Ethical Viewpoint

Ethical Issues in Pharmacogenomics

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ABSTRACT

Progress in medicine has led to the appearance of a new branch - pharmacogenomics. The use of genetic material in the patients' genotype has allowed for the development of new pharmaceutical products. Although pharmacogenomics leads to the production of effective and safe drugs, its applications raise important ethical, legal, social and regulatory issues. This technology will thus have an impact on the research and development of medicines and clinical practices in future. It will have an implication on the use and storage of genetic information as well. The ethical implications refer to the informed consent for genetic testing, personal autonomy regarding decision for DNA testing, confidentiality, the principle of equity. Discriminatory attitudes can be avoided, primarily through the management of the patients' genetic data under conditions of confidentiality.

Key words: ethics, pharmacogenomics, pharmacology

What is pharmacogenomics ?

For many years studies of pharmacogenetics have provided ample examples of causal relations between genotypes and drug response to account for phenotypic variations of clinical importance in drug therapy. The convergence of pharmacogenetics and human genomics in recent years has dramatically accelerated the discovery of new genetic variations that potentially underlie variability in drug response, giving birth to pharmacogenomics [1].

Pharmacogenomics - (pharmaco + genomics) is combination of pharmacology and genomics. It is the study of how genes affect a person's response to drugs. Pharmacogenomics analyzes how the genetic makeup of an individual affects his/her response to drugs. It deals with the influence of genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms [SNP] with pharmacokinetics and pharmacodynamics. Pharmacogenetics focuses on single drug-gene interactions, while Pharmacogenomics encompasses a more genome-wide association approach, incorporating genomics and epigenetics while dealing with the effects of multiple genes on drug response [2].

Pharmacogenomics aims to develop rational means to optimize drug therapy, with respect to the patients' genotype, to ensure maximum efficiency with minimal adverse effects. Through the utilization of pharmacogenomics, it is hoped that pharmaceutical drug treatment can get a novel approach. Pharmacogenomics also attempts to eliminate the trial-and-error method of prescribing, allowing physicians to take into consideration their patient's genes, the functionality of these genes, and how this may affect the efficacy of the patient's current or future treatments (and where applicable, provide an explanation for the failure of past treatments). Such approaches promise the advent of precision medicine and even personalized medicine, in which drugs and drug

combinations are optimized for narrow subsets of patients or even for each individual's unique genetic makeup. Whether used to explain a patient's response or lack thereof to a treatment, or act as a predictive tool, it hopes to achieve better treatment outcomes, greater efficacy, minimization of the occurrence of drug toxicities and adverse drug reactions (ADRs). For patients who have lack of therapeutic response to a treatment, alternative therapies can be prescribed that would best suit their requirements. In order to provide pharmacogenomic recommendations for a given drug, two possible types of input can be used: genotyping or whole genome sequencing [3].

Ethical principles related to pharmacogenomics

Over the years, a number of guidelines have been set to ensure that biomedical research is performed in an ethical manner. The most important of them is the Declaration of Helsinki, which was issued by the World Medical Association in 1964.In recent years, the United Nations Educational, Scientific and Cultural Organization (UNESCO) has also issued declarations regarding the human genome, human genetic data, bioethics and human rights, the latest being the Universal Declaration on Bioethics and Human Rights. This declaration discusses in detail the ethical issues relating to pharmacogenomics and its implications for health in developing countries. With regards to bioethics, the fundamental principles are:

- Respect for other human beings as moral equals (autonomy)
- The absolute need to avoid harming other human beings by our actions (non-maleficence)
- The relative need to do good to other human beings and to ensure that our actions are calculated always to achieve more beneficial than harmful effects (beneficence)
- The need to treat other human beings fairly, without unduly exploiting or otherwise deceiving them (justice).

These principles provide a framework for thinking through ethical questions in pharmacogenomics. Thus, each ethical issue will need to be considered in light of balancing these principles so that the most appropriate course of action can be decided upon [4].

Research and Development

The information to be used in clinical trials needs to be protected. This includes issues relating to consent, privacy and confidentiality [5].

The pharmacogenomics drug trials and genetic databanks require that people submit a DNA sample for analysis. In both contexts, it is important to ensure that consent is obtained before samples or genetic data are gathered and that the privacy of the participants is protected, as is the confidentiality of the genetic material. In pharmacogenomics research, as in other kinds of medical research, consent requires that participants "should be informed about the risks of the study, have the right to withdraw from studies at any point, and must give their explicit consent to participation." The Council for International Organizations of Medical Sciences (CIOMS) emphasizes that consent to pharmacogenomics trials should be voluntary as a matter of respect for autonomy. This means that participation in the clinical trial should not be dependent on the subject's involvement in a pharmacogenomics substudy. In their view, for studies that are specifically designed so that inclusion is based on the subject undergoing a pharmacogenomics test, participation is thus dependent on agreement to undergo such a test and thus participation in the study cannot be separated from their involvement in the clinical trial. UNESCO Declaration on Bioethics and Human Rights emphasizes that any scientific research should "only be carried out with the prior, free, express and informed consent of the person concerned."

CIOMS states following items to be included in informed consent forms [6]

- A statement of clear rationale
- Fields of study for sample use
- Length of time the samples will be stored
- Sample coding
- Options to withdraw the sample
- Expected benefits to the patient or others (if any)
- Potential risks

- Treatment of and participant's access to the study results
- Handling of intellectual property generated from the use of samples
- Ownership or custodianship of sample
- Ownership or custodianship of data
- Access to samples and data
- Liability of the investigator

The implications for patients will depend on how easily samples can be traced back to them. Hence it is essential to maintain anonymity. 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 be suitable for a long term follow-up and in event of an adverse effect of drug. Hence it is imperative 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 [7].

Participants need to know whether the research is likely to give rise to information that is directly relevant to their health. In such cases, researchers may provide individual feedback to patients or offer individual test results only if patients ask for the information.

Before starting the research, it is important to conduct an ethical review of proposed research and that this review process should be undertaken by at least one independent research ethics committee. Independent ethical review is necessary for pharmacogenomics research to ensure that research proposals are ethically appropriate and that proper measures involving consent, privacy, the future use of genetic samples and other research issues are appropriately addressed.

Public policy

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 [8].

Since Healthcare providers operate on limited budgets, Pharmacogenetics will provide information that is relevant to these assessments by allowing more accurate prediction of the cost of a treatment. 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.

Ethnic variation

Although pharmacogenomics offers many potential benefits, one aspect that may hinder further progress in the field is the controversy over the use of race and ethnicity in pharmacogenomics research. 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. 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 ethnic classification. Studies in population genetics, however, have demonstrated that substantial genetic variation occurs within populations [9]. The use of ethnicity in genetics research is controversial in many ways. Despite this controversy, evidence suggests that there may be an association between ethnicity and variable drug response.

Clinical issues

With the introduction of pharmacogenetics many more patients are said to undergo genetic testing than before. Accessible information and reliability of the sources remains important for both 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 and required. These tests could be carried out either in GPs' surgeries, at a hospital, or at specialized testing facilities. However, the nature of the information revealed by the test also needs to be considered. There has been debate whether written consent forms and genetic counselling will be necessary when patients have pharmacogenetic tests. The possible factors to be considered include which information should be revealed and whether the test also reveals any additional information such as likely response to other medicines or susceptibility to an unrelated disease.

However, should testing become available and affordable, in the clinical context it raises ethical issues around the level of informed consent required to carry out pharmacogenomics testing for the purposes of drug prescription, and the risks posed by secondary information gathered through pharmacogenomics testing [10].With the advances in pharmacogenetic the medicines may be licensed after pharmacogenetic test, to ensure a patient is not at risk of a serious adverse reaction. Pharmacogenetic information could be relevant to life insurers as well, either in assessing claims or setting premiums. 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.

Conclusions

Many drugs that are currently available are "one size fits all," but they don't work the same way for everyone. It can be difficult to predict who will benefit from a medication, who will not respond at all, and who will experience negative side effects. These genetic differences will be used to predict whether a medication will be effective for a particular person and to help prevent adverse drug reactions. The introduction of pharmacogenetics will have an impact on the way in which clinical trials are designed and managed. It is speculated that pharmacogenetics can be used to improve the existing medicines as well.

The field of pharmacogenomics is still in its infancy. Its use is currently quite limited, but new approaches are under study in clinical trials. 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. In the future, pharmacogenomics will allow the development of tailored drugs to treat a wide range of health problems.

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