Ethics, genetic screening, and pharmacogenetics

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Pharmacogenetics

The publication of the human genome project results has increased predictions of a paradigm shift in medicine (Schmidt, 1998), and genetic screening and testing are at the heart of the debate. Over the past few years much work has been done on developing criteria for the implementation of population genetic screening, including the seriousness of the condition screened for; the reliability and predictive power of the test; and the possibilities for effective intervention, or scope for action in the light of a positive result. It has been argued, however, e.g. by John Bell in the *British Medical Journal*, that the “development of drugs along genetic guidelines will be a major force driving the implementation of screening by healthcare providers” (Bell, 1998). The term used to describe the use of genetics to show how variations in patients’ DNA may diminish or increase the effects of a drug, or render it harmless, is ‘pharmacogenetics’.

There are predictions that pharmacogenetics might lead to a new understanding of disease (Bell, 1998). Whereas common diseases are currently defined by their clinical appearance, it will become possible to subdivide heterogeneous diseases into discrete conditions, in other words, change our perception of what the condition is for which the treatment is sought (Roses, 2000a). As genetic variants are identified that are associated with drug response there is likely to be a move towards widespread testing before prescribing - in fact it may come to be considered unethical not to carry out such tests (Wolf et al, 2000). The type of testing involved, however, is
different from testing for single gene disorders: it will involve testing for single nucleotide polymorphisms (SNPs) and thus the transferability of guidelines developed for other kinds of testing cannot be assumed (Roses, 2000b).

The first criterion frequently referred to in discussions of genetic screening, e.g in the Euroscreen project, is whether the condition sought is an important health problem, or whether it is ‘serious’ (e.g., Nuffield Council on Bioethics, 1993). There has been considerable discussion over what counts as serious, but despite the difficulties over a precise definition there is a widespread consensus on particular examples of conditions that are life-threatening, including some of the cancers and the haemoglobinopathies such as thalassaemia.

In the case of screening related to pharmacogenetics, however, the condition sought is susceptibility to drug toxicity - in other words, a manufactured or iatrogenic condition. Does this count as an ‘important health problem’ or ‘serious’ condition? It is estimated that adverse drug reactions account for more than 2 million hospitalisations and 100,000 deaths per annum in the United States (quoted in Schmidt, 1998; Stix, 1998). We cannot use these figures, however, to justify any given screening programme, unless what is sought is a predisposition to find all the drugs implicated in these figures toxic. What is envisaged is screening for risk factors for toxicity for particular drugs e.g., women who would be likely to suffer from blood clots from birth control pills; or who would be at risk of adverse side effects from the drug tamoxifen in breast cancer provision or treatment.

The second criterion to be discussed concerns what can be done in the light of a positive result. Where what is sought is a genetic diagnosis of an existing or pre-symptomatic condition, or a prediction of a late onset condition or predisposition, what might be at issue is the availability of
treatment. In the case of pharmacogenomics, however, this criterion again has problematic applicability. What is being tested for is the potential toxicity of the treatment itself, so it is difficult to use availability of treatment as a criterion of screening since the screening is being carried out to establish the extent to which this treatment is an ‘available’ treatment.

What may be envisaged however is not population wide screening but individual testing. Pharmacogenetics has been said to have the potential to individualise prescribing. This potential for predicting individual susceptibility to responsiveness to drugs has major implications not only for therapy but also for participation in clinical trials and research. As regards therapy, one of the principal benefits, it is suggested, is that more genetically informed prescribing will reduce the rates of morbidity and mortality due to iatrogenic disease. It has been estimated that about 1 in 15 hospital admissions is due to adverse drug reactions (cf. Schmidt, 1998; Stix, 1998; Wolf et al., 2000). Pharmacogenetics could affect a prescribing decision for a given patient in at least three different ways: (1) adjustment of dosage of drug A; (2) a choice between prescribing drug A or drug B; (3) drug A or nothing (where there is no alternative treatment available).

Clinical trials in this area may have features that distinguish them from traditional clinical trials: (1) they are likely to involve storage of DNA samples as responses to drugs are tracked over time; (2) the nature of the risks and benefits to which the participants may be liable are of a different kind, such as the possible (mis)use of genetic information on the one hand; genetically informed prescribing on the other. The potential impact on research, however, has other aspects, including the extent to which it will be possible for clinical trials to become more targeted towards specific groups. These potential developments in therapy and research give rise to questions in bioethics of two kinds: (1) substantive ethical issues (2)
professional ethics (3) challenges to existing ethical frameworks.

**Substantive ethical issues**

As already indicated, some of the literature on this topic has described developments in pharmacogenetics as facilitating 'personal pills' (Persidis, 1998), the suggestion being that awareness of genetic variation between individuals will facilitate prescribing in accordance with the specific needs of the individual, thus arguably in accordance with a principle that health care resources should be allocated according to need at the point of delivery. The possibilities of this with regard to monitoring of appropriate dosage as compared with choice of medication need to be considered. The situation where the choice is between drug A and no medication gives rise to the ethical problem of (perceived) abandonment. How pharmacogenetics will affect patient perception is important.

A major feature of the debate about the introduction of other genetic screening and testing programmes has been the right to know versus the right not to know question, supported by competing interpretations of concepts such as autonomy and solidarity (cf. Chadwick, Levitt and Shickle, 1997). It has been argued that there might be a right not to know genetic information about, for example, one's future health status. But it might appear that the same considerations would not apply in relation to susceptibility to drug toxicity - surely it could only be beneficial to have information enabling one to avoid the side effects of drugs? A right to know one's genetic status vis-à-vis susceptibility to drug toxicity might be supported by an autonomy-based argument where autonomy is interpreted in terms of self-determination - facilitating the choice of the individual in relation to treatment. In the event of multiplex testing, however, it might be possible to test at the same time for predisposition to a disease and for susceptibility to toxicity.
for the standard treatment. Then the question arises as to whether having this information is a benefit or a burden, because this is analogous to the situation where there is no treatment available. In such a case the argument for a right not to know comes into play.

What other reasons might ground a right not to know about susceptibility to drug toxicity? One possibility is a quasi-placebo effect. The knowledge that one has a higher risk of toxicity might in itself increase that risk. Further genetic susceptibility to drug toxicity may have insurance implications in the way that genetic predisposition to health problems might - people who because of their genotype are slow to clear drugs from their bodies, or to convert them to nontoxic form, may be identified as belonging to a higher insurance risk category (Schmidt, 1998).

Connected with this problem is the issue of quality control in a situation where hundreds of thousands of tests are carried out annually. External quality assessment schemes (EQAs) of genetic tests in Europe have demonstrated a low but significant error rate in cystic fibrosis testing (Dequeker et al, 2001) and the number of laboratory tests carried out annually as pharmacogenetic testing comes on stream is set to increase dramatically. Mistakes may arise not only through technical error but also out of clerical error or sample mix-up (Dequeker et al., 2001).

Apart from the possibility of error, there are problems with uncritically accepting that an identification of genetic risk factors will determine or assist in determining the appropriate treatment for a particular patient. Other factors such as food intake, general state of health and age may account for someone’s response to a drug (Haseltine, quoted in Stix, 1998; Chadwick and Levitt, 1995); drug efficacy and toxicity may be considered as multifactorial traits that involve some genetic

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component(s) in much the same way as complex diseases do. Apart from the issues for individuals, there is the possibility of ‘patient stratification’, whereby patients could be classified according to genetic risk factors, as they are presently classified by other risk factors such as high blood pressure (Chadwick, 1999; Wolf et al., 2000). The possible implications for particular population groups should be considered, in the light of possible differences between ethnic groups as regards, for example, slow or rapid rate of metabolising a drug.

Thus patient stratification could have discriminatory implications. The Council on Ethical and Judicial Affairs of the American Medical Association in an article on ‘Multiplex genetic testing’ in the Hastings Center Report (1998) argued that “ethnic heritage may contribute to particular concerns, it is clinically relevant and should be considered. Offering multiplex tests that are bundled according to race or ethnicity, however, serves to categorise patients rather than to address their distinct needs...The profession can ill afford the perception that science is being used to bring attention to the genetic flaws present in lines of inheritance” (Council for Ethical and Judicial Affairs, 1998). One possibility is that genetic susceptibility might be correlated with some other characteristic such as ethnicity, leading in effect to a presumption of effective treatment for that condition for that particular group although there might be considerable variation within the group. Indeed, there is some support for the view that the significance of ethnic variation in drug response might have been overstated (Hodgson and Marshall, 1998).

In clinical trials, the extent to which research in pharmacogenetics raises ethical questions that are distinctive needs to be addressed, e.g. the implications for informed consent, feedback of information, privacy issues. Allen Roses, addressing the annual Human Genome Meeting in 2001, argued that there is a lesser privacy issue in pharmacogenetics.
than in testing for predispositions to disease. What interests need to be protected for research participants in this field, and how, needs to be examined.

Professional ethics

Questions for professional ethics arise when considering how pharmacogenetics will affect health care delivery. Different modes of delivery will raise different ethical questions, and countries may differ in how they integrate pharmacogenetics into health care. If genetic testing becomes a standard accompaniment of prescribing, there are questions about how this will be carried out. If doctors carry out pharmacogenetic testing at the time of prescription then this will affect the doctor-patient relationship. On the other hand, what may be envisaged is that there will be a central database, containing patient genotype information, which will be accessed at the time of prescription. If the latter is the case then quality control issues, mentioned above, become particularly important to prevent errors being perpetuated over time. The person who accesses this database, however, need not be the doctor - it may be, for example, the pharmacist. There may be an expanding role here for pharmacists, if for example doctors prescribe generically and pharmacists dispense according to genotype. There is a need however to think through the ethical implications for doctors and pharmacists arising out of these possible changes to their roles. The last scenario may be more appropriate in certain applications of pharmacogenetics e.g., when the choice is between drug A and drug B. There will also be a need for education and training in the ethical implications. What form this training should take will depend on how the ethical issues should be addressed.
Challenges to existing ethical frameworks

In addition to the implications for practice it is important to consider ethical frameworks themselves. Developments in technology have the potential to change the way we look at things and to challenge the boundaries of our concepts. In the case of pharmacogenetics, the implications for concepts of disease have already been mentioned, but the impact is wider than that: the ethical frameworks we use sometimes need to be revised. It cannot be assumed that principles of bioethics are immune to revision. Developments in genetics have led to rethinking, for example, of the meaning of autonomy, the extent and limits of the duty of confidentiality, the right to know and the right not to know. There is a growing body of opinion that it is not sufficient to continue with the traditional principles of biomedical ethics and simply seek to apply them in the new context and there is specific concern about the transferability of existing guidelines to pharmacogenetics: “It is ... incumbent that medical guidelines for mendelian- or susceptibility-gene testing do not extend automatically to discussions of other types of genetically based profiles in pharmacogenetics. Clear language and differentiation of respective ethical, legal and societal issues are required...” (Roses, 2000b).

Discussions of historical precedents in medicine, genetic screening and counselling may nevertheless be instructive: it has been recognised that ever larger amounts of information may be a burden rather than autonomy-enhancing. In her address to the American Association for Bioethics and Humanities in 1999, Onora O’Neill made a similar point: that in the context of the vast amount of information and storage issues, we need to think again about what it means to respect people and protect them, and that bioethics needs to become more political, with individualistic conceptions of informed consent, taken by themselves, perhaps becoming obsolete (cf also Chadwick, 2001). If this were the case, then there
would be clear implications not only for ethical thinking but also practice, and for the medical ethics curricula that are being developed in European countries. To date the philosophical, ethical and legal implications have not been assessed in detail and there is a large agenda to address in terms of the potential paradigm shifts and policy implications.

References


Dequeker, E. et al., 'Quality control in molecular genetic testing', Nature Reviews Genetics 2 (9) 717-23


