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Abstracts

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Ethische, soziale und legale Aspekte
der Pharmakogenetik und -genomik

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Ethical, social and legal aspects
of pharmacogenetics and -genomics

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The individualization of diagnostics and therapy – An ethical problem?

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In the near future, the implementation of pharmacogenetic methods in the development of pharmaceuticals and in therapeutic practice will potentially result in new possibilities for a closer combination of genetic diagnostics and therapy. We will likely be able to optimize the individual effectiveness of pharmaceuticals, to adjust the dosage of medication as individually as possible, to avoid adverse reactions caused by the ingestion of medication and to better control the activity of pharmaceuticals within the organism.

Since diseases or the disposition to develop a disease are due to genetic factors that display individual characteristics, pharmacogenetic diagnostics basically allow an *individualization* of therapies or preventive measures. In this respect, "individualization" does not primarily refer to taking into account the "entire individual" during medical processes but the exclusive consideration of his genetic and biological situation based on the following principle: "Each individual has his or her own disease, disposition for diseases and medical history."

Through individualization and risk adjustment, patients' therapy could be made safer, more effective and more tolerable. For example, patients who are sensitive to pharmaceutical side effects could be identified quickly. By finding the right pharmaceutical with an optimal dosage for patients at an early stage, a high level of effectiveness in therapeutic intervention could possibly be reached at the start of treatment. Monitoring measures for potential toxic effects of administered pharmaceuticals could be decreased significantly. Costs incurred through the prescription of ineffective pharmaceuticals or treatment of the resulting pharmaceutical side effects could possibly be avoided. Furthermore, the required number of doctor's visits could potentially be reduced.

We can not seriously deny that this form of diagnostics opens up a variety of valuable options suitable for decreasing the suffering caused by diseases. However, this does not mean that pharmacogenetic diagnostics come without problems. Each (medical) technology does not just solve certain problems but creates new ones in the process. Ultimately, this also applies to the individualization potential inherent in this technology, which offers numerous opportunities for individual lifestyle planning, prevention and (in the future) also therapy. On the other hand, individualization could also become a vehicle for discrimination and a decline in solidarity.

The hopes for positive effects of pharmacogenetics are offset by a series of risks and problems, primarily relating to

- The *safety* of pharmaceuticals developed through pharmacogenetic methods;
- Ensuring the voluntariness of test participation and the *informed consent* of the tested individuals;
- The problems of *legal data and personality protection;* and
- The danger of the *stigmatization and discrimination* of individuals.

However, whether we will succeed in utilizing the great promise of pharmacogenetics for the benefit of the patients will also greatly depend on the ethical, societal and legal framework. In this respect, ethics must be understood as a quality assurance component of medicine today.

Aspects of pharmacogenetics and pharmacogenomics, patients' greatest hopes and/or worst expectations

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The latest scientific estimates and information state that

- There are about 150 million diabetes patients worldwide, but only about 50 million have been diagnosed as such,

- An increase to 300 million people worldwide is expected by 2025;

- About five million patients are treated for diabetes mellitus in Germany; the number of undisclosed cases may be as high as eight million;

- A total of USD 9 billion is spent on diabetes medication worldwide, USD 3.5 billion of this amount for insulin and USD 5.5 billion for oral antidiabetic drugs.

One needs to visualize these latter figures to get an impression of the possible growth of the pharmaceutical industry. To do so, one must get an idea of the manner of growth.

Interestingly, a human insulin / analogon was among the four new genetically engineered pharmaceuticals in Germany for the year 2000. Genetically engineered antidiabetic drugs worth DEM 843 million were prescribed in 2000, which is the equivalent of 40 percent of all genetically manufactured pharmaceuticals.

As a chronic disease, diabetes mellitus has another interesting aspect: After patients have been pain-free for the longest time, complications occurring at a relatively late stage of the disease will force them to get diagnosed and treated. As a result, screening and prevention require greater attention.

But what are the thoughts of the people affected by the disorder? They will ask for immediate help (freedom from pain, cure prospects, faster or longer effect, avoidance of complications and/or risks and side effects). For the patients, questions regarding the pharmaceutical's composition, basic compounds used and production or technological method are subordinate. This is especially true for those patients with a relatively high average age.

However, attention is garnered as soon as press reports mention acute "risks and side effects" or if even the term cancer and its associated risks enter the discussion. Patients feel threatened, voice their doubts and demand a remedy, including government support.

Certainly no responsible employee in research, technology, application or patient representation can or intends to oppose scientific and pharmacological progress. In the interest of humanity, the use of modern basic scientific research is a necessity. Today, it has wide prospects and narrow limits.

In the described field of application of the chronic disease diabetes mellitus, the motto for the upcoming years will probably be “with design insulins to design regimens” (Professor Matthew Riddle), but there will be no treatment via individual genotypes. In this respect, patients and their representative organizations pursue obvious treatment paths such as

- Transplant opportunities due to increased effectiveness;
- Replacement of destroyed beta cells and protection from destruction through gene therapy;
- Extra-pancreatic insulin replacement production.

In view of the responsible work of research and technology experts, diabetes patients also expect their support organization to get involved. As the German Diabetics Society, we are prepared to do so and will therefore make our own contribution to the “Man, Ethics and Science” institute.

Ethical, social, and legal aspects of pharmacogenetics and pharmacogenomics

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In Germany, therapy with pharmaceuticals is practised frequently and often with success in treating diseases as well as in primary and secondary prevention. Pharmaceuticals are prescribed about 1 billion times a year, mainly for patients covered by the statutory health insurance funds, but also for those in private health insurance funds. In the domain of statutory health insurance alone, about 850 million packs were prescribed in 2000, representing expenditure of DM 40 billion. The 5th Book of the German Code of Social Law governs the requirements for the provision of healthcare to insured patients: Healthcare services have to be in line with generally recognised medical knowledge and must take therapeutic progress into account, their effectiveness and cost-efficiency must be guaranteed, and quality and humanity have to be respected in their provision. “Social” (state-regulated) health insurance does not differentiate between patients with regard to their income or status, and all members have to be treated in the manner that the best possible healthcare requires. Accordingly, when new methods open up the possibility of better treatment or therapeutic progress, and especially if this means a more cost-effective form of treatment or improved tolerability, it is a requirement of the 5th Book of the Code of Social Law to use these methods on patients with the relevant indications.

These considerations should as well be applied to pharmacogenetics and pharmaco-genomics. It has been customary up to now to use pharmaceuticals which have been shown to be effective, up to a certain level of probability, in the treatment of diseases. Therapeutic experience, however, shows that the efficacy of a drug is affected by individual differences that can hardly be foreseen, and that its action can be either increased or diminished and may be accompanied by undesirable or inadequate therapeutic effects. A number of these phenomena can be explained by the pharmacokinetic effect which Cytochrom P450 enzymes have on many pharmaceuticals, which means that genotyping a patient prior to treatment will allow far more carefully targeted use of a drug.

However, a new regulatory framework must be created for this approach. It is indeed reasonable, from an ethical and social point of view, to use pharmaceuticals in such a way that not only the disease is treated but rather the whole patient, taking full account of his or her individual enzyme situation, which entails different metabolisation rates. This can in fact mean that, for instance, patients with a low metabolisation rate need a significantly lower dosage, and that if they are administered the normal dosage the result will in effect be over-dosage, whereas those with a high metabolisation rate would be under-dosed with the normal dosage, and no satisfactory result would be achieved (e.g. with Haloperidol, Metoprolol, or Amitriptylin). Both effects, however, have a negative impact on the quality of treatment, and it would therefore be unethical and also antisocial within the meaning of the

5th Book of the Code of Social Law to withhold this treatment from patients. It would also be wasteful not to take advantage of the possibility of applying "tailor-made" treatment; undesirable side-effects make therapy more expensive to just the same extent as does therapy failure. The prerequisites and consequences of genotyping, however, have to be examined very carefully from the legal point of view since misuse of the data involved must be prevented. Setting this data on the same footing as a blood-group analysis would be oversimplifying the problem; one conceivable solution would be to provide each patient with his or her own personal "enzyme identity-card". This would also avoid a situation where the same genotyping procedure is carried out over and over again unnecessarily.

Overall, there is in fact no actual conflict in German health insurance between pharmacogenetics and pharmacogenomics on the one side and the 5th Book of Social Law on the other, because the new approaches reflect recognised knowledge and therapeutic progress, and can also improve the quality of healthcare. The regulatory framework for protecting personal data and preventing their misuse, however, must be clearly defined before genotyping can become a standard procedure in healthcare.

Pharmacogenetics, Bioinformatics, and Information Technology: "New Methods to Protect Genetic Data and Privacy"

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First Genetic Trust's [FGT] mission is to be the leading provider of genetic banking[1] products and services. It is dedicated to protecting the privacy and security of individuals' genetic information, while facilitating its use to advance medical research, diagnosis and treatment. FGT provides state-of-the-art genetic data handling and bioinformatics services to pharmaceutical companies, medical researchers and healthcare providers engaged in genetic research and molecular diagnostics.

This presentation will provide background on the current state of phramacogenomics/genetics, and the related requirements for data handling and management. The presentation will also cover related ethical and legal concerns. Finally, a summary of the approach and technology used by FGT to develop this state-of-the-art genetic banking capability will be summarized.

[1] Genetic Banking = decision support, dynamic informed consent management, sample procurement and processing,, data acquisition, analysis and management, and secure data/sample storage

Genetics and Genomics: Aspects of Drug Discovery and Drug Development

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Two important developments characterize the last few decades of medical and pharmaceutical research. First, the advent of powerful molecular biology techniques allowed a heretofore not possible understanding of cellular mechanisms, reaching down to the level of the genome, and culminating in the unraveling of disease genes for many rare monogenic diseases. This provides medical sciences with a new mechanistic understanding of biology and of the molecular pathology of disease, and holds the promise of providing us with a better, expanded toolkit for disease risk assessment and prediction, and thus the potential for preventive health care that had until then been the domain of classical epidemiology.

In parallel, and as a consequence of these developments, the pharmaceutical industry experienced during this time the passing of the baton from the chemist to the biologist: where chemistry once played the leading role, handing the biologist newly-forged compounds for testing in a variety of disease models, physiological mechanisms and disease models are now being stripped down by the biologist to reveal the critical targets aimed at which chemists now synthesize their molecules in a target-driven approach.

Lately, these developments have begun to include genetics also on the level of drug discovery and development for those common diseases that play the most important role form the standpoint of public health, that cause most of human suffering and cost society most dearly. Logically so, as we know that heritability plays an important role in all these ailments that range from high blood pressure to diabetes, from rheumatism to asthma: they all show, in addition to their dependence on well-studied external factors, a propensity to cluster in certain families; and for many of these diseases a positive family history has long been recognized as one of the most important risk factors. The elucidation of these factors surely should provide us with useful information on new, causative disease targets.

In addition, in as much as we have made important progress in developing effective and powerful medicines over the last decades, most of them remain fraught with unpredictable and far from perfect efficacy; and almost all of them also cause adverse effects, unpredictably as well. Given that in many instances no clinical parameters have emerged as useful for predicting efficacy or side effects, one may speculate that different genetic predisposition –based on differential disease causation on the molecular level resulting in identical phenotypic manifestations, or based on differential metabolic handling of a drug molecule, may explain some of these differences.

It is along these lines of reasoning that we envision the impact of molecular genetics on the pharmaceutical industry. Some of these aspects will not be realized for some time to come, others may materialize earlier.

Thus, in the long run, the discovery of new drug targets based on the detection of novel disease mechanisms with the help of genetic investigations holds major promise for future, better drugs: because genetic studies provide causative targets –in contradistinction to most other medical research that is only associative in nature—they may serve to give rise to more effective drugs, at least for the subgroup of patients with a certain disease in whom the targeted mechanism is indeed causative. In as much as not all thus-derived targets will turn out to be chemically tractable, their identification opens the door to the discovery of other, linked elements of the same pathway or pathomechanism, among them perhaps more feasible molecules for drug targeting. Research into the genetic roots of common, complex disease has long focused on non-parametric approaches; the lessons learned have been mostly disappointing, and once again collection of large and informative families and pedigrees is seemingly becoming the preferred approach. In any event, the impact of newly found disease genes is envisioned to take considerable time, in as much as the expected higher success rate –based on the targeting of causative mechanisms— may improve the overall success rate and thus, ultimately improve the level of productivity of drug research.

Once a drug target is selected, genetics and genomics offer –this time on a less far-flung timeframe—significant advantages for the compound discovery and optimization process. Genetic epidemiology studies may help validate the target as one that is not only based on physiologic understanding of disease-symptom-associated mechanisms, but as one that may show –upon testing of a genetic variant among cases and controls— association with the disease. Furthermore, any genetic variation – in most cases these will be single nucleotide polymorphisms, or SNPs, of a target—may indeed affect the binding characteristics of chemical compounds being synthesized to modulate them. If this is the case in a target that, based on SNP analysis, shows no particular association with the diseased state, one may want to search for a non-selective compound that has similar affinity for both molecular variants of the target molecule. Conversely, if one were to find that a certain molecular variant is indeed associated with presence of the disease, then this variant may define a subcategory of individuals with the disease, who may be more likely to respond to the drug – thus one might want to synthesize the most selective compound for the disease-associated variant of the target.

Genomic technologies, in particular high throughput expression screening on the mRNA level, in the future almost certainly complemented by similar proteomics approaches, are poised to play an increasingly important role in compound selection –or compound rejection—at an early stage in the drug optimization process. Currently still hampered by the lack of availability of comprehensive data bases, toxicogenomics is expected to help weed out compounds with potential long-term adverse effects based on the recognition of predictive expression patterns; likewise, pharmacogenomic approaches will aid the selection of the compound with an optimal spectrum of activity.

On an even shorter time frame, pharmacogenetic monitoring is expected to play a potentially major role in the understanding of and dealing with differential responses to drugs currently in clinical development. By saving a DNA sample from patients enrolled in phase 2 and phase 3 clinical trials, investigation and recognition of genotype-related

differences in efficacy, as well as potentially in the occurrence of adverse effects, can be built into the clinical development process and may provide important early clues as to how a drug can be best used and marketed. In as much as we are all familiar with examples for this from the area of pharmacokinetics, systematic attention to this is likely to increasingly reveal similar inter-individual differences resulting in differential efficacy also on the level of pharmacodynamics.

Given the sensitivity –rightly or wrongly— with which "genetic" research is commonly met by the general public, it is imperative that anyone involved in these kinds of studies remain keenly aware of the important bio-ethical, societal, and legal aspects of genetic research. Thus, proper attention must be paid to confidentiality and privacy issues, as well as to patients' right to decide about the use of "their" genetic material. However, in as much as data protection is essential, it tends to be counterproductive when it comes to using the data, in particular for a patient's own health-care. To be medically useful, the data need to be *used*, which implies that they need to be shared among a smaller or larger circle of health care workers. Thus, we will also need public dialogue and, ultimately, consensus on what uses of these genetic/medical data society condones ort endorses, and what uses will be considered harmful. It is essential, though, that next to our concerns about the individual's autonomy, we also recognize the solidarity-aspect of bioethics that recognizes a legitimate interst of society at large in biomedical, including genetic, research to progress, based on the principle of altruism and voluntary participation. In other words, it would be just as unethical *not* to conduct research that promises to improve the humen condition.

Although major progress has been made, and genetics has certainly crossed the threshold towards becoming a practical reality in the drug discovery and development process, much remains to be done. Conversely, in the area of common complex disease, we must be careful not to raise expectations higher than what is likely to be delivered. Genetics is not a panacea, just one more arrow in our quiver –albeit a sharp one.

Between ethical concerns and pragmatic considerations: assessing goals, benefits and risks of pharmacogenomics in terms of social accountability

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Molecular medicine is full of promises. However, the molecular transition of medicine is far from being completed. Recently, studies in pharmacogenomics helped to acquired the biomedical knowledge and the technological tools to describe, classify, and explain physiologic and pathologic processes of drug response on a molecular level, to develop the appropriate diagnostic tools for identifying the corresponding molecular findings in individual patients by genotyping, and to develop and test new pharmaceutical interventions with molecular targets. This makes pharmacogenomics one of the most promising fields of molecular medicine. With the combined model data of the Human Genome Initiative (HGI) and the SNP-mapping initiative of The SNP Consortium (TSC), the implementation of clinical studies is the next logical and crucial step for the advancement of pharmacogenomics. Only genotyping of large clinical populations will move the project further down the road to the development of clinically relevant results. Thus, pharmacogenomics is now – as many other fields of molecular innovation in medicine – facing a wealth of ethical, legal and social questions.
Different modes of technology assessment – such as interest driven or evidence based assessments – significantly change professional and public decision making. Given that social accountability has become a touchstone for any kind of medical innovation in general, and for molecular medicine in particular, research and development in the field is now to an ever growing degree subject to public consensus. This is especially true with genomics research that involves individual genetic specimen or data, such as genotyping initiatives related to pharmacogenomics. Nowadays, consensus considering research and development in genomics is by and large negotiated in interest driven modes. Competing assessments of utility are put forward by various interest groups in processes of policy making that determine the use of novel technologies. A specific limitation of interest driven decision making is, that utilization and reimbursement drive innovation and standard of care, a situation inconsistent with rational health care. To overcome these limitations in the case of pharmacogenomics, a model for the evidence based design and implementation of genotype related clinical studies is introduced. The model allows taking into account both, pragmatic and normative issues. High quality empirical data on scientific and pragmatic

issues as well as on ethical, legal, and social issues are indispensable pre-conditions of decision making in the evidence based mode.

Because qualitative and quantitative analysis of the data gathered in pre-clinical studies of Human Genome Epidemiology (HuGE) determines the goals of clinical studies, the generation of empirical data on both, pragmatic and normative issues is a key feature of the model presented. To support quality and process control, clinical studies themselves are designed to generate valid clinical data on one hand and data facilitating assessment of normative issues on the other. Throughout the whole process of assessment, social accountability serves as a means to integrate public acceptability into the design of scientifically meaningful and medically useful studies and applications of pharmacogenomics.

Key features of social accountability discussed in this talk are respect for social values as well as performance and affordability of pharmacogenomics. Observing the principles of evidence and social accountability will finally not only determine the successful implementation of pharmacogenomics as routine medical application but also guarantee that the standard of care drives the utilization and reimbursement of pharmacogenomics and not vice versa.

Evidently, the notion of evidence based decision making implies well informed discourse in the hybrid forum of public interest, a situation clearly not always given. This poses yet another challenge to those involved in pharmacogenomics. There is a new need for professionally managed and socially competent communication to maintain the flow of credible, comprehensible, checkable and extensive information, serving the needs of social accountability. Transforming interest drive debates on molecular medicine, genetics, genomics, and post-genomics into an evidence based decision making process remains a major task that has to be accomplished to effectuate innovation in molecular medicine, such as pharmacogenomics. However, models and methods to fulfill this requirement are still under development and will have to be further validated.

Best Hopes, Worst Fears
The Patient's Perspective

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Genetic disorders are very common, not curable and often seriously burdening the people involved because of the physical, social, psychological and economical consequences. These people experience that (primary) healthcare is hardly capable of dealing with genetics and that society is only minimum ready for using the opportunities and for managing the implications of genetic progress.
Relevant information reaches the people in need for it late or not at all. This in spite of the fact that in most of the European countries there is excellent expertise and are adequate genetic counselings services available.

Genetic bio(techno)logy is providing a range of facilities for early detection of (predispositions for) diseases, accurate diagnosis and determination of prognosis.
Moreover there are rapidly expanding options for genetic therapies. New branches of science are emerging such as bio-informatics, pharmacogenetics, nutrigenetics. Community genetics is fast developing offering a wide range of opportunities for timely decisionmaking, for prevention, for limitation of the burden of disease, for adequate disease management and for health maintenance.

Genetic (bio)technology also raises many concerns such as the scope of genetic screening and testing, privacy and confidentiallity, eugenic pressure and stigmatisation, endangered freedom of choice for off spring, commercial exploitation of human genome data, equity of benefits of human genetic research and the limits of genetic research.
Many involved families live between hope and fear, between (often exaggerated) expectations and (often ungrounded) fears.

Patient organisations, not wanting to be part of the problems but of the solutions, have united on the national, continental and worldwide level, both in disease-bound contexts as well as subject-bound (genetics, disability) contexts forming an enormous potential in terms of numbers (frequency), vision, networks and experience based expertise.
They collaborate or communicate with WHO, UNESCO and the Global Life Sciences Forum to be toplevel informed and to have an input on toplevel decisionmaking. They are active in the European politcal arena in Brussles and Strasbourg.
They closely work together with scientific organisations such as the ESHG and increasingly as well with diagnostic and therapeutic industrial alliances such as EDMA (diagnostic industry) and EFPIA (pharmaceutic industry). They influence legislation and policy making

They contribute to the setting up of disease specific consortia, networks of expertcentres, protocol development, rare disease programs, national awareness campaigns and public debate on genetic topics and dilemmas.
In this way they wish to contribute to an alert and involved society and also to accelerate or catalyse the production of new drugs.

The Dutch Alliance, containing 60 national patientorganisations to which over 150.000 families are affiliated, has over the years organised a series of national awareness campaigns, has produced teaching packets and lesson materials, has given an opinion on many national topics such as screening, prenatal diagnosis, patenting, and has issued an Ethical Manifesto which contains also guidelines for policy development.
Moreover they have established a joint/national policy program on genetics that is promoted and guided by a national forum genetics, health and healthcare.

In the new century, key questions of life and death and the promise of (bio/genetic) technology to improve and lengthen life and its quality, can no longer be addressed without a well-prepared society and structural participation on the part of parents' and patients' organisations and their representatives.

The right drug for the right patient – benefits and problems of pharmacogenetics and - genomics

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Every year, a considerably fraction of the strained health budget is spent on the treatment of drug side effects and wasted on inefficient drug therapy. In the United States, these extra costs have been estimated to amount to 30 to 100 billion dollars. They can partly be explained by therapeutical concepts which do not sufficiently take into account the patient's characteristics and individual needs. Today's drug therapy is largely based on statistics: it provides the individual with the standard treatment that has proved to be efficient for the average patient.

There are numerous factors which might modify the individual's response to a therapeutic drug regimen. Some of these factors – as e.g. personal characteristics (age, sex, body weight), concomitant diseases (kidney failure, liver failure), and personal habits (smoking, alcohol consumption) – are well-known and usually considered by the physician before he starts a drug therapy. However, as genetic factors are the major determinants of the normal variability of drug effects they might be of even greater importance when safety and efficacy of a treatment are assessed for a particular patient.

Many of the genetically determined differences in drug response are due to polygenetic influences on pharmacokinetics (1). Variants in drug metabolizing enzymes lead to greater or lesser amounts of active compound in the body. Polymorphic genes regulate drug transporter activity and thereby a exert strong influence on drug tissue concentrations (2, 3). Each mechanism could cause a significant variation between individuals in drug response, but with all these mechanisms interacting in a very complex way, the clinical consequences are sometimes far from being predictable.

These genetic variances in pharmacokinetics could affect safety as well as efficacy of a drug therapy. Efficacy is impaired or lacking when the plasma concentration of the active compound is below the therapeutic level, whereas very high concentrations might bring about undesired effects or even intoxication. Modifications in drug metabolism pathways could generate toxic metabolites which cause serious side effects. In addition, drug-drug interactions on different pharmacokinetic levels (absorption, metabolism, excretion) could induce all these effects and upset a therapeutic regimen completely.

Our knowledge in the pharmacogenetic field is increasing exceedingly rapidly and has already been partly implemented into clinical practice. Package leaflets refer to serious side effects and important drug interactions which might occur in specific genotypes. In drug development, the most important polymorphisms that could be involved in the

pharmacokinetics of the therapeutic agent are routinely checked. Nevertheless, these are only the first steps on the road to patient-tailored drug treatment. In the past decade considerable progress has been made in identifying the source of variability. However, strategies for dealing with variability in the clinical setting are still lacking.

To design a rational dosage regimen, the clinician must know how to make appropriate adjustments in certain genotyps. He needs tabled dosage recommendation which give precise information about every pharmacogenetically important drug. An initial step towards genotype-based dose recommendations has already been taken for CYP2D6 in the therapy of depression (4) and for certain other enzyme polymorphisms and their various substrates (5). It goes without saying that these dosage recommendations must be based on clinical studies which include a large enough number of participants to provide reliable results.

Our increasing insight into genomic diversity will change our understanding of diseases and make our therapeutic concepts much more complex. The clinician will be in danger of getting lost in the deluge of data. Therefore, it is essential that bioinformatic-based disease management tools are established, which link the data of an individual patient to the whole spectrum of globally available current "knowledge". These new technologies will enable the physician to optimise his medical treatment according to the specific needs of the individual patient. We require complex calculation programs which process the patient's data, utilising a thesaurus of knowledge of the properties of all available drugs. This includes the knowledge of pharmacokinetics and population kinetics, as well as of genetics and genomics. A procedure of this sort is expected to provide the drug dosage regimen that fits the patient perfectly.

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Pharmacogenetics and molecular diagnosis: common grounds and differences

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A substantial portion of the person-to-person variability of drug response is believed to be of genetic nature. Variation in genes for drug-metabolising enzymes, drug receptors, and drug transporters has been associated with individual efficacy of medicines and the occurrence of adverse drug reactions. Pharmacogenetics promises to remove much of the uncertainty currently associated with attempts to predict the reaction of individuals to medicines. It may thus help to improve efficacy and safety of pharmacological treatment.

Pharmacogenetics is not primarily concerned with the diagnosis of disease states or susceptibility to disease, and thus is not usually regarded as part of clinical genetics. Nevertheless, pharmacogenetics aims at gaining genotypic information and exerting measures of genetic surveillance. Information gathered primarily in the context of improving drug delivery may, for example, turn out be predictive of personality and disease development. Community interest in pharmacogenetic information may be particularly high in view of the economic dimensions of pharmaceutics. Pharmacogenetic information, as all other genetic information, thus bears the potential of being used also against the interests of individuals and their relatives.

In this paper, I will first discuss the dimensions of molecular genetic testing, which has now become part of routine medicine. In the *diagnostic* setting, genotype information is increasingly been sought to complement clinical information, which in itself oftentimes cannot go beyond raising suspicions about the cause of a given condition, especially at its early stages, where therapeutic intervention may be especially beneficial. *Predictive* settings comprise carrier testing (aiming at estimating risks for the offspring of tested individuals), prenatal (including preconceptional and preimplantative) diagnosis, and testing for susceptibility to late onset disease. In all of these situations, albeit with variable severety, ethical, legal and social problems may arise. Recommendations and guidelines have been issued by the national and international learned societies, WHO, and health service authorities, with the intention of ameliorating the numerous dilemmata that may arise to individuals, their families, and the society as a whole. I will emphasize that, due to the enormous progress made within the internationally coordinated human genome project, ethical, legal, and social issues associated with genotyping individuals or populations will thoroughly affect doctor-patient relationships in general, and I will argue that the health care system is in no way prepared to cope, in the future, with requirements to gather informed consent.

In contrast to the prevailing view that pharmacogenetic testing is different from other kinds of genotyping testing because its intent is not specifically to determine or predict the risk of disease, I will hold the position that pharmacogenetic testing, nevertheless, raises very similar ethical, legal, and social problems, and that pharmacogenetic testing, therefore, should be embedded in the same ethical and legal framework that has formally been established to ensure personal freedom of choice regarding any kind of genotypic testing. I will, in particular, discuss the recommendations of the European Society of Human Genetics concerning genetic
screening, insurance and workplace issues, DNA banking, and genetic service provision.

Legal limits in the application of pharmacogenetics and pharmacogenomics in medicine

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I.

The development of molecular medicine also brings up considerable legal issues with regard to the development of diagnostics and therapies. While the permissibility and limits of access to the human genome are still widely unresolved, approaches can be found in the human rights agreement on biomedicine. In the Federal Republic of Germany, differentiated legislation will be necessary.

The development of molecular medicine through gene therapy procedures that allow the treatment of diagnosed diseases is only beginning. In this respect, pharmacogenetics seems to be further advanced and to promise the application of genotype-based therapy in the near future. The prerequisite for such therapies are diagnostic procedures with the goal of using genetics to identify, analyze and predict patients' reactions to the administration of pharmaceutical substances. This requires a diagnostic manipulation of the genome to examine patients for their reactions based on the genetic data.

Therapeutic substances with specific molecular functions will be developed based on the genetic information gained in this manner. Research is supposed to be done on the connection of the metabolization of pharmacological substances and the genetic structure. This method is expected to provide improved efficacy and fewer pharmaceutical side effects.

As shown in the workshop program, this does not just involve genetic tests performed on individuals before pharmaceuticals are individually administered but also the genetic characterization of larger populations for the development of pharmaceuticals generally differentiated by genotype.

II.

These research and development efforts require various examinations regarding the efficiency of substance metabolization in organisms with different genotypes. Obviously, several diagnostic manipulations of the genome of many persons are necessary, not just for individual therapeutic purposes but also to examine the response and side effects for various genotypes, i.e. different groups. This requires surveys using a large variety of test

subjects to examine the reactions of various patient groups with a different genetic structure.
III.

For this purpose, the existing procedures for examining pharmaceuticals based on consent following the provision of information do not suffice.

The human rights agreement on biomedicine, which has not yet been signed by the Federal Republic of Germany for reasons that can no longer be justified, contains rules for genetic medicine that will also be of essential significance for pharmacogenetics. The agreement prohibits any kind of discrimination against a person based on his or her genetic information (Art. 11). Article 12 of the agreement permits tests that facilitate the diagnosis of genetic diseases or that serve to ascertain the existence of a gene responsible for a disease or recognize a peculiarity or genetic disposition for a disease; only for health purposes or health-related, scientific research and subject to an appropriate genetic consultation. Processes geared toward changing the human genome may only be performed for preventive, diagnostic or therapeutic purposes and only if they are not aimed at changing the germ line (Art. 13 of the convention).

Since we must assume that the human rights convention will also apply to the Federal Republic of Germany in the future, any surveys will need to take these regulations into account.

When collecting genetic data, it must be guaranteed that they are only used for the respective health-related scientific research purpose and made as anonymous as possible. It must be ensured that the collected data on genetic structures and dispositions are not used for other purposes, i.e. for an employment appointment or rejection or the acceptance of insurance customers. The existing controversy in Germany about the permissibility of such uses of existing data and the permissibility of such examinations must be decided by the legislature. The speaker advocates a ban on the use of genetic data in the employment and insurance sectors. The risk that data collected for medical research purposes may be used in such a manner must be opposed. As a result, there must be no collection of identifiable genetic data from the population either.

Ethical and health-political prospects of pharmacogenetics

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Pharmacogenetics may provide us with individually customized pharmaceuticals with improved efficacy and fewer side effects. The differences in the efficacy of a substance are due to slight differences in the genetic sequences. These individual deviations in the DNA are responsible for the fact that a pharmaceutical is absorbed or metabolized more quickly or slowly. Drug intolerances are also due to genetic variations. In the future, pharmaceutical research will be concerned with the identification of those genes that cause the different reactions to pharmaceuticals in humans.

Initially, the consequence of this development will be a cost increase for pharmaceuticals. However, these costs will be offset by decreased costs in other areas of the health care sector (doctor and hospital costs) as well as optimized treatment success and – due to the reduction of undesirable side effects – an improved quality of life for the individual patient. These perspectives show that the viewing and judging horizon must be expanded in a health policy discussion about future development lines in pharmaceutical research. In doing so, we should take into account not just the costs but also the benefits of medical and pharmaceutical innovation as well as the optimized spectrum of activity of the new pharmaceuticals, which will be optimized through pharmacogenetics. A health-economic consideration should primarily take into account the fact that new pharmaceuticals could result in a shift from expensive in-patient treatments to frequently more cost-effective out-patient treatments. The entire health care system could also directly benefit from such cost savings effects. However, other savings could also have an impact on the economy, albeit more indirectly, e.g. when Alzheimer's patients can delay their moving to a nursery home by years due to targeted, novel medication, thereby avoiding these costs from the outset. Furthermore, whenever patients can return to gainful employment more quickly again due to pharmacogenetic optimization, this can result in savings for the national economy.

Nevertheless, the critics are also voicing their opinions, for example that for clinical trials conducted based on genetic criteria the effect is only tested on a group of people with a certain genetic profile. As a consequence, only pharmaceuticals tailored to a majority of patients can be manufactured in the future. Based on economic considerations, suitable pharmaceuticals may not be developed for people with a rare genetic variation. Despite these concerns, the hope remains that in the future scientists will not only determine more exactly which substances are truly effective for patients but also develop pharmaceuticals that can be offered to patients with rare genetic deviations.

Legal aspects of genetic tests in health insurance

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1. Genetic tests, if conducted by responsible physicians, represent a form of medical diagnostics like others and include both opportunities *and* risks. There is no fundamental difference per se from other *ways of obtaining information,* which is becoming evident through the fact that genetic methods are increasingly used to diagnose non-hereditary diseases subsequent to manifestation. Furthermore, there is no fundamental difference per se from other medical examinations with regard to information *content,* since other examinations are also oriented toward the *hereditary causes* of diseases and disease risks. Also regarding their *informative value* per se, they do not differ significantly from other medical examinations – neither from the viewpoint of predictive accuracy nor from the viewpoint of their character as probability statements. Other medical examinations also aim at recognizing or preventing a *future* disease with more or less certainty or to limit or decrease the *risk* of a future disease, as is clearly shown by the example of diagnosing hypertension.

Furthermore, no alternative relationship to treatability can be established in the sense that discovered and manifested diseases are always treatable, while already discovered, risk-relevant genetic dispositions are never treatable and therefore cause more stress to the patient. Such a difference between therapeutic opportunities in principle does not exist. Finally, many genetic dispositions interact with other genetic traits and/or environmental factors to lead to the manifestation of the disease in question. Therefore, it can not be said for all cases that patients who know of their genetic disposition must be brutally aware that their "final" verdict has been determined and their fate has been unchangeably sealed.

2. As far as insurance law (among others) is concerned, genetic tests and their results basically must not be treated differently from other medical tests and their results. In a country where a social security system ensures sufficient existential provisions for its citizens independent of their genetic disposition (as is the case in Germany), neither the right to self-determination regarding (genetic) information of the potential insurance customer nor the ban on discrimination speaks radically in favor of a ban on the performance of such genetic tests prior to the conclusion of non-compulsory insurance contracts, whose result is suitable, required and commensurate for the insurer's risk assessment. Furthermore, such a ban does not take care of the risk of data misuse or the concern of (insurance-inadequate) elimination of insecurity. On the contrary, such a ban would contradict the fundamental principles of private insurance law and violate important liberty rights of private insurers that are protected by constitutional law.

3. Furthermore, what speaks in favor of permitting insurers' requests for conducting genetic tests before concluding insurance contracts is the fact that this is the only effective way to counter the risk of anti-selection, i.e. the risk that a potential insurance customer knows about a risk-relevant genetic disposition and takes out personal insurance for this very reason to procure unjustified insurance protection for himself or another designated beneficiary.

Even if the insurers' request for conducting (risk-relevant) genetic tests before the conclusion of a contract is not permitted in general, the insurer must have the opportunity in individual cases (e.g. if false information is specifically suspected, if a large policy sum is requested or if the usual waiting times before a policy becomes effective are to be waived) of making the conclusion of the contract – according to past practice – contingent on a medical examination of the individual to be insured. If there is a medical indication in the case at hand, the examination should also be permitted to include a genetic analysis.

4. A consistent ban of requests for genetic tests on the part of the insurers would violate the principle of equality, since insurers may indisputably demand other (incl. predictive) medical examinations and a family medical history and use their results and since there is no *fundamental* difference between genetic and other medical analyses and the results in question. Furthermore, it can not be justified that an applicant must disclose information about a certain disease, if this information was obtained during a "traditional" medical examination, but has the right to withhold the same information, if it was obtained through a genetic analysis. Such a "method discrimination" can not be justified.

5. In addition, regarding the conclusion of insurance contracts, a genetic analysis is not *necessarily* concluded *"long"* before the disease, for which an individual has a genetic predisposition, manifests itself: By no means will genetically caused diseases typically manifest themselves at an advanced age and not every insurance policy is taken out when the policyholder is still young. As a result, it is more than a coincidence (and no sufficient reason for different treatment) whether a genetic analysis is performed (possibly immediately) *before* or (possibly immediately) *after* the first (potentially incorrectly interpreted) symptoms occur.

6. If there were ethical or legal concerns regarding the use of predictive information for risk assessment in concluding private insurance contracts, any risk tariffing by private insurers should consequently be rejected (which rightly nobody demands). And as long as potential insurance buyers have the right to seek out a "cost-effective" insurer, we can not deny insurers their right to offer advantageous policy terms.

7. If we assume that there needs to be a solidarity compensation in favor of individuals with congenital dispositions for diseases, this refers to the original task of *statutory insurance* (*social security* in Germany) and not to private insurance, which is based on *freedom of contract* and the concept of *risk equivalence*. However, if we view this solidarity compensation as a *fundamental principle* of society, then it would appear to be a construction flaw in the social security system, if basic insurance membership is either not obligatory or even not available to certain groups of the population (e.g. civil servants, self-employed people and high-income earners). Consequently, this deficit must be eliminated in social security in accordance with the system. However, this should not be done through system-inadequate "over-socialization" of private insurance, i.e. through unilateral use of

the specific private insurer, who was chosen – for whatever reasons – by a potential insurance buyer as contract partner. For this reason alone, the private insurer would need to fulfill this task of the welfare state without the opportunity of appropriately putting into proportion payments and benefits at his own expense and at the expense of the policyholders' community he established. Therefore, we need to deliberate very carefully, whether it would be truly appropriate – as is demanded more and more – to increasingly shift the population's existential provisions from the social security into the private insurance system.

8. For the above-mentioned reasons, the ban on conducting predictive genetic tests to identify diseases apart from health-related purposes, which is contained in Article 12 of the European Council's human rights convention on biomedicine, is arbitrary *with regard to the German legal situation.* While it corresponds to the German social security system, it contradicts the principles of private insurance and, in this case, leads to an unconstitutional special treatment of a certain medical method. As a result, Germany must declare a reservation pursuant to Article 36 of the convention (with regard to the area of non-compulsory insurance).

9. On the other hand, a reservation against Article 11 of the convention, which forbids any form of discrimination against an individual based on his or her genetic heritage, is not required. This article only prohibits "unfair discrimination," as was made clear by the authors of the convention. However, no "unfair discrimination" can be seen in the risk-adequate (i.e. suitable, required and commensurate) consideration of genetic information in the field of insurance. In case Germany accedes the convention, this should be clarified through an interpretative explanation.

10. Based on the above-mentioned remarks, a ban regarding requests for the results of *already conducted* genetic tests (suitable, required and commensurate for risk assessment) directed at private insurers is even less justifiable. Such a ban of inquiries violates the right and the opportunity to achieve *contractual parity* through *information parity*. It can not be derived correctly from the human rights convention on biomedicine either, since Article 12 of the convention is not applicable in this respect (it only refers to *conducting* tests) and no "unfair discrimination" can be seen in the risk-adequate consideration of genetic information in the insurance sector for the above-mentioned reasons pursuant to Article 11 of the convention.

Pharmacogenetics: the ethical context

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The development of and application of pharmacogenetics in health care promises to move genetic testing into a new era. Through the application of pharmacogenetics, it will soon be possible to characterise variation between DNA of patients to predict the responses to specific medicines. It has been widely predicted that the availability of a predictive medicine response profile patient will change practice and economics of healthcare. A move away from the strategy of producing a medicine for general use by genotypically diverse patient populations will increase the number of drugs that need to be designed to target a more segregated patient population. Thus medicines for general use will need to be replaced by subsets of compounds that comprise a major drug class. The consequent introduction of pharmacogenetics into the clinical setting will bring genetic testing into much wider usage. Although there is disagreement about the degree to which the pharmacogenetic approach will become the standard for the development of new medicines and over what time scale, there is growing recognition of the need to anticipate the ethical issues that are likely to be raised. This talk will focus on three key aspects: the existing ethical framework for genetic testing with a particular emphasis on consent, whether pharmacogenetic testing is distinctive from other kinds of genetic testing and the ethical issues posed by the genotypic stratification of patients in clinical trials.

Experience of genetic testing has developed over the past decade through the identification of a growing number of single genes for rare diseases. Prenatal screening, screening of neonates and screening of adults for carrier status and late onset disorders are now available for several genetic diseases. Accumulating experience and debate has led to the formulation of ethical guidelines for genetic testing by several advisory bodies. These guidelines are the starting point for the expansion of genetic testing that pharmacogenetics will bring.

The principal ethical issues that have been raised by genetic testing in monogenic disease have concerned patient consent and confidentiality, prenatal testing, the testing of children and the mentally incompetent and research procedures. Some of these ethical issues apply at several levels. For example, confidentiality of patient information in relation to genetic testing may raise questions that concern family members or issues that involve external agents such as the insurance industry or employers.

An important principle in ethics is the respect for human beings and their autonomy and dignity. This ethical principal underlies the legal requirement to seek consent prior to any genetic counselling or testing of adults. In a rapidly evolving field such as pharmacogenetics, it is inevitable that research and clinical work will be closely entwined. The more complex ethical issues may be raised when DNA samples collected for research, including clinical trials, yield clinically significant information. How should such information

be handled? For those who have a specific polymorphism (e.g. non-responders to a medicine or an associated disease susceptibility) there could be implications for a relative. The ethical difficulty arises because the process of obtaining informed consent required for research does not usually include consent for the disclosure of identifiable data to clinics outside the strict environs of research.

Genetic tests have been largely based on the detection of specific mutations in genes known to be implicated in a particular disease. In the case of phamacogenetic testing, the nature of the information being analysed promises to be rather different. Not only will the majority of genes involved be specific to drug metabolism rather than disease, the variants of interest within populations will be relatively common polymorphisms rather than rare mutations.[2] There may be some instances where a gene involved in drug metabolism also has a role in disease susceptibility. A number of bodies have concluded that genetic testing for susceptibility genes which offer relatively low predictive or diagnostic certainty should be discouraged unless there is clear medical benefit to the patient. [3]

As pharmacogenetics becomes increasingly well established in the process of drug discovery, clinical trials will require patient stratification. This raises a number of questions which researchers would not normally need to consider in a conventional trial where a genotypically diverse patient population is being tested with a single medicine. Clearly, pharmacogenetic profiling will identify patients that do not respond to specific treatments as well as those who are at high risk from side effects. Researchers will need to decide whether high-risk patients identified in research should be informed of their status. Questions will also raised over non-responders who may receive greater exposure to a drug.

While the development of pharmacogenetics does not appear to raise new ethical issues, careful assessment of research procedures and the management of genetic information is needed. In encouraging debate on these issues, a clear distinction needs to be made between genetic testing for monogenic disease and disease susceptibility and genetic testing for pharmacogenetic profiles, although some caution will be needed over the relationship between genotype and phenotype.

[2] Liggett, S B (2001) Pharmacogenetic applications of the Human Genome Project. Nature Medicine, 7:281-283.

[3] The Nuffield Council on Bioethics (1998). Genetics and mental disorders: the ethical context. The Nuffield Council on Bioethics, London UK.

Which basic ethical questions does pharmacogenomics touch upon?

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This lecture attempts to put the objective of pharmacogenomics – improved, more precise individual therapy – into a historical context. The use of pharmacogenomics pursues a goal medicine has been pursuing for at least as long as it has been science-oriented. In principle, this goal is worth pursuing, but we must ask the question at what price it can be achieved. The possible risks include a mistaken assessment of the potential of pharmacogenomics and the premature dissemination and handling of genetic knowledge. These ethical aspects can also be viewed in terms of the cost-benefit calculation for the individual patient and under the aspect of self-determination with regard to information.