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

R3 – The question whether pharmacogenetic testing of participants in trials should be a regulatory requirement for the development of medicines in the future is complicated, because the answer depends on background knowledge (which

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changes from time to time). That is, genetic testing of variant susceptibility to adverse effects or to efficacy/effectiveness of medications may be required when existing theory and evidence suggest – even if indirectly – that such variance exists. For example, when experimental evidence demonstrates that a strain of laboratory animals is susceptible to certain adverse effects of a medicine, there may be sufficient grounds to require pharmacogenetic testing of participants in trials involving the development of this medicine. The implication is that when there is no suggestive background knowledge, there may not be sufficient grounds to require pharmacogenetic testing of participants in trials involving the development of such medicines. Hence, pharmacogenetic testing of participants in trials should not be a regulatory requirement for the development of medicines in the future, at least not one that applies to all medicines in all knowledge-situations.

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 though medical practitioners as part of a decision about the use of a prescribed medicine?

R4 – The question of who should be responsible for providing a pharmacogenetic test can be divided into two problems. First, who should be responsible for providing a pharmacogenetic test in clinical research, and second, who should be responsible for providing a pharmacogenetic test in clinical practice. As for the first problem, it seems obvious that the research agency, whether public or private, should be responsible for providing a pharmacogenetic test in clinical

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research. As for the second problem, the situation may not be that different from other clinical situations, where tests that test for common or major abnormalities (such as Down's syndrome) are commonly provided by the government, whereas tests that test for rare or minor abnormalities are commonly provided by the private sector. And as for the question whether for individual therapy tests should be available directly to patients over the counter (OTC) or on the internet, or only available though medical practitioners as part of a decision about the use of a prescribed medicine, one should weigh the expected harms versus benefits of these alternatives. The harms of non-prescription pharmacogenetic testing may be the reduction of trustworthiness of these tests, particularly if taken from the internet. The benefits of non-prescription pharmacogenetic testing may be the increase in use of such tests, which may provide more information to patients and thus increase their decision-making capacity. The harms of prescription pharmacogenetic testing may be the increase in power of the medical community, which some claim is already too much. The benefits of prescription pharmacogenetic testing may be the increase in informed use of these tests. Overall, the expected harm-to-benefit ratio of prescription pharmacogenetic testing may outweigh the expected harm-to-benefit ratio of non-prescription pharmacogenetic testing, given that the latter can always be followed up by the former, and hence non-prescription pharmacogenetic testing may be preferable.

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

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R5 – The implications of pharmacogenetics for pharmaceutical companies and providers of healthcare regarding legal liability for adverse reactions will depend on the legal standing of pharmacogenetic testing. If such testing is accepted as a guiding standard according to which marketing and prescription of pertinent medicines is to occur, then adverse reactions resulting from serious deviation from the use of such a guiding standard (i.e., either non-use or incorrect use) will be legally liable. On the other hand, adverse reactions appearing in spite of correct use of such a guiding standard may not be liable.

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?

R6 – Medicines which have been developed for administration in conjunction with a pharmacogenetic test should be distributed to countries in which testing facilities are not available, so long as there are few serious adverse reactions expected if the medicines are given unknowingly to individuals or populations that are at (genetic) risk for adverse reactions, and so long as the population expected to benefit from the medicines is a large enough part – perhaps 50% or more (i.e., well above average placebo response rates) – of the population with the illness in that country.

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?

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R7 – Predictions of efficacy and safety, as well as cost, should 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 the following ways: (a) For a public healthcare system, pharmacogenetically-based efficacy and safety data should contribute to – yet not dominate – the formulation of policy-making, in order to improve the benefit-to-harm ratio and, hopefully, reduce costs (at least in the long term). (b) For a private healthcare system, considerations should not be dissimilar, except for efficacy, where considerations may be more or less lenient so as to allow for a wider range of judgment. (c) And for both types of systems, it is important to note that they exist in dynamic balance, so that the characteristics of one depend to some extent on the characteristics of the other in any given locality, and hence the considerations relevant to one depend to some extent on the considerations relevant to the other.

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?

R8 – The application of pharmacogenetics might exacerbate inequalities in the provision of healthcare, if its benefits will only be affordable or available to the wealthy. Such a turn of events may challenge the principle of solidarity that lies at the basis of the provision of national healthcare in the UK (and other countries with national health insurance programs, such as Canada and Israel), if

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preventive and remedial action is not attempted, such as implementing differentially subsidized insurance programs for pharmacogenetic testing.

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?

R9 – In my view, the storage of genetic information for the purpose of pharmacogenetic analysis is not categorically distinct from storage of other kinds of genetic information, for example information about susceptibility to disease, because, like other kinds of genetic information, it predicts clinical outcomes, although not fully. Yet, it may deserve special attention, as it may predict clinical outcomes most precisely, and hence may require special protection so as not to be misused, e.g., by third parties such as employers and insurance agencies.

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

R10 – The level of anonymity that should be accorded to genetic information stored as part of research in pharmacogenetics should be as high as possible, so as to protect subject anonymity as much as possible. That is, such information should be anonymised or anonymous as much as possible. In case subjects are or might be interested in personal results from pharmacogenetic tests conducted as part of such research, provisions can be made to supply identified tests for these subjects.

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Q11 – What kinds of consent should be required for the collection of samples for research in pharmacogenetics? Should pharmaceutical companies 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?

R11 – Full and written informed consent should be required for the collection of samples for research in pharmacogenetics. Pharmaceutical companies should not be able to use such samples for any purpose, but rather consent of the donor should be restricted to allow usage only for specific kinds of research, preferably detailed in advance.

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

R12 – Researchers should provide individual feedback about genetic information obtained from participants in research in pharmacogenetics, but only if research subjects are or might be interested in personal results, and preferably by means of an added identified test so as to enable anonymity in the research itself.

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

R13 – In my view, appropriate methods of regulating scope, storage and access with respect to pharmacogenetic information used in clinical practice would be the following: At the very least, the same rules and regulations applying to other personal medical information should be applied to such pharmacogenetic information, i.e., the scope should be that targeted by the clinical objectives and

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specified in the process of obtaining informed consent, storage should be at least as secure as that of the personal medical file, and access should be restricted to the treatment team and the person tested (unless public health considerations are involved, which may require disclosure to others, such as genetically-implicated relatives; discussion of such a possibility is beyond the scope of this paper).

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?

R14 – The ethical and legal issues raised by the use of pharmacogenetic tests in primary care do not seem to differ significantly from those raised by other forms of genetic testing, except for the implications for providers of healthcare, where physicians may be requested by patients (or healthcare insurance programs) to provide medicines without conducting relevant existing pharmacogenetic tests. Such requests may go against the physician`s professional moral code, in which case it may be reasonable for the physician to refer the patient for treatment to another physician, and may put the prescribing physician at risk of being liable if complained against for not conducting the test, unless a detailed informed consent (or, rather, refusal) process is conducted and documented carefully. As for similarity to non-genetic tests, such as tests for cholesterol, there may not be much difference here for the patient, as a test for cholesterol provides a measure of risk (e.g., of ischemic heart disease), similarly to a genetic or pharmacogenetic tests. Of course, non-genetic tests do not implicate the family as genetic or

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pharmacogenetic tests do, which is a point of difference (and one that simplifies things for non-genetic tests).

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?

R15 – The psychological implications for individuals of pharmacogenetic tests might be increased fear of taking medicines if this requires undergoing pharmacogenetic tests, particularly if these may reveal information that is of relevance outside the context of testing for response to medicines. Yet, such fear may not be common and may not carry significant consequences, behaviorally and otherwise (as has been demonstrated in relation to the doctrine of therapeutic privilege). As for the question whether such tests are likely to reveal information that is of relevance outside the context of testing for response to medicines, this remains to be seen, but it is plausible that such information may be revealed, particularly through linkage data.

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

R16 – Pharmacogenetic tests might have the following implications for family members: (a) Genetic implication, where relatives are genetically implicated by a positive result of a pharmacogenetic test of a patient, (b) psychological implication, where relatives are psychologically impacted (e.g., by fear) by a positive result of a pharmacogenetic test of a patient, particularly if they are also

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genetically implicated, (c) social implication, where relatives are socially and economically impacted (e.g. by possible stigma and discrimination) by a positive result of a pharmacogenetic test of a patient, particularly if they are also genetically implicated. All this may carry a heavy burden, which may be eased by appropriate support.

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

R17 – In my view, controversies are not likely to arise about who ultimately decides which treatment is prescribed in light of a pharmacogenetic test, at least not uniquely so, as the authority of the prescribing physician is not expected to be weakened following pharmacogenetic testing, at least no more than has happened following the managed care era (and its local variants). Managed care may approach the issue of prescription in light of a pharmacogenetic test in a typically restrictive manner, but the final decision will still rest with the prescribing physician.

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

R18 – The answer to the question whether patients should be able to refuse a genetic test to determine response to medicines but still expect to receive a prescription, depends on the features of the disease, the pharmacogenetic test and the treatment involved, as well as on general principles such as respect for persons (autonomy) and doing good and no/least harm (beneficence and non-maleficence, respectively). For instance, if the pharmacogenetic test has relatively poor power of prediction and the treatment has few serious adverse reactions, it may be relatively easy to accept a refusal of pharmacogenetic testing

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yet still prescribe the medicine. Other circumstances may make it more difficult to resolve this problem.

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?

R19 – This question touches on some philosophical foundations. A central problem here is whether pharmacogenetic information refers to traits or diseases, and whether there is a distinct enough difference between the two. It is widely agreed that providers of health insurance should have access to information about diseases, yet not so regarding traits (both physical and mental). This is even more so for other parts of the insurance industry, for example life insurance. Pharmacogenetic information may be a borderline case, in that it largely refers to variants and traits, yet clearly to ones that are related to clinical outcomes. Hence, it may be argued that providers of health insurance should have access to pharmacogenetic information. As for other parts of the insurance industry, for example life insurance, the answer may depend on the type of insurance and the extent that the pharmacogenetic information is related to the outcomes of interest to that type of insurance (e.g., in life insurance - risk of death due to adverse reactions or to poor response to medicines).

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?

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R20 – The question whether pharmacogenetics will increase the likelihood of the grouping of patients according to racial or ethnic groups for medical purposes, is an open question. It would depend whether such grouping is supported genetically, and we do not have sufficient information on that to date. But if such grouping is supported genetically, the social implications may be grave, as racial discrimination may be more likely, and hence the ethical implications of such a possibility may be that additional safeguards – legal and others – may be required to prevent such discrimination from occurring.

One other important issue not directly addressed by these 20 questions needs to be raised:

Q21 - Should the pharmaceutical industry be encouraged to develop and market pharmacogenetic testing? And how is the relationship between this industry and the medical profession expected to develop following such pharmacogenetic development and marketing by the industry?

R21 – Pharmacogenetic testing can be regarded as medical technology in all important respects. As such, it is a candidate for development and marketing, particularly by the pharmaceutical industry. This industry should be encouraged to develop such testing, so as to improve the efficacy and safety of the medicines that it develops and markets. The relationship between this industry and the medical profession is problematic as it is, and it is expected to become even more so if the industry develops and markets pharmacogenetic tests, as the dependency of the medical profession on the industry will become even greater than it is now. Yet the remedy for this dependency, although not specific to

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pharmacogenetics, will have to address pharmacogenetics. Needless to say, such a remedy is not yet in sight.

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