Ethical questions in the field of pharmacogenetics

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Abstract
This article, which is partly based on an article by Delden et al [1], discusses ethical issues which play a role in pharmacogenetics. Developments in pharmacogenetics have a big impact on many different areas, such as clinical trials, the practice of medicine and society at large. In clinical trials, questions arise regarding the exclusion of genetic subgroups that may be non- or poor-responders to the experimental drug. Also, there is the question of how pharmaceutical companies should deal with their growing knowledge about the relationship between genetic variation and adverse effects. Moreover, pharmacogenetics could provide disease-specific predictive information which could have a significant impact on the relationship between physicians, patients and their relatives in the practice of medicine. Here, issues also arise regarding responsibility of patients and physicians for health and disease. In society at large, the high cost of new pharmacogenetic possibilities leads to questions concerning equitable distribution at a national, as well as an international, level. It is concluded that in the near future, ethical research should be focused on the themes of responsibility, inclusion and exclusion and global justice.

Keywords
Pharmacogenetics, ethical aspects, responsibility, (global) distributive justice

Introduction

Developments in pharmacogenetics have changed — and could affect — pharmaceutical research, drug development, practice of medicine and society in a significant way. Current scientific debate also pays attention to ethical questions related to these developments. Some say that because of problems associated with the introduction of genetically-modified food in Europe, the industry is aware of the importance of ethical concerns and the opinion of the general public; to quote Hedgecoe: "The ethical debate is an integral part of bringing a product to the market" [2].

In the field of ethical debate, one important question to ask is that about the difference between genetic testing in relation to pharmacological effects of drugs, and genetic testing in relation to predisposition of diseases. According to Roses [3], these two forms of genetic testing differ in important ways; genetic testing for predisposition of diseases raises serious ethical issues such as the right (not) to know and the access to insurance (e.g. life, medical), whereas pharmacogenetic testing does not raise such issues. Roses believes that genetic testing in relation to pharmacological effects of drugs does not deal with the same problems, because these tests only give us informa-

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tion about drug response. This article, however, will show that pharmacogenetic testing can lead to similar problems. Furthermore, it will bring up examples of ethical questions beyond those related to these two forms of genetic testing. Ethical questions that could arise as a result of possible developments in pharmacogenetics will occur in several fields: scientific research and pharmaceutical industry, medical practice and society at large.

Drug research and pharmaceutical business

Pharmacogenetics is essentially about the stratification of patients or diseases into new sub-groups or types. Genetic variation can contribute to differences in drug response. This potential to show genetic variation and to stratify patients into subgroups raises ethical questions regarding justice. The moral principle of justice holds formally that equals should be treated equally and those who are unequal treated unequally [4]. Such a formal principle, however, does not give us much guidance: we have to determine what kinds of differences between individuals or groups are morally relevant. Context is of importance in answering this question: for example, access to health care should be determined by medical need whereas in the field of education, students have to be judged upon their intellectual capacities and effort. The crucial question is whether the potential of pharmacogenetics to stratify can lead to injustice: are subgroups unjustly being excluded or included [5]?

As a result of the developments in pharmacogenetics, the process and design of drug research could change (and is already changing). Currently, large numbers of subjects are included in trials to test for benefits and side effects. If dangerous side effects result in some of these patients, the new drug has to be discarded. This situation can be prevented by including in phase II and phase III studies only those subjects who are expected to respond well to a drug on the basis of their genetic profile. This will make drug research more efficient, less expensive and increase the chance of a drug being introduced on to the market. The counter effect of the genetic selection of trial subjects implies that the drug is no longer fully tested on the general population and therefore no guarantee can be given that the drug can be used by other patients outside the tested group. Considering the wide-spread off-label use, this could have dangerous consequences.

Panel: Sources of information

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Pharmacogenetic screening can be carried out before subjects take part in a trial. This screening could yield important information on the relationship between genotype and drug response and even about disease risks. Apart from concerns regarding the possibility of informing subjects adequately about such complex information, privacy should be respected by separating genetic data from their personal information. However, when clinical trials produce clinically useful data, subjects should be given the opportunity to receive feedback as part of the informed consent process [6]. A conflict between respecting privacy and the need to provide subjects with useful information arises.

Stratification into patient and disease subgroups raises questions about what kind of strategy pharmaceutical companies will and should choose: should they keep their markets as large as possible by developing drugs suited to multiple genetic subgroups of patients or should they divide their markets by developing a variety of drugs tailor-made to different subgroups of patients? The consequence of the first option would be the exclusion of individuals with rare disorders and the creation of new orphan populations [7]. Although the scientific and technical possibilities are there, organisational barriers and weak financial incentives can undermine responsible development and application of pharmacogenetic technology [7].

Finally, genetic screening of participants in drug research will increase the pharmaceutical companies' knowledge about the association between genetic profile and drug response. An ethical question arises: does the growing knowledge of pharmaceutical companies imply a greater responsibility regarding drug safety? A few years ago, a pharmaceutical company introduced a vaccine for Lyme disease. The company was sued by patients with a specific genotype who suffered severe drug-induced arthritis after vaccination. It was known that the vaccine may somehow trigger treatment-resistant arthritis. However, there was no such warning on the product [8]. The pharmaceutical company stopped selling the vaccine in February 2002 and agreed in 2003 to an out-of-court settlement of more than 1 million dollars (700,000 euros) for the plaintiffs for legal fees and costs [9]. Pharmaceutical companies are obliged to report available knowledge about drug response and genetic profiles in patient information and product labels. However, what should we do when the amount of information keeps increasing? To what extent should the results of pharmacogenetic tests be included in drug labelling [10]? At some point, the amount of information could simply be too much to provide to each individual patient. In addition, this assumes that every patient is aware of his/her pharmacogenetic profile.

Medical practice

If pharmacogenetic screening is shown to have clinically significant outcomes, pharmacogenetics could have a profound impact on clinical practice. It could change the nature of a consultation radically, as currently the policy is most often "let's try and see" [11]. Patients could experience less reluctance in taking medicines which could lead to more medication compliance. Less harm caused by side effects will occur which could result in a more cost-effective health service. However, using pharmacogenetic testing in medical practice requires adequate knowledge of healthcare practitioners. Hospital pharmacists could play an important role here in informing physicians, particularly because of the "issue of polypharmacy and phenocopies" (an environmentally induced phenotype mimicking one usually produced by a specific genotype) [11]. Hapgood mentions the example of "a genotypic fast metaboliser who requires a high dose of a SSRI (selective serotonin reuptake inhibitor) in order to be effective, but if given haloperidol (which inhibits the activity of the enzyme concerned) becomes a phenotypic slow metaboliser prone to side effects" [11]. As well as knowledge, the health professional needs a high level of expertise in order to communicate to patients the advantages and disadvantages of testing. This will not be an easy task to perform considering the complex nature of the information; test results are probabilistic instead of binary, and the decision will also be based on health economics [11]. Studies show that patients have a poor recollection of information; according to one study patients remember 20% of the information provided by the physician [12].

Apart from the informed consent issue, there are other ethical questions that could occur concerning genotyping. For example, testing could reveal a patient to be a non- or poor-responder for all available drug options. In such cases, genotyping could provide no advantage but only the knowledge that he or she probably cannot be treated. When a test result is probabilistic, who determines when treatment should be withheld — the doctor, the professional organisation, or the patient? Should the patient's wish to be prescribed medication without a test be respected? Situations like these raise new questions concerning the responsibilities of physicians and patients.

Another ethical question concerns the influence of increasing knowledge on the relationship between physicians, patients and relatives. Some have argued that it is important to distinguish between genetic testing in relation to pharmacological effects of drugs, and genetic testing in relation to predisposition of diseases [3]. Roses argues that it is important to distinguish between both forms of

genetic testing because such testing in relation to risk factors predisposing for diseases is burdened with important issues regarding privacy, the access to employment and insurance, and the right to decide about relevant information on life-threatening diseases (or the right not to know) [3]. Roses believes that genetic testing in relation to pharmacological effects of drugs does not deal with the same problems, because these tests only give us information about drug response; this is knowledge with restricted implications.

However, pharmacogenetic testing also raises ethical questions that are linked to disease-specific predictive genetic testing [10]. As a fictitious example, we can take an elderly woman who suffers from Alzheimer's disease. For one subtype of this disease, which is strongly genetically determined, an effective drug is available that slows down the progress of the disease. To know whether or not the woman has this subtype, she should be genotyped. This could, however, also affect the woman's children: if she turns out to have this genetic subtype, they will know that they have a markedly increased risk of developing Alzheimer's disease themselves. What should the physician do if the children do not want to acquire this kind of information? If they refuse to let their mother be genotyped, it will not be safe to treat her with the new drug, which is possibly most effective.

Such ethical concerns are not restricted to the above-mentioned case: pharmacogenetic testing for other conditions such as heart disease, stroke, bladder cancer and schizophrenia can also unveil risks for family members. According to Hedgecoe, clinicians attributed the 'indigenous morality' of Alzheimer's disease to the fact that pharmacogenetic testing is not current practice in Alzheimer's disease clinics [13]. Instead of characterising it as an *indigenous* morality, this practice can result from a critical evaluation of the arguments for and against testing [relevant arguments are, for example, the existence of a link between genetic status and a patient's response to a drug, reliability of the test (false positive and false negative test results), the severity and onset of the disease, availability of adequate therapy and hereditary transmission]. However, Hedgecoe rightfully emphasises the importance of taking ethical concerns seriously [13]. The question whether or not, and under which conditions it is morally right to offer genetic testing to individuals for late-onset diseases, for which adequate therapy is lacking, should be evaluated case by case. What the above case of Alzheimer's disease shows is that developments in pharmacogenetics could strengthen mutual dependence between relatives, and important ethical principles, such as the principle of autonomy and the right not to know, should be reconsidered.

Society at large

It is expected that drugs that are tailor-made for a smaller subgroup of patients will be more expensive than "bulk drugs". On a national level, the question arises: should these new pharmacogenetic applications be reimbursed by health insurance companies or should these costs be paid by the patients themselves? In many countries, healthcare systems are based on the principle of equity. However, insurance companies will not be able to reimburse all drugs that will be developed. This situation could create inequality between people who can pay for new technologies themselves and people who cannot afford to do so.

Pharmacogenetic testing produces information that is of interest to third parties such as employers and health insurers. For example, being a non- or poor-responder could be an indication for a shorter life-span. These issues will primarily arise in life and disability insurance companies which can decide who gets access to life insurance and for what premium. At present, however, in some countries a moratorium exists on the use of results of genetic tests in setting insurance premiums.

Problems regarding equity and distributive justice play a central role on a global level. ("Distributive justice refers broadly to the distribution of all rights and responsibilities in society, including, for example, civil and political justice" [14].) If it is true that pharmacogenetic-based drugs will be expensive, developing countries will have no chance of profiting from such developments, because they simply cannot afford it. On the other hand, developing countries need generic and affordable drugs that are suitable for large populations, suffering from, for example, malaria, tuberculosis, HIV and common parasites. If the pharmaceutical industry will invest heavily in pharmacogenetic-based drugs for western populations, this could reinforce the gap between the privileged and the non-privileged.

Finally, pharmacogenetics raises important ethical questions regarding race and ethnicity (15). Although pharmacogenetics is introduced as "personalised" and "individualised medicine", it is focused on stratifying patients in subgroups rather than by individual differences. Although the biological reality of race is widely criticised, research on human variation is being conducted along the lines of race and ethnicity [15]. Using race as an instrument to identify therapeutic populations can lead to negative consequences. For example, BiDil (isosorbide dinitrate and

hydralazine hydrochloride) was the first drug labelled exclusively for a racially-identified population, in this case to treat heart failure in African Americans. By using race as a target, companies can avoid the costly route of developing pharmacogenetic testing [15, 16]. Kahn wrote: "Medical researchers may say they are using race as a surrogate to target biology in drug development, but corporations are using biology as a surrogate to target race in drug marketing" [16]. Moreover, focusing on notions of racial biology can lead to a neglect of socio-environmental factors that cause population-based differences in health status [15].

Conclusion

This article focuses on the ethical questions raised by developments in pharmacogenetics. Pharmacogenetics has the potential to influence scientific research, pharmaceutical industry, practice of medicine and society at large profoundly. This could generate its own unique dynamics which will require new ethical research. We suggest the notion of "responsibility" will be a major focus of such research.

First, there is the responsibility of companies involved in the pharmaceutical industry: considering the special nature of health, does their responsibility involve more than the pursuit of gain and if so, which moral principle should guide prioritisation of drug discovery? Secondly, the responsibilities of healthcare providers need to be defined: who (doctors, pharmacists, clinical chemists) is responsible for applying pharmacogenetic knowledge and products (genotyping)? What kind of counselling is needed? What should be the response to non- and poor-responders refusing genotyping? What about conflicting interests of relatives regarding genotyping? For practising (hospital) pharmacists this could increase their responsibility to inform physicians adequately as well as ensuring that prescriptions are compatible with the genetic profiles of their patients. Thirdly, pharmacogenetics could lead to more knowledge among patients and clients: such increased knowledge could move them to take more responsibility for their lifestyle and behaviour. Finally, the responsibility of the government has to be discussed. For example, what kinds of policies are necessary with respect to anticipated problems of new "genetic orphan populations" (i.e. small populations of individuals with a less prevalent genotype that may respond to drugs), the regulations and monitoring of clinical trials, the control of off-label use, the risk of discrimination and stigmatisation of populations stratified by race or ethnicity, guaranteeing access to life and disability insurers?

The first examples of utilisation of pharmacogenetic knowledge in medical practice are already here and it is expected that it is increasing. Ethical thinking about these themes will contribute to the progress and future of pharmacogenetics. The ethical questions raised in this article could be a helpful tool to initiate discussions that revolve around this topic. Because of their expertise and the multidisciplinary character of the profession, pharmacists should take a liaison position between the parties concerned in these discussions, and take the responsibility to communicate the outcomes.

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