

Pharmacogenetics: ethical issues

a guide to the Report

Introduction

People often respond differently to the same medicine. Few medicines are effective for everyone; all may cause adverse side-effects and occasionally death. These different responses are partly due to our different genetic make-up. Research in pharmacogenetics investigates how differences in our genes can affect the way in which we respond to medicines.

Pharmacogenetics has the potential to improve both the safety and efficacy of medicines. However, pharmacogenetic research and its applications raise important ethical, legal, social and regulatory issues. This important technology will

have implications for the research and development of medicines, clinical practice and treatment, and the use and storage of genetic information.

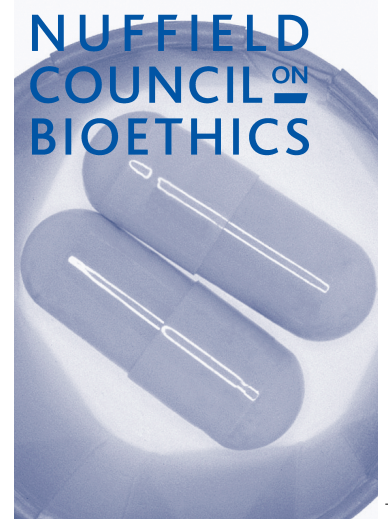
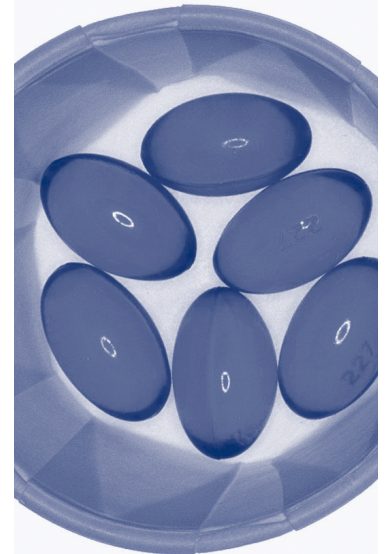
The Nuffield Council on Bioethics has published a Report, *Pharmacogenetics: ethical issues*, which aims to encourage discussion of the issues and makes recommendations for future policy and practice. This summary sets out some of the arguments and recommendations which are discussed in more detail in the Report.

[Notes in square brackets throughout refer to chapters and paragraphs in the Report].

What is pharmacogenetics?

The study of how genetic variation affects our response to medicines.

A **pharmacogenetic test** is a test to detect the presence or absence of, or change in, a particular gene or chromosome in order to predict a person's response to a medicine. The test could be done directly, by analysing a person's DNA, or indirectly, by examining the products of the DNA such as proteins.



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SCIENTIFIC BACKGROUND

How do genes affect our response to medicines?

Differences in our genes can affect the way in which we respond to medicines in two ways:

■ Variation in the way the body processes a medicine [Differentiating people]

Variation in DNA can lead to altered activity of enzymes that are responsible for the absorption, metabolism and excretion of medicines. If a medicine is broken down too quickly it may not be effective. Alternatively, slow metabolism can lead to the build-up of toxic levels of a medicine. Even a single change in the DNA can affect the way the body processes a medicine [paras 2.11-2.14].

Example:

An enzyme in the liver, CYP2D6, is involved in the metabolism of nearly one quarter of medicines, including anti-depressants and beta-blockers used to treat heart disease. Variations in the CYP2D6 gene may alter the activity of this enzyme. People with reduced levels are unable to process some medicines properly. In some cases the medicine will not be effective; in other cases patients will suffer serious side effects. For example, the painkiller codeine has no effect on approximately 7% of Caucasians because of a CYP2D6 variant. There is currently no routine pharmacogenetic testing for CYP2D6; but a diagnostic chip that will test for a large number of 2D6 variants will be introduced in 2003.

■ Variation in the genetic characteristics of a disease

Potential benefits of pharmacogenetics

■ Improving safety

Some medicines have side-effects (adverse reactions) and may even occasionally cause death. If a genetic variant is found to be associated with an adverse reaction to a certain medicine, doctors could avoid prescribing the medicine to patients with this gene variant. However, there are other reasons why medicines may be dangerous. These include errors in prescription or administration, patients' not following instructions accurately, or interactions between medicines or other substances.

■ Adjusting dosage

Genetic information could be used to adjust the dosage of a medicine, reducing the trial-and-error approach which is often used today to determine the best dose.

[Differentiating diseases]

Many diseases that are currently diagnosed as a single clinical condition may actually have a number of underlying causes, based on different genetic characteristics. Understanding more about the genetic basis of disease may provide information about what medicine would be effective. Some cells, for example those in cancerous tumours, have an altered genetic make-up. This change only occurs in the cancer cells, and not in normal tissue, and may influence treatments [paras 2.15-2.16].

Example:

A particularly aggressive form of breast cancer is associated with a genetic variation which leads to overproduction of a protein called HER2. Patients with breast cancer can be tested to find out if they have high levels of HER2. If they do, the medicine Herceptin (trastuzumab) is given to treat this specific type of cancer.

There are a number of factors that affect our response to medicines, including age, sex, interaction with other medicines, and diet. A genetic variant alone will rarely provide a precise prediction of the response of a particular patient.

RESEARCH AND DEVELOPMENT

New medicines

The introduction of pharmacogenetics will have an impact on the way in which clinical trials are designed and managed. Some clinical trials already include the collection of genetic information and this practice is likely to become more widespread [Chapter 3].

How will pharmacogenetics be used in clinical trials?

Pharmacogenetic analysis could influence the design of clinical trials. Smaller groups of genetically similar participants could be selected, potentially leading to more reliable research results. People who are likely to suffer adverse reactions from a new medicine could be identified and excluded from trials, protecting research participants. However, there is currently not enough information available to reliably assess the impact of pharmacogenetics on the design of clinical trials, and therefore also on the cost of developing medicines.

Will pharmacogenetic testing become mandatory in trials?

It is difficult to predict at this stage just how widespread the use of pharmacogenetics in research will become. Regulatory requirements or concern about litigation could put pressure on companies to include pharmacogenetic analysis in trials. However, this approach may not always be feasible or appropriate. One possibility is that pharmaceutical companies will collect genetic information at the time of a trial, but not analyse the data unless it becomes necessary.

We recommend that the appropriate use of pharmacogenetics in clinical trials should be promoted. Collection of samples for possible future pharmacogenetic analysis should be encouraged [paras 3.5-3.12].

Will pharmacogenetics be used to improve existing medicines?

Pharmacogenetics could also be applied to existing medicines to improve the safety and efficacy of prescribing. The importance of such research depends on a number of factors:

- How widely used is the medicine?
- What is the nature and severity of any adverse reactions?
- How accurate would a pharmacogenetic test be?
- Do alternative treatments exist?

It is unlikely however that the pharmaceutical industry would have a sufficient economic incentive to carry out this research, especially if the medicine is not covered by patent protection. The Department of Health has recently announced that new funding of £4 million will be directed towards pharmacogenetic research over the next three years.

We recommend that pharmacogenetic research on existing medicines should be encouraged. Funding and support should be made available within the public sector and public-private partnerships should be encouraged [paras 3.20-3.26].

RESEARCH AND DEVELOPMENT

The use of pharmacogenetic information in clinical trials

It is important to ensure that patients are protected if information about them is used in clinical trials. The Report discusses a number of recommendations relating to consent, privacy and confidentiality [Chapter 3].

What level of anonymisation is appropriate?

The implications for patients will depend on how easily samples can be traced back to them. The Report considers the various degrees of anonymisation that could be used, ranging from samples that are directly identifiable to those that are fully anonymous. One likely approach would be to use anonymised data. Genetic and clinical data would be collected during a trial, but a code linking patients with their samples would be destroyed after the trial so they could not be matched subsequently. However, this approach would not allow longer term follow-up of an individual. New samples would need to be taken from patients if adverse reactions occurred.

We suggest that the greatest degree of anonymity compatible with the research should be used to protect the privacy of participants. Researchers should explain to prospective participants how the samples will be stored and the implications for them. [paras 3.31-3.43].

Should participants be given individual feedback?

Participants need to know whether the research is likely to give rise to information that is directly relevant to their health. In some cases, researchers provide individual feedback to patients. In others, researchers offer individual test results only if patients ask for the information. Provided their data has not been anonymised, research participants in the UK are able to request access to information about themselves. However, it is not clear to what degree results from pharmacogenetic trials will be reliable or clinically useful.

We recommend that the feedback of the overall results of research should be promoted. We are sympathetic to the view that patients should be given individual feedback if the information is clinically useful and validated. But this will not often be the case with results from early-stage pharmacogenetic research. Decisions regarding the provision of individual feedback should be explained to the relevant research ethics committee [paras 3.44-3.49].

Is genetic information special?

Some people believe that genetic information is fundamentally different from other forms of medical data. This view is called 'genetic exceptionalism'. There are a number of reasons for this belief, including the idea that genetic information is uniquely identifying and highly predictive, for example revealing susceptibility to a disease. The information may also be of interest to third parties including insurers and employers. However, in the context of pharmacogenetics, an undue emphasis on the fact that information is genetic can be unhelpful. Not all genetic tests convey highly predictive or diagnostic information

about a patient or their relatives. Equally, blood tests, cholesterol tests and HIV tests can also give reliable predictive information, without analysis of DNA. And non-genetic tests may also provide indirect genetic information.

Genetic information does not necessarily raise different ethical issues from other types of medical information. We believe that the most important aspect to consider is the information that a test reveals and its implications for the patient, not whether the information is directly genetic [paras 1.8-1.14].

PUBLIC POLICY ISSUES

How should pharmacogenetic tests be regulated?

The Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for the licensing of new medicines and genetic tests, based on an assessment of quality, efficacy and safety. The approval of pharmacogenetic tests and medicines will also be under its remit. It is important that these tests should be reliable and of high quality. In some cases, a medicine will only be licensed if it is used in conjunction with a test. Herceptin, for example, is licensed for use only for patients who have been shown to have high levels of HER2 [paras 4.3-4.6].

How will pharmacogenetic information affect decisions about the provision of healthcare?

Healthcare providers operate on limited budgets and need to assess whether a medicine is cost-effective, offering good value for money in light of the expected health benefits.

Pharmacogenetics will provide information that is relevant to these assessments by allowing more accurate prediction of the cost of a treatment. If groups of patients are identified who are less likely to respond to a medicine, or more likely to have an adverse reaction, will it still be cost-effective to treat them? Decisions about cost-effectiveness of treating different groups of people with the same medicine may be affected by pharmacogenetic information.

However, an exclusive focus on cost-effectiveness, could lead to the possibility that small groups of people with rare diseases or genetic variations might not be given treatment. Justice and equity also need to be considered. Sometimes it will be right to allocate resources to treatments or conditions that might otherwise not be considered cost-effective, in order to ensure a fairer distribution of health care.

Pharmacogenetic information may affect decisions about which treatments to fund, by revealing information about the effectiveness of treatments. It is important that decisions should take into account considerations of fairness. The National Institute for Clinical Excellence (NICE) is responsible for assessing cost-effectiveness in England and Wales. We endorse NICE's approach of reviewing cases on an individual basis, considering equity as well as cost-effectiveness [paras 4.11-4.32].

Is there a risk that some patients will be neglected?

The categorisation of patients into sub-groups according to genetic features (either of their disease, or their inherited DNA), could also have an impact on the development of new medicines. This could be beneficial, if medicines that would otherwise have failed could be targeted to a smaller group of patients for whom the medicine is likely to be safe and / or effective. However, some of these groups might be so small that developing specific medicines to treat them could be prohibitively expensive.

Incentives might be necessary to encourage pharmaceutical companies to develop medicines that would provide benefit to only a small number of patients. One possibility would be to apply existing legislation which encourages the development of medicines for 'orphan diseases', by offering tax credits, incentives for research and extended patent protection.

Orphan medicine legislation may need to be reviewed if pharmacogenetic information leads to a reclassification of diseases. A subgroup of a single disease would have fewer patients, but it is not clear whether the condition would qualify as an 'orphan disease' [paras 4.33-4.40].

Racial groups

There may also be stratification of patient populations based on racial or ethnic groupings with respect to treatment response. Some genetic variants are more common in certain racial or ethnic groups than in others. For example, one variant of CYP2D6 which leads to slow processing of many medicines, is present in approximately 7% of Caucasians, but only 1% of Chinese. The fact that some genetic variants are more or less likely to be found within particular groups has implications for the design of clinical trials, and for public health decisions. At the same time, since there is considerable genetic variation within ethnic groups as well as between them, pharmacogenetics should provide a much more reliable way of predicting response to a medicine than relying on racial or ethnic classification.

We recommend that pharmacogenetic tests should be validated in the populations in which they are to be used. Those involved in pharmacogenetics research should be sensitive to the potential for misunderstanding and prejudice arising from racial stereotyping [paras 4.41-4.47].

TREATMENT AND CLINICAL PRACTICE

The introduction of pharmacogenetics will mean that many more patients are exposed to genetic testing than before. Currently, patients tend only to encounter genetics in the context of serious diseases such as cystic fibrosis and Huntington's disease. Pharmacogenetics could make genetic testing much more routine. We make a number of recommendations to help ensure that the delivery of pharmacogenetics in clinical practice will be as straightforward as possible [Chapter 5].

- Reliable and easily accessible information from independent sources will be important, both for doctors and patients.
- Health professionals need to be given training to communicate information about pharmacogenetics.
- Additional resources will be needed to implement pharmacogenetic testing. Doctors will need more time with patients, to discuss tests and to take samples.
- New facilities for testing will be needed, allowing results to be obtained quickly and efficiently. Tests could be carried out either in GPs' surgeries, at a hospital, or at specialised testing facilities.

Should tests be made available directly over the counter or on the internet?

Most people accept that not all medicines should be freely available over the counter or on the internet to patients. Should the same apply to pharmacogenetic tests? The tests themselves do not pose the same direct risks as medicines, so it could be argued that patient choice should be important. However, the nature of the information revealed by the test also needs to be considered.

We recommend that the direct provision of tests to patients needs to be assessed on a case-by-case basis. If an approved test provides clear, readily interpretable information about medicines that can be purchased over the counter, the test could be provided direct to consumers. However if, as is more likely, a test generates complex information, with less certain predictions, it would not be appropriate to provide the test direct to the consumers. It is likely that professional advice will be needed before and after taking the test [paras 5.19-5.22].

Will consent forms be necessary for pharmacogenetic tests in clinical practice?

Some medical procedures, for example giving an anaesthetic, require written consent from the patient. Currently consent must be obtained for HIV tests and some genetic tests, although not for other tests, including most routine blood tests. There has been debate whether written consent forms and genetic counselling will be necessary when patients have pharmacogenetic tests. Possible factors to consider include:

- What information about a patient's condition might be revealed?
- Could the results have a profound psychological effect, for example if a test reveals that a patient is effectively untreatable?
- Will the test also reveal additional information, either now or in the future, such as likely response to other medicines or susceptibility to an unrelated disease? (Genetic variants can influence more than one trait).

We recommend that each test be assessed on a case-by-case basis, according to the nature of the information revealed. It is important to point out that non-genetic tests may reveal similar information. In most cases, written consent forms will not be required, but in some circumstances they may be appropriate. Written information should be provided, particularly if tests will reveal complex information [paras 5.9-5.17].

Should patients be prescribed a medicine even if they do not wish to take an associated test?

Who should decide whether a patient takes a pharmacogenetic test? Should patients be entitled to be prescribed a medicine, even if they do not wish to take an associated test? This question will become particularly pressing if advances in pharmacogenetics mean that some medicines may be licensed only because they can be used with a pharmacogenetic test, to ensure a patient is not at risk of a serious adverse reaction.

Where a pharmacogenetic test is part of the licence conditions of a medicine, it is unlikely that a doctor would wish to prescribe the medicine without the test, particularly if this would mean putting the patient at risk. If the test is not part of the licencing conditions, doctors should be guided by regulatory authorities and professional bodies when making a decision [paras 5.23-5.29].

Who will have access to pharmacogenetic information?

The increasing storage of genetic information by GPs or pharmacists will raise questions about the privacy of the information, as it does in relation to the storage of all medical data. The privacy and confidentiality of patients must be protected [paras 5.31-5.35].

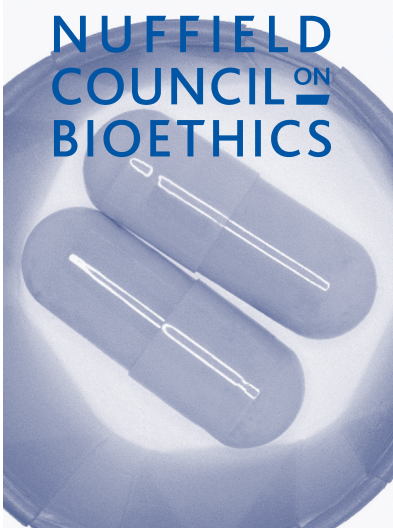
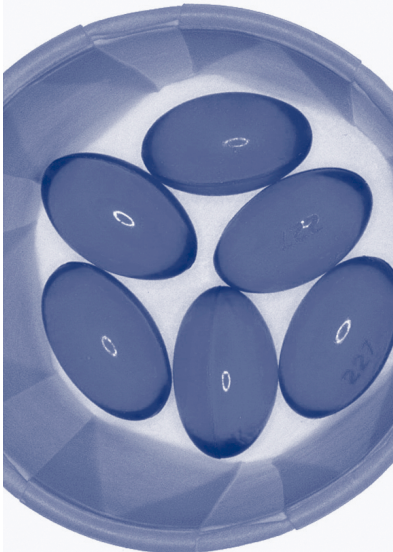
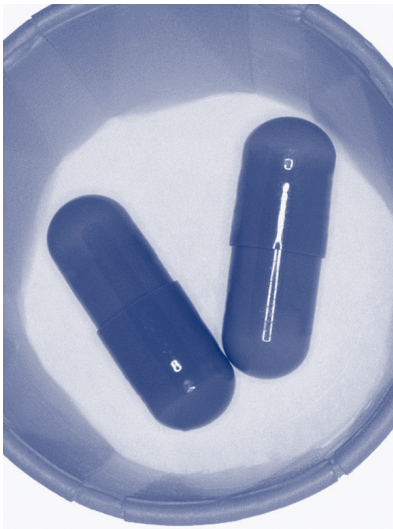
- Test results are likely to be stored in medical records. We do not think that special arrangements for storing genetic data will be feasible.
- In a few cases, information revealed by pharmacogenetic tests will be relevant to family members, for example if a pharmacogenetic test also indicates susceptibility to another disease. This can be dealt with by existing practice regarding sharing medical information.

Should pharmacogenetic information be used by insurance companies?

Pharmacogenetic information could be relevant both to health and life insurers, either in assessing claims or setting premiums [paras 5.36-5.41].

- **Assessing claims:**
Pharmacogenetic information could be useful to inform decisions about which treatments should be funded for particular groups of patients. This would be similar to the use of information by public health providers to make decisions about the allocation of resources.
- **Setting premiums:**
The Association of British Insurers has commented that pharmacogenetic information would not be useful in setting premiums. This is partly because pharmacogenetic tests will have low predictive value compared to tests for single-gene disorders. Other information would also continue to be more useful in assessing risks, for example information about medical history. But there is a risk that patients will not take pharmacogenetic tests because of fears about obtaining insurance. Patients could then lose the benefit of taking the test. There is currently a moratorium in the UK until 2006 on the use of genetic information by life insurers in setting premiums (except for Huntington's disease in life insurance policies of over £500,000).

Pharmacogenetic information falls under this moratorium and we recommend that this moratorium should continue.



Summary

It is difficult to predict the extent to which 'personalised medicines' will become a reality. Claims of designer drugs, or 'the right medicine, for the right patient, at the right dose' are misleading, but it is important to discuss ethical, legal, regulatory and social issues that may be raised by improvements in predicting response to medicines.

To obtain maximum benefits from pharmacogenetics we need to address legitimate concerns and safeguard against inappropriate use. There must be the right combination of constraints and incentives to protect and promote the interests of patients and society as pharmacogenetic testing is more widely introduced.

Copies of the Report are available to download from the Council's website: www.nuffieldbioethics.org

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