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TAILOR-MADE PHARMACOTHERAPY: FUTURE DEVELOPMENTS AND ETHICAL CHALLENGES IN THE FIELD OF PHARMACOGENOMICS

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ABSTRACT

Pharmacogenomics is the study of the myriad interactions between genes and pharmacotherapy. Developments in pharmacogenomics have changed and will affect pharmaceutical research, drug development and the practice of medicine in a significant way. In this article, we make an inventory of the ethical implications that might arise as a result of possible developments in pharmacogenomics and investigate whether the present ethical framework will be able to adequately answer arising questions.

We think that many of the questions related to the consequences of pharmacogenomics are answerable along the lines of present ethical thinking. We also believe, however, that many 'changes of degree' may result in a 'change of kind.' We therefore think that pharmacogenomics may potentially have such a profound influence on scientific research and the pharmaceutical industry, the practice of medicine and society at large, that this will generate its own unique dynamic, which will require new ethical research. We suggest that the notion of 'responsibility' will be a major focus of such research.

I INTRODUCTION

Knowledge of the human genome is expanding rapidly. In February 2001, its entire nucleotide sequence was pub-

lished,[1] drawing scientific attention to the complex networks of genes and their products, and to the complex relations between genes, diseases and drug response. The field of bio-informatics plays an important role in this research, with its fast computerised processing of large amounts of data. As a result of the increasing knowledge of the genome, there have been unprecedented advances over the past few years in the understanding of genetically determined factors affecting the actions of drugs.[2] Furthermore, the increase in knowledge has raised expectations for a better classification and understanding of diseases, and the identification of genes related to diseases that might enable discovery of new drug targets and new indications for current drugs.

The field of 'pharmacogenomics' is a study of the myriad interactions between genes and pharmacotherapy. There is at present no consensus in the literature on the definition of this term, nor of the term 'pharmacogenetics.' Although these terms are often used interchangeably, in this article we prefer to use the term 'pharmacogenomics', which has a broader meaning. 'Pharmacogenetics' is the study of inter-individual variations in DNA sequence related to drug response. 'Pharmacogenomics' is the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response. The term is broadly applicable to drug design, discovery and clinical development.[3]

Developments in pharmacogenomics have changed and will affect pharmaceutical research, drug development and the practice of medicine in a significant way. The current scientific and social debates show confusion concerning the ethical, social and legal implications related to these developments. Some authors argue that these developments will be relatively harmless because predicting patients' responses to medicines yield information that is much less charged and comprehensive than knowledge regarding genetic risk factors for disease.[4] Other arguments exist that

[1] D. Baltimore. Our Genome Unveiled. *Nature* 2001: 409: 814–816. G. Venter, M.D. Adams, E.W. Myers, P.W. Li. The Sequence of the Human Genome. *Science* 2001; 291: 1304–1451.

[2] W.E. Evans & M.V. Relling. Pharmacogenomics: Translating Functional Genomics into Rational Therapeutics. *Science* 1999; 286: 487–491. H.L. McLeod & W.E. Evans. Pharmacogenomics: Unlocking the Human Genome for better Drug Therapy. *Annual Review Pharmacology Toxocology* 2001; 41: 101–121.

[3] European Agency for the Evaluation of Medicinal Products. 2003. *Position Paper on Terminology in Pharmacogenetics*. Cf. Food and Drug Administration. 2003. *Guidance for Industry Pharmacogenomic Data Submissions*. Draft guidance. Washington. FDA.

[4] A.D. Roses. Pharmacogenetics and the Practice of Medicine. *Nature* 2000; 405: 857–865.

the related ethical, social and legal problems are comparable to those known in genetic testing for disease predisposition.[5]

In this article, we pose the question of whether there are and will be significant ethical questions regarding pharmacogenomics. We aim to make an inventory of the ethical implications that might arise as a result of possible developments in pharmacogenomics and to investigate whether the present ethical framework will be able to adequately answer arising questions.

II STATE OF THE ART

Inheritance is located in the DNA, which consists of paired chains of chemical elements called nucleotide bases. Random mutations in the DNA occur on average once in every 200 base pairs.[6] If a certain genetic mutation can be found in at least 1% of the population, it is called a genetic polymorphism. Genetic polymorphisms can in principle be easily determined by a genotype test. The simplest type of DNA mutation is called a single nucleotide polymorphism (SNP), or mutations in single nucleotide bases of the DNA. SNPs exist throughout the human genome with an incidence of approximately 1 per 1000 base pairs. Mutations have a major effect on the way that DNA is translated to proteins, and play a large role in the variation of a drug response that can be observed between individuals. Genetic polymorphisms influence drug response via three different routes: by affecting the processing of drugs by the body (pharmacokinetics), by modifying the proteins that are targeted by drugs (pharmacodynamics) and by influencing the risk of acquiring certain diseases (disease pathways). In the following sections, we will examine in detail the current scientific knowledge of all three routes.

II.i Inter-individual variation in drug response: pharmacokinetics

Side effects of medication occur more commonly than previously thought: in the United States, serious side effects occur in about 7% of the hospitalised population using medication and excluding incorrectly prescribed medicines.[7] Many side effects occur

[5] G. de Wert & R. Vos. 1999. Farmacogenetica: Een Ethische Verkenning. In *Ziekten Maken en Breken. Over Farmacogenomie.* J.J.E. van Everdingen, A.F. Cohen & G.T. Feenstraet, eds. Amsterdam. Boom: 99–112.

[6] J.J.E. van Everdingen, A.F. Cohen & G.T. Feenstraet, eds. 1999. *Ziekten Maken en Breken. Over Farmacogenomie.* Amsterdam. Boom.

[7] J. Lazarou, B.H. Pomeranz & P.N. Corey. Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-Analysis of Prospective Studies. *JAMA* 1998; 279: 1200–1205.

because patients differ in the way their bodies process a drug. This difference is caused by genetic polymorphisms that influence the proteins that absorb, distribute, metabolise and eliminate drugs.[8] Variation between individuals in drug processing because of genetic polymorphisms is called pharmacokinetic variability. Patients may be classified as poor, intermediate, extensive or ultra-rapid metabolisers – labels that give an indication of the speed with which a drug is processed. This processing influences the concentration of the drug in the cell plasma: if a drug is not metabolised quickly enough, it may reach a concentration so high that it may become toxic. Normally, high plasma concentrations of an active compound are associated with an increasing risk on side effects, while low plasma concentrations will diminish the therapeutic effect.

Knowledge of genetic polymorphisms can be of interest for a great number of patient groups, particularly in psychiatry and oncology.[9] An example from psychiatry is the tricyclic antidepressant, amitriptyline, which is metabolised by the cytochrome P-450 enzyme CYP2D6. In the Netherlands, about 3.5% of the population is a ultra-rapid metaboliser for CYP2D6,[10] which means that the enzyme breaks down the drug so quickly that there is not enough time for the drug to fully exert its therapeutic effect. Ultra-rapid metabolisers thus present an increased risk for therapeutic resistance. For a large number of psychiatric drugs, the therapeutic effect can be observed only after four to six weeks; for a depressed patient, therapeutic failure after six weeks means a substantial decrease in the quality of life. Instead of a trial-and-error process, knowledge of the patients' CYP2D6 genotype can be a helpful tool in the decision making process: ultra-rapid metabolising patients could then be prescribed another antidepressant, which depends less on the CYP2D6 metabolism.

Thus, knowledge of the patient's genotype for metabolising enzymes can aid in the choice of the most suitable drug, in the adjustment of the dose that is given, and in predicting interactions between different drugs as a result of pharmacokinetic characteristics.[11]

[8] U.A. Meyer. Pharmacogenetics and Adverse Drug Reactions. *Lancet* 2000; 356: 1667–1671.

[9] Gezondheidsraad (Health Council). 2000. *Farmacogenetica*. Den Haag. Gezondheidsraad.

[10] L.W.S. Steijns. Snel Geneesmiddelenmetabolisme: Detectie van Cytochrome P450–2D6-genduplicatie. *Ned Tijdschr Geneeskunde* 1998; 142: 2604.

[11] F.S. Collins & K.G. Jegalian. Deciphering the Code of Life. *Scientific American* 1999; December: 50–55.

II.ii Inter-individual variation in drug response: pharmacodynamics

Similar to the focus of pharmacokinetics on interactions between drugs and metabolic enzymes, pharmacodynamics is concerned with interactions between a drug and the proteins the drug is meant to target. Simplified, one could say that pharmacodynamics is concerned with the desired effects of a drug (related to the question whether someone responds or not), while pharmacokinetics deals with the course of a drug through the body from intake to elimination. Most drugs exert their pharmacological effect by means of their interaction with target proteins such as membrane receptors, enzymes, or ion channels.[12] Individuals with identical concentrations of a certain drug in the plasma can still vary in their response.[13] This variation depends on the type and amount of receptive target molecules a patient has for that drug. Genetic variation can influence those target molecules by changing the amount of receptors, or by changing the structure of the target proteins.

One of the best-studied polymorphisms influencing a drug receptor is the homozygote Gly16-genotype in which there is a decreased amount of beta2-adrenergic receptors. This receptor is the target of beta agonists, a type of asthma medication. Patients with the homozygote Gly16-genotype have a minimal response to beta2-agonists because they have less target receptors than other patients; steroids are an alternative for some of these patients.

II.iii Inter-individual variation in drug response: disease pathways

The third route through which genetic polymorphisms influence drug response focuses on the interactions between genetic predisposition to disease and the effect of drugs. Genetic polymorphisms that influence the risk of certain diseases can also be a major determinant of drug efficacy or toxicity. Patients with a genetic variation called 'Factor V Leiden' have an increased risk of a venous thrombosis (a clotting of blood in the veins). The use of oral contraceptives itself results in a somewhat higher risk of this adverse event, but women who have both the mutation and use oral contraceptives run a much larger risk than the sum of the risk factors for mutation and contraceptive use alone.[14] This

[12] J. Drews. The Role of Innovation in Drug Development. *Nature Biotechnology* 1997; 15: 1318–1319.

[13] D.M. Roden & A.L. George, Jr. The Genetic Basis of Variability in Drug Responses. *Nature Reviews* 2002; 1: 37–44.

[14] J.P. Vandenbroucke, F.J.M. van der Meer, F.M. Helmerharst & F.R. Rosendaal. Factor V Leiden: Should we Screen Oral Contraceptive Users and Pregnant Women? *Br Med J* 1996; 313: 1127–1130.

example highlights that a drug known to cause a certain adverse event in combination with a genetic polymorphism associated with the same adverse event can lead to a marked increase in the risk of drug toxicity.

An interesting finding is that disease-associated polymorphisms may also influence the effect of a drug, when the proteins that are expressed by that polymorphism are not itself directly involved in the pharmacological actions of the drug. An example of this type is seen in the treatment of Alzheimer's disease with the drug tacrine. The apolipoprotein E-genotype (apo E) determines the extent of choline acetyltransferase expression in patients. Several apoE-subtypes exist in the population, which have no direct relation with the target proteins of tacrine. However, it was found that 40% of the patients with an apoE4 genotype showed an improvement in total response and cognitive response to tacrine therapy, compared with 83% of the patients without an apoE4 genotype. Although the specific interaction between the apo-genotype and tacrine therapy has not yet been elucidated, the relationship provides a putative genetic approach for selecting therapy for this disorder.[15]

Interactions between genetic polymorphisms influencing disease risks and drug response indicate that pharmacogenomics and the discipline of disease genetics do overlap.[16] Knowledge of an individual's pharmacogenomic profile may in several cases also give information about disease risks. We will return to this point, which is connected with ethical questions, later.

III POSSIBLE FUTURE DEVELOPMENTS

In this section, possible future developments in pharmacogenomics will be sketched, together with the ethical implications of such developments. As a framework for discussion, we will distinguish three different social fields in which these developments will manifest themselves: scientific research and pharmaceutical industry, the practice of medicine, and society at large.

[15] M.R. Farlow, D.K. Lahiri, J. Poirier, J. Davignon, L. Schneider & S.L. Hui. Treatment Outcome of Tacrine Therapy Depends on Apolipoprotein Genotype and Gender of the Subjects with Alzheimer Disease. *Neurology* 1998; 50: 669–677. McLeod et al., *op. cit.* note 2.

[16] H.G.M. Leufkens. 2001. De Betekenis van 'Genomics' voor de Toekomst van de Farmacotherapie. In *Geneesmiddelen nu en in de Toekomst: Volksgezondheid Toekomst Verkenning 2002*. H. Timmerman & A. van den Berg Jeths, eds. Bilthoven. RIVM: 491–504.

III.i Scientific research and pharmaceutical industry

Drug Discovery

At the end of the last century, only 483 different molecules were used as targets for available drugs.[17] Substantial investments have currently been made in the pharmaceutical and biotechnological industries to use genomic strategies for the discovery of novel targets. Two broad pharmacogenomic strategies are used to identify disease-related genes and to search for protein products that can be used as drug targets: discovery genomics and discovery genetics.[18]

Discovery genomics attempts to identify all kind of genes that code for receptors and enzymes, whose function can be readily modified by chemical compounds and against which a lot of compounds can be tested. In general this genomic identification process does not provide information on the relevance of a gene to a disease, but results in a collection of genes that code for proteins that could possibly be drug targets. Functional genomic technologies can then be used to gain insight into the role of these genes and the proteins they encode in disease processes. Discovery genetics, on the other hand, identifies genes that are involved in the susceptibility to major common diseases. A susceptibility gene may influence the age of onset of a disease, contribute to its rate of progression, or protect against it (resistance gene). Once a gene associated with a disease has been identified, the function of that gene needs to be defined by using functional genomic technologies. For example, a disease-associated gene variant may code for a specific enzyme. Once the role of the enzyme has been identified and its relationship to the disease is understood, it might provide a target for new drugs.[19]

Such developments in pharmacogenomics could make it possible to develop new drugs in a systematic and grounded way. Knowledge of causal processes, together with knowledge of the compounds that are involved in it, can then be a lead for finding appropriate ways in which drugs could intervene.[20] Modern data mining techniques in bio-informatics will enable automated processing of large amounts of data. It is estimated that by employing

[17] J. Drews. Biochemical Classes of Drug Targets of Current Therapies. *Science* 2000; 287: 1960.

[18] A.D. Roses. Pharmacogenetics and Future Drug Development and Delivery. *Lancet* 2000; 355: 1358–1361.

[19] Evans et al., *op. cit.* note 2. Roses, *op. cit.* note 18. Roses, *op. cit.* note 4.

[20] F.S. Collins & V.A. McKusick. Implications of the Human Genome Project for Medical Science. *JAMA* 2001; 285: 540–544.

these new research strategies, the human genome will ultimately reveal at least 5000 to possibly 10 000 novel protein targets for potential drugs.[21] Some of these new pharmacogenomic drugs are already on the market.

A first issue that might arise as a result of such developments is the prioritisation of research: which disease should be the first target? It is expected that the first future drug discoveries based on pharmacogenomics research will be found in the field of frequently occurring diseases such as cancer, cardiovascular diseases and asthma.

Secondly, such new strategies in drug discovery combined with increasing possibilities to genotype patients might contribute to a more or less tailor-made pharmacy. Patients might be divided into subgroups with similar genotypes, for which drugs could be developed to specifically fit patients with that genetic profile. However, there will always be patients who turn out to have a rare genetic profile that does not fit in any of the 'common' subgroups: possibly, many small groups might emerge for whom no tailor-made drugs will be developed because the target group is just too small to make it profitable. This might raise problems of equity and fair distribution: patients who genetically fit into one of the subgroups could be treated with a tailor-made drug, while other patients would receive the 'bulk drug' that is known not to be the ideal medicine for them, due to the lack of a specific alternative.

Clinical Drug Trials

The process (design) of clinical trials will probably change because of developments in pharmacogenomics and, in fact, is already beginning to change. Until recently, large numbers of subjects were included in trials to test for benefits and side effects. If dangerous side effects resulted in some of these patients, the new drug had to be discarded.[22] This is one reason for the current slowdown in innovative medical therapies reaching patients, as the FDA recently noted.[23] The failure of a drug may be prevented by including, in later phases of the drug testing process, only those subjects who are expected to respond well to a drug on the

[21] N.P. Peet & P. Bey. Pharmacogenomics: Challenges and Opportunities. *Drug Discovery Today* 2001; 6: 495–498.

[22] M.A. Rothstein & P. Giffin Epps. Ethical and Legal Implications of Pharmacogenomics. *Nature Reviews Genetics* 2001; 2: 228–231.

[23] Food and Drug Administration. 2004. *Innovation or Stagnation?* Washington. FDA.

basis of their genetic profile. This selection would make clinical trials cheaper and more efficient, and reduces the risk that a drug has to be discarded. But every coin has its flip-side: the genetic selection of trial subjects implies that the drug is no longer fully tested on the general population and the pharmaceutical company can give no guarantee that the drug can be safely used by patients with a genotype different from that of the tested group.[24]

Another consequence of changes to the process of clinical drug trials is that all subjects will be genetically screened before taking part in a trial. Linking genetic profiles of research subjects to their responses to the tested drug in an early phase of the study (before the good-responders are selected) could yield important information on the relations between genotype and drug response. This screening does, however, yield information about the subject being a responder or a non-responder, and might even give information about disease risks. In most cases genetic data are separated from their personal information. Conversely, in some cases, knowledge might be acquired that might be useful or advantageous for individual patients to know; for instance, if an adequate treatment or preventive measure does exist. When a clinical trial is likely to produce validated and clinically useful data regarding individual participants, they should be offered the opportunity to receive individual feedback as part of the process of obtaining consent.[25]

Pharmaceutical Business

As scientific knowledge on inter-individual variation in disease processes and drug response increases, the pharmaceutical industry will probably be confronted with an increasing differentiation in patient categories. For instance, patients with breast cancer might be subdivided into several (small) groups with different genetic profiles. Regarding such differentiation, a first important issue for pharmaceutical companies is to decide which route to follow. They might try to develop drugs that are suited to multiple genetic subgroups of patients, to keep their markets as large as possible. Or, they might decide to divide their markets and start developing a variety of drugs tailor-made to the different subgroups of patients. Some, however, argue that only the latter option is viable: as scientific and technological possibilities for

[24] A.M. Issa. Ethical Considerations in Clinical Pharmacogenomics Research. *Trends in Pharmacological Sciences* 2000; 21: 247–249.

[25] Nuffield Council on Bioethics. 2003. *Pharmacogenetics. Ethical issues.* London. Nuffield Council.

differentiated drug development proceed, the industry will have the responsibility to use those possibilities. The tendency that consumers do hold companies more responsible for side effects occurring as a result of genetic variation than in the past can already be observed. Rothstein et al. describe an example of a lawsuit that a group of patients filed against a pharmaceutical company, alleging that the manufacturer of a vaccine for Lyme disease knew that some individuals would be susceptible to arthritis on exposure to the vaccine because of their genotype, but failed to provide appropriate warnings.[26]

Another issue regarding differentiation of patient categories is related to costs. Controversial opinions exist concerning the way the costs of such 'individualised drugs', would develop. Some expect more efficiency in the drug development process and/or more efficiency in the application of drugs to patients (because the trial-and-error process can be replaced by a more grounded drug prescription), which might save a lot of money. On the other hand, the development of more tailor-made drugs will also imply that the markets for these drugs will become smaller, which will raise prices for consumers. Also, some argue that developing pharmacogenomic drugs will require large financial investments by pharmaceutical companies, for instance to set up costly technological facilities. Such investments are translated into rising prices.

III.ii Practice of medicine

Conceptualisation of Disease

Pharmacogenomics could reinforce changes already initiated by human genetic research at large. By accumulating knowledge about the exact genetic and biochemical routes via which disease processes operate, the conceptualisation of disease could change. The concept of disease might be widened to include not only present illness but also a genetic predisposition to disease. This could imply that the boundaries between health and illness become more vague, as it is likely that almost every individual does have some genetic predisposition for some disease. Also, the genetic component of the causation of disease will probably play a larger role in the future disease concept. Medical diagnosis and treatment will no longer only be focused on symptoms (the phenotype), but also on genetic causal factors (genotype).

[26] Rothstein et al., *op. cit.* note 22.

A first consequence of such a change in the conceptualisation of disease could be that less attention is paid to the behavioural and environmental influences on disease. Patients and healthcare professionals might start embracing a version of determinism in which their genes are held completely responsible for their health and their illness: attention towards life style and environmental influences might diminish.[27] This tendency has been described as 'geneticisation',[28] which can be seen as a specific type of medicalisation. It is important to keep realising that genetic influence is by far not the only causal factor in the occurrence of disease. It is certainly unwarranted to present human life as being almost completely genetically determined.

A second consequence could be that the structure of the disease system would change because, at present, a disease is defined by its symptoms, by its phenomenology. On that basis, categories of distinct and related diseases are formed, organising medical disciplines along these lines. This structure may change with more knowledge of the exact genetic and biochemical pathways of disease. For example, it might turn out that specific disease phenomenon result from different biochemical processes, and various distinct disease symptoms might be reduced to (almost) identical biochemical routes. Recent studies have discovered several significant differences in gene expression patterns of tumours in breast cancer and in leukaemia.[29] With such developments in mind, the question might be raised whether the organisation of medical disciplines using the organ system as a framework will still be adequate in the future.

Another consequence of the described change in the concept of disease could be an increase in opportunities to not only treat symptoms but also (genetic) causes, and prevent diseases from occurring by means of influencing lifestyle habits and preventive medication. Such an emphasis on prevention could come into conflict with the increase in genetic determinist attitudes in patients that was described earlier. The appeal to individual responsibility of patients for their own health and disease might become stronger with increasing knowledge about predispositions. As a patient learns more about his health risks, he could

[27] A.M. Issa. Ethical Perspectives on Pharmacogenomic Profiling in the Drug Development Process. *Nature Reviews* 2002; 1: 300–308.

[28] A. Lippman. Led (Astray) by Genetic Maps: The Cartography of the Human Genome and Health Care. *Social Science and Medicine* 1992; 35: 1469–1476.

[29] G.S. Ginsburg & J.J. McCarthy. Personalized Medicine: Revolutionizing Drug Discovery and Patient Care. *Trends Biotechnology* 2001; 19: 491–496.

adjust his lifestyle habits accordingly. On the other hand, it is also possible that the patient may hold his genes responsible for the occurrence of disease and feel reduced personal responsibility for his health.

Genotyping in the Practice of Medicine

Many experts seem to expect that genotyping before the start of a pharmacological treatment will become a standard diagnostic procedure in the (near) future. The benefit will be that the occurrence of serious side effects in medication could be reduced.[30] The dosage and type of a drug that is administered can be adjusted on the basis of a patient's pharmacokinetic profile. By reducing side effects, it can be expected that compliance of patients to their treatment will grow; these two related effects could make pharmacological treatment in general more effective and efficient.

The prospects for genotyping in the practice of medicine are thus promising; still, some precautionary remarks should be made, and some problems mentioned. Although it has long since been possible to monitor pharmacokinetic and pharmacodynamic effects of medication (for instance by means of monitoring liver function), this is done relatively seldom by physicians, mostly because of time-pressure. Therefore, it remains to be seen whether new monitoring possibilities of genotyping shall be integrated in the medical practice routine. Besides, only recently is attention being paid to the role of genetic variability in the practice of medicine. The knowledge of inter-individual variation is accumulating fast, revealing more and more of the complexity of the relationships between genes, diseases and drug response. This complexity might make application in medical practice difficult.

The first problem that might occur in genotyping is that by testing the patient it might be revealed that the patient is a non-responder for all available drug options. The patient turns out to be an 'orphan' for whom genotyping provided no advantage, but only the knowledge that he probably cannot be treated. Secondly, as was stated earlier, genetic testing for pharmacogenetic profiles might in some cases also provide information on disease risks. New technologies are creating inexpensive ways of testing for many polymorphisms at one time.[31] People could then be tested for several kinds of diseases and for pharmacological profiles all at once, a technique called multiplex-testing. Even apparently

[30] Gezondheidsraad, *op. cit.* note 9.

[31] D. Melzer & R. Zimmern. Genetics and Medicalisation. *Br Med J* 2002; 324: 863–864.

neutral information on drug response might have unforeseen consequences: someone may turn out to be a non-responder for multiple drugs, which might give him the general label 'hard to treat.' Therefore, some patients might not want to be tested for pharmacogenetic profiles, as they do not want to gain knowledge that might put them in a disadvantageous position.

This leads to the question of what a physician should do if a patient refuses to be genotyped. He could give the patient the 'bulk drug', but by doing so he in fact gives the patient a sub-optimal treatment. Besides, he knowingly increases the risk of potentially dangerous side effects by not testing the patient. If such side effects emerge, who can then be considered to be responsible for them, the physician or the patient? Increasing knowledge about genetic influences on disease and drug response could thus change the relationship between doctors and patients in situations where medical decisions have to be made.

Another problematic issue could be that patients will *have* to make more choices: knowledge and possibilities increase, and this implies that more crossroads will appear at which a choice has to be made. An increase in possibilities for choice is not always only a positive thing. It is therefore important that scientific knowledge of the relations between genetic make-up, disease and drug response is translated into clear and reliable information for patients, which is available when wished for.[32] Besides, it is just as important that healthcare professionals advise and support patients with respect to the choices they have to make, and are able to give additional information where needed.

A final complicating feature of genetic testing is that knowledge about the patient might imply knowledge about his relatives as well. Just as patients might not want to acquire knowledge by a genotype test, other family members might not want to know either. The issue gets complicated in cases in which genotyping might be necessary to give the patient an effective treatment. A good illustration is the case of 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 the woman has this subtype, she should be genotyped. This information could however also have an effect on the woman's children: if she turns out to have this genetic subtype, they will know that they have a markedly increased risk for developing Alzheimer's disease themselves.

[32] Nuffield Council, *op. cit.* note 25.

III.iii Society at large

Scientific developments that are related to the field of genetics are often viewed with some suspicion, and can easily induce anxiety in laypersons.[33] Dynamics of attitude change, however, make it hard to predict how public opinion will develop; attitudes can change quickly over time. Concerning the public acceptance of developments in pharmacogenomics, an indicator might be that a general shift can be seen towards a more positive, accepting attitude towards biological influences on health and disease. This is, for instance, reflected in an increasing acceptance of biological treatments in psychiatry. It might be that the opinion towards developments in pharmacogenomics will be influenced by this positive attitude.

Information and education of the public seems of paramount importance as developments in pharmacogenomics proceed. A negative observation in this respect is that debates on genetic issues tend to be polarised. In discussions, the developments in pharmacogenomics are often labelled as either a miracle or, the other extreme, a monster. Such polarisation should be avoided as it paralyses the public discussion.

Developments in pharmacogenomics could change the self-image of individuals, and influence their conceptualisation of familial relatedness. With regard to the practice of medicine, such changes have already been discussed in the section on genotyping; here, the emphasis is on a more general public change in conceptualisation. A public attitude shift towards geneticisation, wherein health and disease are supposed to be for the larger part genetically determined, could diminish the experienced amount of personal freedom. The concept of familial relatedness might become more charged with interdependence when the importance of genetic relatedness increases. The way individuals deal with knowledge about their genetic make-up in many cases has consequences for other family members as well; therefore, individuals could acquire a new kind of responsibility for relatives.

Changing Relations between Consumers and the Healthcare System

An important issue is related to health insurance, especially with respect to the rising prices of drugs.[34] It is expected that drugs

[33] D.W. Nebert & E. Bingham. Pharmacogenomics: Out of the Lab and into the Community. *Trends in Biotechnology* 2001; 19: 519–523.

[34] M. Angell. The Pharmaceutical Industry – To whom is it Accountable? *New Engl J Med* 2000; 342: 1902–1904.

that are tailor-made for a smaller subgroup of patients will be more expensive than 'bulk drugs.' The question is, which costs should be reimbursed by healthcare insurances, and which costs should be paid by the patients themselves? Insurance companies will certainly not be able to reimburse all drugs that will be developed and the line has to be drawn somewhere. There is, however, a risk that a social situation will arise in which bulk drugs and certain cheap tailor-made drugs will be included in the health insurance package, while the expensive tailor-made drugs have to be financed personally, implying that these are only available for the 'privileged part' of society. Controversy may result between a growing emphasis on individual possibilities on the one hand, and solidarity and fair distribution on the other hand.

Also, the fact that consumers will have increasing possibilities for obtaining information about their genetic profile might have important consequences for insurance as well. Information about drug response might be interesting for insurance companies, as, for instance, being a non-responder to cholesterol-lowering drugs might be an indication for a shorter life span. These issues will primarily arise in life insurance companies, which can decide whether someone receives an 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.[35]

International Developments

Scientific research is getting more and more internationally organised. Therefore, increasing co-operations between international science groups are expected, especially as information technologies enable easy sharing of data. Also, social regulations and laws associated with scientific and technological developments will, within Europe, be increasingly organised on a centralised basis. Countries cannot decide for themselves which position to take on issues concerning pharmacogenomics; they would have to take international developments into account.

In some parts of Europe, these internationalising tendencies in regulation have caused a counter-current to emerge: small local movements have been formed that emphasise local colour, familiarity and craft (an example is the 'slow food movement' in Italy). The emergence of such movements can be seen as a protest to centralising tendencies, a local response to 'Brussels', the centre of power in the European Union. With regard to pharmaco-

[35] Nuffield Council, *op. cit.* note 25.

genomics, a similar field of tension between internationalisation and locality can be observed: the supply of drugs is regulated more and more on an international scale, whereas regulation of demand and reimbursements, on the other hand, becomes more and more regionally and locally organised. This creates problems with regard to tuning supply to demand.

Another important issue is the contrast between the developed and developing part of the world where problems of justice and solidarity play a central role. Unfortunately, it is expected that the gap between the privileged and the non-privileged will further increase as a result of developments in pharmacogenomics because technological progress will flow exclusively into the developed part of the world. If it is true that the drugs that will be developed on the basis of pharmacogenomic knowledge will be costly, developing countries will have no chance of profiting from such new developments, as they simply can not afford it. Also, on the other side, pharmaceutical companies will only develop drugs for which they can expect a reasonable profit. This development is reinforced by the recent rise in investment required to market a successful drug.[36] This could mean that in developing countries, a great number of orphan patients could emerge, for which the industry will not develop pharmaceutical treatments.

With respect to the development of new drugs, there seem to be different tendencies for developed and developing countries. In developed countries, there is a growing inclination towards differentiation in drug development, where drugs are tailored to genetic subgroups of patients. In developing countries, on the other hand, there is a need for generic and affordable drugs, which are suitable for large populations; the development of medication against AIDS is a logical example in this respect. This issue is also related to the regulation of patents on drugs. Pharmaceutical companies in developed countries might appropriate drugs that would on a global scale raise ethical and legal issues. Such patents would make it impossible for developing countries to produce cheap equivalents of existing costly drugs and, thus, widen the inequality in possibilities between the developed and the developing world.

Issues of justice and solidarity also play a role within the developed part of the world. Within the West, the United States does determine the market for the pharmaceutical industry. The United States determines which drugs are being developed because it forms the major part of the drug market. Europe has

[36] Food and Drug Administration, *op. cit.* note 23.

the advantage of being genetically related to Americans; therefore, they can profit from the same pharmaceutical therapies.

IV CONCLUSION

This article aimed to make an inventory of the ethical implications that might arise as a result of possible developments in pharmacogenomics. We also investigated whether there is in fact anything new, ethically speaking, in pharmacogenomics. Well then, is there?

It is sometimes argued that to deal with the moral consequences of pharmacogenomics, a new ethical framework is not needed.[37] We agree that many of the questions related to the consequences described above are answerable along the lines of present ethical thinking. We also believe, however, that many 'changes of degree' may result in a 'change of kind.' In this article, examples of these changes were described. We think therefore that pharmacogenomics potentially may have such a profound influence on scientific research and pharmaceutical industry, the practice of medicine and on society at large, that this will generate its own unique dynamics which will require new ethical research. We suggest that the notion of 'responsibility' will be a major focus of such research.

Future developments in pharmacogenomics raise important ethical issues that make the study of the meaning and range of responsibility urgent. We discern four stakeholders that are confronted with issues concerning responsibility. First there is the responsibility of pharmaceutical companies: should pharmaceutical companies take a moral responsibility that involves more than simply the pursuit of gain? Should they focus on 'bulk drugs' in order to make a profit or on orphan drugs? Which moral principles should guide prioritisation of drug discovery (which diseases first)? Does the fact that pharmaceutical companies are solely (financially) capable of developing pharmacogenomic drugs imply that it is also up to them to develop tailor-made drugs to small subgroups of patients?

Secondly, the responsibility of healthcare professionals will need to be defined: who (doctors, pharmacists, clinical chemists) is responsible for the application of new possibilities (genotyping)? What kind of counselling of patients is needed by whom?

[37] A. Buchanan, A. Califano, J. Kahn, E. McPherson, J. Robertson & B. Brody. Pharmacogenetics: Ethical Issues and Policy Options. *Kennedy Institute of Ethics Journal* 2002; 12: 1–15.

How to respond to patients refusing genotyping? How to deal with conflicting interests of relatives regarding genotyping?

Consumers are the third party whose responsibility will change in such a way that important ethical questions arise: there will be an increased responsibility for the (ill-)health of individuals (lifestyle, behaviour); genotyping will confront consumers with questions concerning their responsibility for relatives: does genetic interdependence imply a moral responsibility?

Finally, the responsibility of the government has to be discussed for the healthcare of the 'lost cases': patients for whom no tailormade drugs are available. The unavailability of these drugs can originate both from the specific genotype of the patient(s) involved as from the lack of money to buy them. The orphanisation problem, both of drugs and of patients, of course, returns on the level of the practice of medicine. There, real doctors have to deal with real orphan patients and we can only begin to imagine what this implies.

Of course, many of the possible implications described are precisely that: they are just possible and it is far from certain that they will come into effect.[38] Much depends on the success researchers have and much also on the way societies and governments respond to scientific developments in this field. Different scenarios are possible: they might react as a lame duck (just wait and see), a hawk (trying to regulate everything), an ostrich (ignoring the changes) or as a flamingo (focussing on the possible merits of these developments). This response will clearly influence the need for ethical deliberation. One thing will not change, however: even if pharmacogenomics fulfils only part of its promises, the resulting effects will require ethical thinking.

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[38] D.W. Nebert, L. Jorge-Nebert & E.S. Vesell. Pharmacogenomics and 'Individualized Drug Therapy': High Expectations and Disappointing Achievements. *American Journal of PharmacoGenomics* 2003; 3: 361–370.

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