Predictive genetic diagnosis

Scientific background,
practical and social implementation

Memorandum by
the Senate Commission on Genetic Research

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Foreword

The rapid development in molecular genetic research and genome research has paved the way for a host of new diagnostic and predictive genetic tests. But the increasing use of such tests raises a number of ethical and social issues which need to be considered at an early stage. This is of particular importance in those cases where genetic tests are involved that can predict the possible occurrence of an adult-onset disease. Consequently, it is the responsibility of society to create a general setting suitable for the performance of predictive genetic tests. In keeping with its statutes the Deutsche Forschungsgemeinschaft advises parliaments and authorities on scientific issues; with this statement it wants to contribute to the debate on predictive genetic tests.

The Senate Commission on Genetic Research feels that, since the DFG's statement on Human Genome Research and Predictive Genetic Diagnosis was published in 1999, more recent research has produced important new aspects.

First, the draft of the human genome sequence which was presented earlier than expected was a step that represented a milestone not only for research, but also for the development of new tests. Second, in the past few years there has been a sharp rise in the number of genetic tests offered in the marketplace. However, the unrestricted supply of these tests causes a certain uneasiness. It raises the question of how important principles, such as ensuring the autonomy of the individual and the protection against discrimination, can be safeguarded in view of the fact that the quality and power of many of these tests are unsatisfactory and that the tests are not preceded and followed up by genetic counselling. The Senate Commission on Genetic Research feels that urgent action is called for. As a result, the recommendations presented in this statement suggest specific possibilities of handling predictive genetic tests in a responsible manner.

The Deutsche Forschungsgemeinschaft has addressed its statement to the interested public and the persons responsible in politics, the health care system and the administration who are confronted with issues of predictive genetic diagnosis.

I would like to extend my sincere thanks to all those who have contributed to this statement, especially Professor Bärbel Friedrich who chairs the Senate Commission, and Professors Claus Bartram, Hans-Georg Kräußlich, Peter Propping, Bettina Schöne-Seifert and Jochen Taupitz who, together with Professor Friedrich, drafted the text of this statement.

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Bonn, March 2003

1 Recommendations

The great successes that genome research has been able to achieve in the past few years promise major progress in the field of medical applications. Such possible applications also include predictive genetic diagnosis which makes it possible to identify a predisposition to a disease even before the manifestation of clinical symptoms or to predict the probability of occurrence of the disease. This statement focuses on the scientific basis of predictive diagnosis and its practical and social implementation. The Senate Commission on Genetic Research of the Deutsche Forschungsgemeinschaft gives the following recommendations:

Research A key concern of basic medical and biological research is to understand the mechanisms underlying the development and treatment of human diseases. It is the results of basic molecular genetic research in particular which at ever shorter intervals are reflected in the development of procedures for the diagnosis, therapy and prevention of genetic diseases. These research areas need to be promoted and supported on a long-term basis because they are important for the generation of scientific knowledge and are the drivers of medical progress.

The triad of counselling – testing – counselling Predictive genetic testing should go hand in hand with qualified genetic counselling before testing and again when the test results are available. Prior to undergoing predictive genetic testing the persons concerned should be given detailed information about the objective and significance of testing and the consequences that the test result may have. The individuals concerned should give their legally binding informed consent. Both counselling and informed consent should be documented. The test results obtained and their implications should be explained to the persons tested in in-depth counselling sessions. In addition, the individuals should receive a written report describing the test results.

Performance of genetic tests to be restricted to medical professionals In order to decide freely for or against a test the individuals concerned have to be able to judge the risks and opportunities, the power and individual consequences of possible test results. This is why the Senate Commission suggests that the performance of predictive genetic tests should be legally restricted to medical experts. By entrusting the medical profession with this task it will be possible to protect the autonomy of the persons to be tested and at the same time ensurethat tests are restricted to patients for whom they can be useful. Such an approach would also guarantee compliance with appropriate quality standards and the requirements of professional secrecy and data privacy. Genetic testing pursuing predominantly commercial objectives should not be permitted.

Quality assurance In Germany, regulations governing the quality assurance of genetic testing procedures have not, up to now, been specifically geared to the special quality requirements of genetic diagnosis. Both the legislative and the professional organisations concerned need to take adequate action in this respect.

Genetic specimen and data banks To study the interplay of genetic and non-genetic factors in the development and treatment of diseases it may be necessary to draw on large collections of specimens (e.g. blood, DNA, tissue) and data. The collection, storage and processing of

specimens and data must go hand in hand with the reliable protection of donors against the misuse of the specimens and data they donated. In addition, donors must in a position to consent freely to the processing of their specimens and data. This implies that they have to be informed of the legal provisions applying to data protection and donor privacy, the possibility of a future withdrawal of consent and the implications of their consent. Provided these conditions are met, the collection of specimens and data is ethically and legally justified, even where it is not directly linked to specific research projects. Donors should not receive any information about their own results; they should rather be given general reports while research activities are still going on. Based on these reports, they can then decide whether or not it is advisable and/or necessary to undergo individual genetic testing.

It would not be justified to demand that genetic samples and data be invariably destroyed after a certain period of time, because in this way humanity would lose a considerable part of its genetic knowledge potential. But nevertheless donors must have the choice of making their own genetic specimens and data available for scientific purposes for only a specific period of time which has to be determined in advance. As a matter of principle, donors – by withdrawing their consent at a later date – have the right to decide that data already collected should not be used any more or that they should be deleted. The same applies to the destruction of tissue samples. On the other hand, the donation agreement should provide for the possibility of limiting the period within in which such a withdrawal would be possible. In such a situation it is necessary to balance the protection of the donors' personal rights and the legitimate expectations of scientists.

Labour and insurance law Predictive genetic testing in connection with an employment relationship should only be performed if the tests serve to protect the employee and if the outbreak of a genetic disease directly related to the workplace can be foreseen. Testing should also be performed if the consequences of the foreseeable manifestation of such a genetic disease put other people at a considerable risk.

Predictive genetic testing should not be made a condition to insurance. However, this does not prejudice the obligation of the applicant to disclose knowledge of diseases that already are manifest or will most probably become manifest at a later point in time.

The Senate Commission feels that there is currently no need to take legislative action with regard to genetic testing for insurance purposes,. For the time being, the voluntary commitment appears to be adequate which the German Insurance Association (Gesamtverband der Deutschen Versicherungswirtschaft e.V. – GDV) undertook in January 2001 and which will end in 2006.

2 Introduction

Earlier than expected, the first draft sequence of the human genome was presented to the public in February 2001. For genetic research this publication represented a dual milestone. On the one hand, it permitted a better understanding of the structure, organisation and variability of the human genome. On the other hand, it provided an excellent stepping stone to the targeted study of the functions and interplay of genes and their products. But it has to be taken into account that many biological mechanisms are still understood and that it will take a lot of time and of basic research before they can be explained. Research into the genetic causes of diseases serves not only to generate new knowledge, but also, first and foremost, to develop new diagnostic, therapeutic and preventive methods in medicine.

As early as 1999, the Deutsche Forschungsgemeinschaft published a statement on "Human Genome Research and Predictive Genetic Diagnosis: Possibilities – Limitations – Consequences". Since that time rapid scientific progress in genome research has created the basis for an increasingly better understanding of how a genetic predisposition can contribute to the development of diseases. Consequently, the application of genetic testing procedures is also spreading rapidly.

In the following the scientific basis, the medical significance and a desirable social environment for this research and, above all, the resulting predictive testing procedures will be discussed. This statement will not address issues of prenatal diagnosis and its specific legal and ethical aspects.

3 Scientific background

3.1 Fundamentals

The nucleus of each of the about 10^{14} cells of the human body contains 23 pairs of chromosomes carrying genetic material, i.e. DNA (desoxyribonucleic acid). This genetic material, in turn, provides the genetic programme to control all vital cell functions such as cell division, functions of nerves, sensory organs and muscles, maintenance of the stability of bones and connective tissue, energy production from food, the immune defence system, the production, transport and catabolism of biologically important molecules, signal transduction and the regulation of all these processes. The cellular functions of the various tissues are co-ordinated to ensure the harmonious interplay within the overall organism.

DNA is a long-chained molecule and serves as carrier of the cellular control programme. Human DNA contains 30,000 to 40,000 information units known as genes. Information is contained in a defined linear arrangement (sequence) of certain building blocks called nucleotides. They consist of one out of four possible bases (guanine, adenine, thymine and cytidine) linked to a sugar (desoxyribose) and a phosphate group. The total genetic material of a cell or an entire organism is referred to as genome. The Human Genome Project succeeded in determining most of the sequence of these bases. A working version of the human genome sequence is now available. Gaps that still exist at present are expected to be closed during 2003.

Genes account for only a small part (less than 2 per cent) of the total DNA sequence. The presence of a gene is derived from specific sequence patterns. The functions of a large number of genes are not yet known.

Genes on chromosomes

In the nucleus of each cell genes are linearly arranged along the 23 chromosomal pairs. Each chromosome – and hence the genes it carries - is present in duplicate, i.e. one from each parent. Exceptions to this rule are the genes on the X chromosome which in males is present only once. Males have an X chromosome and a Y chromosome, while females have two X chromosomes.

Based on their sequence and function, genes may be grouped into gene families. It is a long-term challenge for biological and biomedical research to explore the nature and function of all genes. Knowledge of these mechanisms will permit in-depth understanding of the physiological processes underlying the functions of the human organism.

Having a full set of genetic material consisting of paired chromosomes in the body cells is a special characteristic of higher organisms and hence of humans (diploidy, 2 x 23 chromosomal pairs). Gametes (germ cells), on the other hand, contain a single set of chromosomes (haploidy, 23 chromosomes), i.e. a single copy of each gene.

In a human body cell perfectly identical base sequences may be present in matching (homologous) DNA regions or the two homologous DNA regions may be different. If two identical DNA copies are present at homologous chromosome locations, this is called homozygosity. If the two DNA copies differ from each other, this is termed heterozygosity.

The information contained in genes is passed on from generation to generation by means of a complicated mechanism (halving and subsequent recombination of the genetic material; development of spermatozoa in males and oocytes in females; fertilisation of the egg cell by a sperm cell; development of embryo and foetus). This mechanism ensures the stable transmission of genetic information and, at the same time, produces differences in genetic make-up as a result of recombination. This leads to boundless interpersonal variability while the underlying biological pattern remains unchanged.

In addition to the chromosomes present in the cell nucleus (nuclear genome) the mitochondria which are abundant in the cytoplasma of the cell contain another genome (mitochondrial genome) which consists of annular DNA. This genome contains 16,569 base pairs with a total

of 37 genes, i.e. it is much smaller than the nuclear genome. Mitochondria are also present in egg cells. This is why mutations of mitochondrial DNA are practically always passed on from mother to embryo (maternal inheritance).

3. 2 Variability in the human genome

In the genetic process which precedes the development of germ cells (meiosis), changes in DNA (mutations) may occur which are passed on to the next generation. If the genetic programme is changed in this way, mutations will have an adverse effect on cellular function and perhaps on the function of the entire organism. But mutations may also have no functional effects whatsoever and thus remain phenotypically silent. There are several explanations for this phenomenon. Either the mutations affect non-coding sequences of the genome or, even though they are located within coding sequences, they do not change the genetic information. It is extremely rare that mutations result in functional improvement.

The observable expression of genetic information which is caused by genetic control mechanisms is referred to as phenotype. The phenotype includes not only visible characteristics (such as body size, skin disease, deformity etc.), but also those that can only be detected by means of specific equipment (X-ray, sonography, blood tests etc.).

Most cells of an organism have a limited life span. Throughout the life of an organism its cells are renewed as a result of ongoing cell division. In the process genetic information is passed on from cell generation to cell generation. When body cells divide (somatic cell division), DNA mutations may occur as well which at first affect only one cell. If the body does not eliminate or repair such mutations or the cell carrying them, all daughter cells of this particular cell will carry the mutation. The result is a cloned cell with changed characteristics. This, for example, is the usual developmental pathway of malignant tumours (cancer).

A gene contains encoded information necessary for the development and control of all cellular processes. In a complicated process the information carried by DNA is passed on step by step: First, the information is transmitted to RNA (ribonucleic acid), a process referred to as transcription. Then the genetic information is translated into amino acids, so-called proteins.

The characteristic nature of a protein is determined by the number and sequences of its amino acids.

A complicated control system regulates the expression of genes as gene products. Only active genes are expressed as gene products. Depending on tissue and cell type, only certain genes are active in a cell at a given point in time, others are temporarily or permanently switched off. As a result, cells with identical sets of genes produce specialised cells which accomplish specific tasks in the organism.

As a rule, the specialised cells of a certain tissue (e.g. liver, kidney or connective tissue cells) pass on their characteristic pattern of activation to their daughter cells. During such an "epigenetic" regulation process changes occur in the phenotype of a cell or tissue. In addition, the activation patterns of particular chromosomal regions (e.g. 11p15, 15q11-q13) differ, depending on whether they are of maternal or paternal origin: When germ cells develop, this region is inactivated in one of the two sexes, a phenomenon known as imprinting. After fertilisation the "imprinted" region will suppress the expression of genes of the chromosomal sequence concerned. Some genes are not translated into proteins, but the RNA itself will carry the information. Some regulatory molecules are also involved in this process.

Exploring the regulation of gene activity is an important task of genetic research. One of the major foundations of this work is the Human Genome Project which was launched in 1990 by the US Department of Energy and the US National Institutes of Health in co-operation with international research centres. This project is aimed at sequencing all 3.2 billion DNA building blocks of the human genome. But the term 'human genome project' is misleading in a way because it implies the existence of one single human genome. In fact, the DNA sequence is characterised by considerable variability. If you compare the genomes of any two individuals, you will certainly find that the base sequence tallies in 99.9 per cent of the cases, but the remaining 0.1 per cent means that on average there are about 3 million differences in sequence. Most probably, the greater part of these differences does not have any functional effects. But the remainder has an impact on the phenotype. These differences form the basis for the genetic contribution towards variability in humans, in terms of both "normal" aspects such as appearance, personal characteristics or talents, and a predisposition to certain diseases. Knowledge of genetic variability is of extraordinary importance for biomedical research.

Since mitochondrial DNA is subject to a mutation rate ten times higher than that of nuclear DNA, the variability of the mitochondrial genome is much greater than that of the nuclear genome.

Certain sequence repeats in the human genome (see box) are of great significance for human genetics because they can be used as landmarks within the genome. They are also extremely important for research purposes because they serve as genetic markers. In fact, these markers helped to map a large number of genes whose mutated forms are responsible for hereditary diseases even before the function of these genes was known. The US human geneticist, Victor McKusick, compared the total knowledge relating to morbidity to an anatomical atlas of diseases in the human genome ("morbid anatomy of the human genome"). This comparison underlines the extraordinary importance that genetics has for understanding the causes of disease.

The variability of the human genome also has a great impact on forensics, especially when it is used for identification purposes. Genetic markers make it possible to distinguish one individual from another by examining their genetic material (e.g. blood samples).

Variability in the human genome

Variability in the human genome can mostly be categorised in two groups, sequence repeats and polymorphisms. Sequence repeats account for about 55 per cent of the genome.

Sequence repeats in turn can be broken down into two categories: ***Minisatellites*** (also referred to as VNTRs, variable number of tandem repeats) with repeats of 12 to 500 base pairs, and ***microsatellites*** (also called STRs, short tandem repeats) with repeats of 1 to 11 base pairs. As the sequences can be repeated several times they are referred to as tandemly repeated DNA sequences. The number of repeats is highly variable. 70 to 80 per cent of humans have a different number of sequence repeats in the minisatellites at the corresponding (homologous) sites of their genome, in other words, they are heterozygotes. Microsatellites (especially dinucleotide and trinucleotide repeats) make up about 0.5 per cent of the genome. There are about 80,000 dinucleotide repeats and approximately 50,000 to 60,000 trinucleotide repeats in the genome which are also extremely variable. As a rule, minisatellites and microsatellites are located in the non-encoding segments of the genome. According to current knowledge this

means that they do not have an impact on the phenotype. But a few trinucleotide repeats are known to cause various neurological diseases once their number exceeds a certain threshold.

Substitutions of single nucleotides ***(single nucleotide polymorphisms, SNPs)*** in the genome are very frequent. Their total is estimated at 11 million of which 2.1 million have so far been identified. Originally, a gene locus where several alternative forms (alleles) occur in the population with a certain frequency was defined as a polymorphism; in this case the frequency of the rarer allele has to be at least 1 per cent. Many SNPs do not have any functional impact. Deviating from this definition, the term 'polymorphism' – irrespective of the allele frequency - is often used nowadays to describe the variable loci in the genome which do not affect the phenotype. Today, the term 'sequence variation' is preferred in international literature. This term is used to describe the existence of two or more alleles occupying a DNA locus, irrespective of the frequency of occurrence in a given population and of the phenotypical effects.

3.3 Genetic diseases

Genome changes (mutations) may have an impact on functions. If these changes affect body cells only (somatic mutations), the mutations are not hereditary. Most forms of cancer, for example, develop in this way. If mutations are present in all body cells and in germ cells (germ line mutations), they can be passed on to the next generation. It is germ line mutations that are the cause of genetic diseases.

Based on the type of mutation involved and its functional impact, three categories of genetic disorders can be defined:

- Diseases caused by chromosomal aberrations
- Monogenic (single-gene) disorders
- Complex (multifactorial) genetic disorders.

Chromosomal aberrations

In the nucleus of a cell the entire DNA is distributed along its 2 x 23 chromosomes. There is a fundamental link between the size of the chromosomes and the number of genes they carry. Chromosomes also differ in terms of gene density. Each chromosome contains a substantial number of genes. A balanced regulation is a characteristic of cell and tissue metabolism. If there is a loss or addition of chromosomal material, a large number of genes is usually affected.

There are two types of chromosomal abnormalities, those where the *number* of chromosomes has changed (numerical chromosomal aberrations) and those where the chromosome *structure* is altered (structural chromosomal aberrations). Except for the sex chromosomes, numerical chromosomal abnormalities always have phenotypical effects associated with severe diseases. If only the sex chromosomes are affected by numerical chromosomal abnormalities, the phenotypical effects may be minor in nature. Should structural chromosomal aberrations be associated with a loss or addition of genetic material, an imbalance will result which usually leads to severe functional disorders. Numerical or structural chromosomal aberrations occur in about 0.5 per cent of all newborns. The better part of these abnormalities occurred in the germ cell of one parent for the first time (de novo mutation). Often chromosomal disorders cause characteristic clinical features; Down's syndrome, for example, occurs when a person has three copies of chromosome 21 (trisomy 21). Apparently, the increased number of all genes on chromosome 21 leads to a relatively uniform overall picture of functional disorders. There are also structural chromosomal disorders (translocations within a chromosome or between two chromosomes) which are genetically balanced und usually do not have any phenotypical effects.

Monogenic diseases

Monogenic diseases are caused by the alteration (mutation) of a single gene. McKusick's list (OMIM) currently contains more than 14,000 entries. Each entry indicates a monogenic hereditary trait. At present, 1,700 such traits have been characterised in molecular genetic studies, covering 1,336 genes. Monogenic diseases can be diagnosed independently of their manifestation, also by prenatal diagnosis.

The great majority of monogenic disorders are rare, but there may be major differences between various ethnic groups. Some single-gene defects, on the other hand, occur quite

frequently. About 100 million people worldwide are affected by certain disoders of haemoglobin (blood pigment) synthesis, called thalassaemias (autosomal recessive inheritance). In 400 million people the gene of glucose-6-phosphate dehydrogenase has undergone mutation (X-linked recessive inheritance). This mutation is associated with reduced enzyme activity, thus affecting the metabolism of certain chemical substances, including drugs. In the persons affected this may lead to severe effects. The great majority of persons of Asian or African origin are affected by autosomal recessive lactose intolerance, while most people of Central or Northern European descent are free from this disorder.

A mutation will cause a clinical disease if a functional disorder results which is so severe that the organism cannot develop any compensatory mechanisms. This is why detecting the cause of a monogenic disease often provides an idea of basic biological functions at the same time. In many cases monogenic diseases are like a keyhole permitting a glimpse of and some insight into biological mechanisms that were previously not understood. Knock-out mice which are specifically produced for animal experiments are the animal equivalents of patients with monogenic disorders. In these experimental animals genetic engineering methods were used to knock out a gene so that the mice develop a monogenic disease. Knock-out mice play a major role in detecting pathogenic mechanisms. The animals may also be used to test new therapies for genetic diseases.

Functional disorders caused by monogenic diseases may be severe. In such cases therapy is usually difficult. But there are also monogenic diseases whose course can be influenced. The effects of lactose intolerance, for example, can be prevented by excluding lactose from one's diet.

All humans are heterozygotes for several mutations which in the case of homozygosity will lead to an autosomal recessive disease. As this disease is asymptomatic there is no reason to search for these mutations. But in principle, it would be possible to detect the heterozygous mutations in healthy persons by employing molecular genetic methods.

Types of monogenic diseases

Depending on a gene's effects, genetic diseases within a family occur in the members of this family according to a certain pattern based on Mendel's laws.

Autosomal dominant diseases. Irrespective of the sex of the person affected these disorders already become manifest when only one of the two gene copies has mutated (clear phenotype deviation from normal of the heterozygous state) and the gene locus is not on the X chromosome (autosomal). Children of a patient run a 50 per cent risk of inheriting the mutation. The more severe the effects of the condition are at a young age, the more improbable it is that the patients will have any offspring. Severe early-onset autosomal dominant diseases therefore are mostly caused by de novo mutations.

Autosomal recessive diseases. These diseases become manifest - irrespective of the sex of the person affected - when both gene copies contain a changed sequence (mutation) (homozygosity in the case of identical mutations, compound heterozygosity in the case of two different mutations) and the gene locus is not on the X chromosome. Both parents, though heterozygotes for the mutation concerned, are usually healthy. The statistical risk of the disease manifesting in their children is 25 per cent. When two partners have common ancestors, the probability that autosomal recessive disorders will occur is higher. As a rule, autosomal recessive diseases do not manifest in the ancestors of patients, unless it is a population where consanguinity is common. Mutations resulting in autosomal recessive diseases are relatively frequent in the population (heterozygote incidence 1:10 to 1:100). De novo mutations do not play a major part in the manifestation of diseases.

X-linked recessive diseases. Females have two X chromosomes, while males have an X chromosome and a Y chromosome. Diseases occur as a result of a mutated gene located on the X chromosome. As a rule, only members of the male sex are affected. Female heterozygotes for the mutant allele (carriers) show only a mild clinical manifestation, if any at all; it is only in exceptional cases that they develop the disease. On average, carriers pass on the mutation to 50 per cent of their offspring, but only males will develop the disorder. In the case of severe early-onset X-linked recessive diseases a considerable part of the disorders is attributable to de novo mutations.

Mitochondrial diseases. Genes contained in mitochondrial DNA are mostly related to the energy metabolism. Consequently, mutations of these genes manifest particularly in high-energy tissues such as brain, muscles and sensory organs. Mitochondrial diseases can affect

both sexes. Generally, mitochondria are inherited via the mother which is why maternal inheritance is characteristic of these diseases.

Complex (multifactorial) diseases

Many diseases have a certain high familial incidence, but do not comply with Mendel's laws. This applies in particular to the most common diseases such as hypertension, diabetes mellitus, allergies, epilepsy and many psychiatric diseases. In many cases, a genetic predisposition (susceptibility) is probably underlying these diseases. It will then depend on environmental factors (in the widest sense) or the interplay of various genes whether or not this predisposition will lead to manifest disease.

A traditional method used to assess the contribution of genetic factors towards the development of a disease is the study of twins. There are two types of twins, monozygotic twins who are genetically identical, and dizygotic twins who, like ordinary siblings, on average share half of the genetic make-up. A comparison of the concordance rates in the two types of twins allows an assessment to be made of the relative role that genetic and non-genetic factors play in pathogenesis. The rate of discordance in identical twins, for instance, is a measure of the importance of exogenous pathogenic factors. With most multifactorial diseases, the concordance rate in monozygotic twins is around 40 to 60 per cent, in dizygotic twins around 10 to 15 per cent. On the one hand, these findings point to the effects of genetic factors, but on the other hand they also show that it must be environmental factors which determine whether or not a multifactorial disease will become manifest.

There is still little understanding of the type of genetic predisposition to most of these diseases. A predisposition may be based on a genotype which only under very specific circumstances leads to functional disorders, or on the combination of two or more genotypes which are passed on to the next generation independently of each other. Unlike monogenic genetic diseases, the gene changes which predispose a person to complex genetic diseases have a high incidence among the population.

Often multifactorial diseases are not difficult to manage therapeutically since they are determined not only by genetic factors, but also by environmental factors which can be changed. But so far drugs have mostly been developed without any clear idea of the aetiology

of the diseases concerned. Consequently, understanding the underlying genetic mechanisms will be of far-reaching importance for the development of new therapies. The following consideration may serve to illustrate the therapeutic possibilities available: Monozygotic twins, as outlined above, often have a 40 to 60 per cent concordance for multifactorial diseases. Based on the example of schizophrenia, a realistic estimate shows that the power of molecular findings will be limited. Twin studies have demonstrated that both genetic and environmental factors play an important part in the development of this psychiatric disease. If one of a pair of monozygotic twins develops schizophrenia, the risk for the other twin to develop the same condition is not 1 per cent which would be the basic risk of the population at large, nor is it 100 per cent which would be the case if this disease were exclusively genetically determined. Rather, the initially healthy twin will develop symptoms in about 50 per cent of the cases. This goes to show that genetic predisposition indeed plays a key role; but even if in future every single factor accounting for the genetic contribution to pathogenesis were known (several dozen rather than a few genes are expected to be involved), one simply could not say whether or not an affected person will actually develop the disease, because non-genetic factors also contribute substantially to the process of disease development. Consequently, there must be exogenous factors which either prevent a genetic predisposition from turning into a full-fledged disease or further this process. The manifestation of a genetic predisposition can be modified by exogenous influences. If scientists knew the exact mechanisms involved, they should be able to use this knowledge for developing appropriate therapies.

In order to understand the role played by genetic risk factors and environmental influences and their interaction it is necessary to study large groups of patients and healthy persons and even conduct epidemiological studies among the population at large. To this end, DNA samples of selected persons need to be collected (see section 5.5). In future, research will increasingly depend on such collections which is why they have to be made available to science. A better understanding of the interactions between genotype and environment will also permit new preventive strategies to be developed.

Even if mutations have been identified which predispose a person to a multifactorial disease, the link with the disease will always have only a statistical, i.e. probabilistic, quality and hence permit conclusions to be drawn only in terms of probability. It is possible to determine the "relative risk" of the carrier of the mutation of developing a certain disorder. Even if all

genetic risk factors are known which, taken together, account for the genetic predisposition to a disease, the level of predictability of this disease will at most reach the concordance rate of monozygotic twins. Consequently, it will never be possible definitively to predict or preclude the occurrence of a multifactorial disease by employing genetic methods. This is why it is wrong to assume that there is such a thing as genetic determinism, and concerns along those lines are unfounded.

The situation is even more complicated when it comes to functions of the human brain such as intelligence, creativity or sexual preference. It is true that studies of family members and especially monozygotic twins suggest that here, too, genetic influences can play a certain role and may be responsible for some of the differences between different people. But it is still open whether it will ever be possible to establish a clear and unambiguous correlation between such phenotypes and specific genes.

4 Genetic diagnosis in medical practice

4.1 Methods

Genetically (co-)determined diseases may be diagnosed at different levels. These include the physical examination of a patient and the classification of, for example, skeletal deformities or dermatological symptoms as being associated with a certain clinicalcondition. Various test procedures may be used to confirm or disprove the diagnosis of a suspected disorder. A case in point would be the use of colour perception tables to diagnose X-linked red/green blindness. Hereditary types of arrhythmias (e.g. long-QT syndrome) can be made visible by means of an ECG. Imaging procedures such as ultrasonography can show pathological organic structures (e.g. renal cysts as the manifestation of an autosomal dominant polycystic kidney disease). Familial adenomatous polyposis (FAP) can be established by an endoscopic examination of the colon.

Laboratory tests offer a wide range of additional diagnostic possibilities, with different types of specimens being analysed. Biochemical procedures make it possible to examine gene products and thus establish the presence of certain metabolites indicating a hereditary metabolic disorder. Analyses of the genetic material proper, i.e. of entire chromosomes, DNA segments or RNA, can reveal functionally relevant deviations from the normal structure.

Specific molecular genetic studies are of great importance for basic biomedical research and are playing an ever greater role in the diagnostic process. They permit a better sub-classification of disorders and a more precise prognosis. Moreover, it is possible, based on the knowledge of the pathomechanisms underlying a clinical picture, to develop new therapeutic concepts specifically geared to the disorder concerned. Methodological progress such as chip technology enables a host of data to be collected in a single experiment; without such developments it would be necessary to perform a large number of individual analyses. But in qualitative terms the information they yield does not differ from that produced by conventional procedures.

Diagnostic chips

The principle underlying chip technology is that narrow, orderly arrays of molecules are applied to a flat surface, e.g. glass. As a result of the technical developments of the last few years it is possible today to arrange more than 250,000 different oligonucleotides on a chip with a surface of 1 cm^2. Chip technology permits the parallel study of interactions between a large number of molecules such as nucleic acids or proteins; accordingly, there is a distinction between DNA chips and protein chips. The molecules on the chip make it possible to identify the specific bonding partners in the mixture of the analysed sample. This miniaturisation goes hand in hand with automation which permits a high throughput of samples to be analysed and evaluated.

The complete sequencing of all 3.2 billion DNA units of the human genome provides a much better starting point for exploring and understanding the molecular basis of diseases. But we are still a far cry from genuine understanding, i.e. the actual decoding of the human genome. Quite apart from the fact that so far not even the exact number of human genes has been determined, their functions and complex interactions in different tissue and developmental phases are very little understood.

The method used for genetic diagnosis does not per se determine the diagnostic depth or power. The diagnosis of dyschromatopsia by means of molecular genetic procedures does not have to be assessed differently from a conventional examination using colour perception tables simply because the genotype and not the phenotype is analysed. What is of great importance here is the context in which the genetic examination is performed, e.g. the differential diagnosis of a clinically manifest disease, determining a predisposition to a late-onset disorder, or the assessment of the physical fitness and performance of an athlete.

4.2 Application and interpretation of genetic test procedures

To interpret the results of genetic tests one has to consider various points, as illustrated by the example of monogenic hereditary diseases. Different mutations in a single gene, for instance, can trigger different symptoms.

- More than 950 mutations in the CFTR gene are known; this gene is defective in patients suffering from cystic fibrosis. The clinical consequences of these mutations range from severe life-shortening pulmonary disease to digestion problems due to loss of the pancreatic function to infertility in males as a result of a constitutional disorder of the seminal ducts.
- A particular mutation in the gene for a growth factor receptor (FGF receptor type 3) leads to hyposomia with a normal life expectation (achondroplasia), while a contiguous mutation in the same gene causes skeletal deformation and lethal respiratory distress immediately after birth (thanatophoric dysplasia).

Establishing the correlation between specific genotype and phenotype will contribute to individualising medicine.

It is not only that different mutations in a gene cause different clinical pictures, but conversely a specific clinical picture may be triggered by different genetic defects. A heterogeneous group of diseases of this type is retinitis pigmentosa, a retinal disorder which causes a progressive loss of vision and eventual blindness. This retinopathy may be caused by mutations in several dozens of different genes.

Even when there is an identical mutation in a gene, e.g. in several members of the same family, the clinical picture may vary considerably. In the case of type I neurofibromatosis, possible clinical findings range from pigmented brownish patches on the skin to benign, but cosmetically undesirable tumours consisting of connective tissue and nerve cells, to skeletal deformations and even to malignant brain tumours. It is not possible to infer the symptoms of one family member from those of another. Such differences are due to the fact that other, still unknown genes also influence the phenotype. This means that monogenic diseases, too, are actually complex in nature and that they can be considerably modulated by other genes and also by environmental factors.

It has also to be taken into account that the penetrance of a dominant genetic disorder varies and does not always lead to a manifest disease. While there is a 100 per cent certainty that in carriers of Huntington's disease the disorder will break out at some point in their life, the probability that women with an inherited predisposition to breast cancer as the result of a mutation in one of the BRCA genes, will actually develop a tumour is between 25 and 85 per cent, depending on the type of mutation. At about 5 per cent, the risk of disease in male carriers of the same mutation is even lower.

A number of exogenous noxious agents (e.g. drugs) can damage the embryo during pregnancy and cause diseases whose symptoms are identical with those of monogenic disorders. Such phenocopies are not associated with an increased risk of repetition if the teratogenic agent (the substance damaging the embryo) is discontinued. In other words, a clear distinction between environmental influences and genetic causes is of essential importance.

The pathogenesis of single-gene disorders is much more complex than expected. But this applies even more to diseases which are caused by a wide variety of genetic disorders and their interactions with environmental factors. These include many common diseases. Conversely, it is becoming more and more obvious that almost all diseases also depend on the genetic constitution of the person concerned. A case in point is the defence against infective agents. About one per cent of the people in our population are substantially resistant to AIDS because they do not develop one of the two docking sites which the HIV virus needs to penetrate into host cells. The reason is a homozygous mutation (CCR5Δ32 allele) in a chemokine receptor gene. On the other hand, the susceptibility to, and mortality caused by, infectious diseases such as tuberculosis or streptococcal pneumonia may be increased for genetic reasons.

Another interaction which is more and more shifting into the focus of medicine is the response of an individual to drugs, i.e. the field of pharmacogenetics. Various components which recognise, transport or metabolise chemical compounds decide on whether a particular drug will produce the desired effect, whether it will be not efficacious at all or whether it will cause lethal complications. Cases in point are variants of the ryanodine receptor which under halothane anaesthesia may dispose the patient to a life-threatening increase in body temperature (malignant hyperthermia), and variants (so-called poor metabolisers) of the

CYP2D6 enzyme (sparteine/debrisoquine hydroxylase) which lead to a slower metabolism of certain drugs, including psychoactive drugs. Consequently, this may result in an accumulation of the drug and adverse effects.

Knowledge of the hereditary predisposition to complex diseases of different organ systems is growing rapidly as a result of human genome research. This applies to the propensity of carriers of mutations in the NOD2/CARD15 gene to develop Crohn's disease, an inflammatory bowel disease, and to the association of polymorphisms in the ADAM33 gene with the predisposition to bronchial asthma. Scientists today feel that they have succeeded also in identifying some of the genes involved in the development of psychiatric diseases such as schizophrenia.

Not every genetic test is per se related to medicine. A case in point is the DNA fingerprint which plays a major role in forensic investigations and whose use and quality control have in part already become subject to the Code of Criminal Procedure (*Strafprozessordnung*).

4.3 Types of predictive diagnosis

Predictive diagnosis (or predictive testing) offers the possibility to identify a predisposition to a particular disease even *before* clinical symptoms are manifest or to predict the probability of occurrence of the disease. Depending on the type of disease concerned, it is possible to make predictions based on simple clinical examinations, imaging or biochemical procedures and genetic methods. Among these, genetic methods have the greatest importance due to their universal applicability. When a genetic predisposition has been identified, all that is possible in many cases is to predict the probability of disease manifestation. The time of the potential future onset of the disease cannot be precisely derived from the findings, either. Many years or even decades may elapse between obtaining the test results and the occurrence of the first signs of the disease, involving a phase of uncertainty which may vary in length. On the other hand, predictive diagnosis can provide the opportunity to identify a disease at an early stage and start a therapy or take preventive measures. A stressful situation can be relieved when it is possible to exclude an assumed higher risk of disease which, for instance, was derived from a family history. But predictive genetic diagnosis may also entail certain dangers as a result of

wrong, contradictory or undesirable information. This is why in any case the performance of predictive tests should be subject to special conditions, as discussed in detail below.

Contrary to a common notion, there are no search procedures which would cover all genetic risks across the board. Rather, each test addresses specific issues. This is why it is necessary to determine in advance which person is to undergo which test to identify which risk. There have to be indications of such a risk, e.g. the family history pointing to the occurrence of a disease in other members of the family. But not every genetic disease is associated with a higher familial incidence.

There are several areas of application for predictive tests to which different conditions apply.

4.3.1 Newborn screening

One example of testing an entire population is the screening of newborns for congenital metabolic disorders. But the implementation of such a diagnostic scheme which affects all neonates in a given country has to meet a number of criteria. It should only be considered if the disease in question causes severe harm, if untreated, and if the test helps to diagnose it in time before it becomes manifest. The test itself must be reliable and affordable. What is of particular importance, however, is the availability of an effective therapy. A typical example of successful preventive intervention is phenylketonuria (PKU) which, if untreated, leads to severe brain damage. Since newborn screening was introduced about 30 years ago, it has been possible to save several thousands of children in Germany from this fate. Therapy consists in a low-phenylalanine diet. But the protein hydrolysate used in this diet has such a revolting taste that the affected children and adolescents are eager to end the diet as soon as possible. Unlike untreated and hence severely mentally disabled patients, successfully treated adults with PKU are able today to start a family. Surprisingly, however, a severe complication was found in young women with PKU who were permitted to discontinue their unpleasant, strict diet after the brain had fully matured. Their phenylalanine level would rise again and in case of pregnancy severely damage the unborn child. This teratogenic effect of phenylalanine, an amino acid, had previously not been known. This example demonstrates that the introduction of meaningful diagnostic and therapeutic strategies can lead to unforeseeable problems at a later stage. This is why it is of fundamental importance that even after they have been

introduced into regular patient management regimes, such procedures are evaluated by means of accompanying scientific studies.

4.3.2 Prenatal diagnosis (PND) and preimplantation genetic diagnosis (PGD)

In principle, it is possible to perform predictive genetic tests on the unborn child, using the methods and addressing the issues described above. Since the 1970s the examination of foetal cells has been an established method. These cells are obtained by amniocentesis after the 14th week of pregnancy. Since the 1980s it has been possible to establish a genetic diagnosis as early as the 10th week of gestation by studying placental cells (obtained by means of chorionic villus sampling). In addition to these invasive techniques of prenatal diagnosis (PND) which are legal also in Germany, the method of preimplantation genetic diagnosis (PGD) has been available abroad since the 1990s. For PGD one or two cells are taken from three- to five-day old embryos generated in vitro in order to confirm or exclude the suspected genetic predisposition to a disease before the embryo is transferred into the uterus. There is an ongoing highly controversial debate on the legal and especially the ethical admissibility of this technique in Germany where so far it has been prohibited. A similar discussion, albeit much less heated, is going on about the ethical aspects of PND (cf. the statement of the German National Ethics Council on PND/PGD of January 2003). These debates focus on issues such as the protection of embryos, the problem of selection and the limitation of indications. These specific and complex aspects would require a separate discussion which is not intended in this statement.

4.3.3 Screening programmes for autosomal recessive diseases

One possibility to establish whether there is an increased risk of children being born with autosomal recessive diseases is to identify carriers (heterozygote test). In these instances the carriers themselves are clinically healthy; however, there is a 25 per cent probability that two carriers will produce children in whom the clinical picture is manifest. Some countries where the incidence of specific mutations is high offer population screening programmes, e.g. for carriers of haemoglobinopathies (thalassaemias) in Mediterranean countries. As at-risk couples underwent prenatal testing or decided not to have any children of their own there was a clear decline in the incidence of this disease in those countries. But such heterozygote

screening programmes also have some weaknesses. The problem lies in the information about the test result and in how it is taken into account. A few years after having been told about the test result, many carriers of cystic fibrosis, for example, were no longer aware of the significance of the findings (they felt that they themselves had a health impairment) or of their own status as carriers. It is also problematic to describe these measures simply as methods of disease prevention without taking into account that subsequently family planning decisions will be taken – including, not least, decisions on pregnancy termination.

Also in the case of autosomal recessive predispositions to diseases the penetrance of a mutation may vary considerably. Genetic haemochromatosis, for instance, leads to an increased absorption of iron from the diet. About 8 to 10 per cent of central Europeans are heterozygotes for a mutation in the HFE gene which predisposes to this disease. The clinical symptoms are caused by the progressive functional loss of various organs (liver, heart, pancreas) due to an increasing iron overload which may even cause hepatocellular carcinoma. More than 90 per cent of patients with hereditary haemochromatosis have a specific HFE mutation (C282Y) in a homozygous form. On the other hand, pilot studies for population screening showed that only 1 per cent of all persons with this genetic constellation had clinical symptoms at the time of analysis and that their lifetime risk of clinical manifestation was 10 to 40 per cent at most. Other genes regulating the iron metabolism modify the penetrance of HFE mutations, as do exogenous factors which may have a protective (e.g. chronic blood loss in women due to menstruation) or negative effect (such as alcohol consumption). Although there is a simple and effective method to prevent organic lesions in patients with hereditary haemochromatosis, i.e. phlebotomy (blood letting), further studies are needed because the penetrance of HFE mutations is low and cannot be safely assessed in the individual case. These studies will help to clarify the benefits of an extensive genetic screening programme.

Similar considerations also apply to a mutation in the factor V gene (factor V disorders) which, with a prevalence of 1 to 5 per cent, is common in Europe. This mutation leads to a predisposition to venous thrombosis and its sequelae such as embolisms. In this case, too, the activities of other coagulation factors and exogenous risk factors (e.g. oral contraceptives) have an influence on the clinical manifestation of this genetic predisposition.

4.3.4 Predictive diagnosis of adult-onset diseases

The predictive genetic diagnosis of adult-onset diseases such as Huntington's disease or other hereditary neurodegenerative disorders involves special problems. Huntington's disease usually becomes manifest in the fourth decade of a person's life, leading to progressive impairment of cerebral function and dispersonalisation over a period of about 15 years and eventually to death. This means that often the first symptoms occur when the patients already have children who have a 50 per cent risk of being a carrier of the mutation themselves and of then almost inexorably developing the disease as well. At present, there is no causal therapy. There are easily understandable arguments for and against testing; the decision to undergo such tests can only be taken individually by each member of an affected family. But it is important to make sure that the individual is aware of the implications of his or her decision. It must be borne in mind that the right to know and the right not to know must be weighed against each other not only with regard to one's own person; a test result may also have implications for other family members who might take a different attitude to this diagnostic procedure. It is also necessary to point out the possibility of paradoxical reactions after the findings have been communicated. For instance, a person may develop a depressive disorder after learning that their own test results are normal, because they feel guilty that other members of the family are affected by the disease. Counsellors should also address issues that are outside the actual medical context, such as the right time to take out a life insurance policy. This is why it is important to couch the genetic diagnosis in a comprehensive counselling and care concept covering the period both before and after the actual testing phase.

Another area in which predictive diagnosis is gaining in importance is oncology. It is estimated that an inherited predisposition to tumours is underlying 10 to 15 per cent of all manifest cancers; many of the genes responsible are already known. However, this situation is different from Huntington's disease, because in some cases there are successful concepts for the prevention of the cancerous disease concerned, mostly involving surgical intervention. The prophylactic removal of the thyroid, for example, is recommended for familial types of thyroid cancer; removal of the entire colon while preserving continence has turned out to be successful in familial adenomatous polyposis (FAP), a hereditary colonic cancer. These examples prove that there is a positive side to predictive diagnosis as it permits cancer prevention in an affected carrier.

While FAP carriers – like carriers of Huntington's disease – run an almost 100 per cent risk of developing the manifest disease, the detection of a mutation in the BRCA genes associated with hereditary breast cancer does not allow a safe prediction to be made of the outbreak of the disease. Depending on the mutation, the risk varies between 25 and 85 per cent. For the time being, it is not possible to establish a precise correlation of genotype and phenotype and a clear-cut risk definition. Furthermore, the clinical evaluation of the options for the prevention or early detection of breast cancer such as imaging procedures, prophylactic medication and surgical intervention has not yet been completed. Before a molecular genetic test is performed, the patient must be informed of this situation.

4.3.5 Lifestyle tests

In future, applications for predictive tests may develop which are at the interface between diagnosis of a disease and influencing a person's lifestyle. A case in point would be a polymorphism in the ACE (angiotensin-converting enzyme) gene where specific genotypes were associated with above-average physical performance. If it turned out that individual medical aspects need to be included in the interpretation of such test results, these tests should be performed on the initiative of a physician.

4.4 Quality assurance of genetic testing procedures

There is a large number of genetic testing procedures. They differ in terms of objectives, accuracy, predictive power, possible applications, reliability and effort required. Genetic tests are performed in hospital laboratories, some doctors' practices, companies and other laboratories. There are such a variety of providers and such a broad range of genetic testing procedures that the situation is rather confusing. Each laboratory offering genetic tests can only provide a limited number of testing procedures due to the complexity of the tests involved. This restriction to certain rare diseases ensures the laboratories' expertise in establishing a diagnosis and interpreting the test results. Genetic tests and the laboratories performing these tests must meet the currently valid professional standards (e.g. round robin tests providing the possibility of imposing sanctions).

4.5 Genetic counselling

Genetic counselling is the task and responsibility of physicians. They have to inform patients or family members seeking advice of the possible presence of a genetic disease, the diagnostic means available, the basic biological aspects of inheritance and whether there is a special genetic risk within the family. Counselling physicians have to explain about genetic testing in such a way that the person tested can easily understand its significance. They must explicitly draw attention to uncertainties involved in the interpretation of results and in the prognosis of consequences. In addition, it is necessary to assist the person tested and, if so required, their family in dealing with the test result and its implications. This information is to serve as a basis for decisions to be made by those seeking advice, e.g. decisions on family planning or the possibility of future treatment and care. Consequently, genetic counselling requires extensive knowledge of theoretical and clinical human genetics and a high level of interpersonal skills in individual counselling. Such knowledge and skills have to be acquired in continuing education courses required for the recognition as *Facharzt für Humangenetik* (medical specialist in human genetics). This needs to be taken into account when new testing procedures are introduced and applied.

So far, predictive diagnosis in Germany has mostly been part of the medical domain due to the voluntary self-restriction of all those concerned. The German Medical Association (*Bundesärztekammer*) in particular has made a quick and important contribution to ensuring this situation by publishing its code of continuing professional development and its quality assurance guidelines. The guideline for diagnosing a genetic predisposition to cancerous diseases deserves special mention in this context. It marks the first time in international medical history that the entire medical community of a country has been committed to an interdisciplinary care concept. This is based on the recognition that a physician is not able on his own to provide adequate information on all aspects of predictive diagnosis. In the USA, for example, an analysis of the cases where physicians had ordered and interpreted a genetic test for familial adenomatous polyposis (FAP) revealed severe error rates. In about one third of the cases the physicians who had ordered the test were not able to interpret the result correctly. This is why organ specialists, human geneticists and, if appropriate, psychotherapists each have to make their own important contribution towards the necessary holistic care and management of the individual patient.

On the other hand, it happens more and more often that also in Germany commercial laboratories offer genetic testing without any sound scientific basis. These laboratories advertise genetic tests for an anti-ageing risk profile and for a predisposition to hypertension, obesity, periodontitis, osteoporosis or drug addiction which lack a validated scientific and clinical basis. Another alarming feature is that for some indications, such as establishing genetic proof of an inherited predisposition to breast cancer, only a limited number of possible mutations in the BRCA genes are analysed without informing the person tested about the associated loss of predictive quality of the test result. Often this type of diagnostic offer is linked neither to an individual indication nor to adequate counselling. Increasingly, predictive genetic testing and counselling (without any medical indication) are also offered on the Internet.

These developments will gather momentum through the introduction of DNA chips (see section 4.1). At present, a genetic test is performed only if there is the individually determined and well-founded suspicion that the person concerned is predisposed to a certain disease. This principle would inevitably be overruled by the use of a DNA chip permitting a check of the mutational status of the most common monogenic diseases, since adequate consideration of the numerous individual components associated with each of the clinical pictures could not be guaranteed at all.

The ethical and legal considerations regarding the appropriate handling of predictive genetic diagnosis which will be outlined in the next section will look into these issues in more detail.

5 Ethical and legal aspects

5.1 Introduction

After sequencing the human genome the interest of the research community is focusing on the link between genetic predisposition on the one hand, and the pathogenesis and course of diseases and the possibility to influence them on the other hand. The resulting body of knowledge which is growing at an enormous rate doubtless offers humanity great potential benefits, but also entails considerable damage potential. This is why right from the outset international human genome research has been supported by parallel ethical, legal and sociological studies. They focus on identifying and evaluating potential risks, burdens or injustice and the regulatory action that may be required.

5.2 Special characteristics of genetic knowledge

The above observations have shown that there are four different aspects which can make handling the growing body of genetic knowledge especially difficult for both the individual and society:

(1) Genetic knowledge permits only limited predictions to be made with regard to disease, health or special abilities or skills. Tests performed to identify the predisposition to a specific disease serve either to diagnose the disease when symptoms already exist or to predict the future occurrence of the disease. In view of the multifactorial causes of many diseases and their often widely varying degrees of severity these predictions are mostly risk prognoses – often without being able exactly to quantify the risk and qualify the severity. These facts are complex enough as they are and even more so when looked at in detail, and by no means are they widely known.

(2) Like other areas of medical knowledge a large part of current genetic understanding tends to be diagnosis-related rather than therapy-related. In the foreseeable future the knowledge of genetic aetiologies will be much greater than the knowledge of how the outbreak of such diseases can be prevented or how they can be cured. Whenever there are such knowledge

gaps, predictive testing can provide a prognosis of diseases, illnesses or functional losses with a certain probability (probabilistic forecast) without at the same time providing the means for therapeutic management. This discrepancy may entail a major distress potential for the persons affected.

(3) Knowledge about a person's genetic constitution is supra-individual in the sense that it allows conclusions to be drawn as to the predisposition of other family members. This means that the control of, and access to, genetic data cannot be individualised in the same way as is the case with "conventional" disease data. But the limits are blurred. Phenotypical disease data, too, permit conclusions to be drawn regarding the predisposition and health of family members in those cases where it is known that the disease in question (also) has genetic causes. It is true that to a certain extent such conclusions could already be drawn in the past, based on the family history; but as genetic knowledge grows, such cases are becoming more frequent and the information obtained more precise.

(4) Like many other medical data, the genetic characters of an individual also have a certain importance for third parties who are not safeguarding any personal health interest, but in their capacity as employers or insurers are interested in the state of health and functional performance of the person tested.

Given that some genetic data provide indications as to the life span and quality of life of the person tested and may also touch upon issues such as choosing a partner and starting a family, it becomes clear that human genetics confronts medical ethics and medical law with major new challenges.

5.3 Ethical and legal principles

What is new about these challenges is not so much the fundamental issues that are raised, but rather the necessary concrete assessments, considerations and social solutions. They call for ethical sensitivity, far-sighted legislation and social responsibility.

The first fundamental principle which is of relevance in this context is that of **respect for the self-determination of the individual**. Our culture, our ethics and our constitution accord high

value to a person's unrestricted right to decide freely on issues affecting their own life and lifestyle. As long as it does not violate the interests and rights of other people, an individual's self-determination deserves to be respected, protected and furthered – as a value in itself, as an expression of human dignity and as a means to achieve personal well-being and implement personal values. This is the point of convergence of political liberalism, the value system underlying our constitution and ethics as it has developed since the era of enlightenment.

And this is also why it has to be ensured – with regard to genetic tests and data - that individuals themselves can decide what aspects of their genetic constitution they want to have tested, what they want to know and what information they want to disclose – and what not. Since knowledge of one's own genetic make-up cannot only open up, but also destroy possible courses of action, everybody must have the opportunity to prefer the uncertainty and openness of their own future to its predictability. But it is not enough merely to respect such decisions by recognising the "right to know" and the complementary "right not to know". Ethics and the law rather have to make sure that such decisions are *informed* choices, that the individuals concerned really understand the power and limitations, the concrete benefits and the stress potential involved in predictive tests. Consequently, education of the public, competent genetic counselling and the offer of psychosocial assistance are fundamental measures that need to be taken in this context.

The second relevant fundamental ethical principle is that of **care for a person's welfare and prevention of damage**. Obviously, the basic legitimisation of medical research and medical care is to further the well-being of patients and to alleviate diseases, ailments and impairments – if the persons affected so wish. Also in the case of genetic information, as outlined above, it is hoped that this knowledge will lead to preventive or therapeutic action. The persons affected will be enabled to take measures for early detection and to avoid risks which otherwise would lead to the outbreak of diseases (co-)determined by genetic factors. Physicians will be enabled to use therapies in a more individualised fashion by taking into account the genetic make-up of their patients. As described in section 4.3.5, this has already become reality in individual cases (such as hereditary susceptibility to tumours).

On the other hand, the only benefit offered by some predictive tests – as described above - has so far been that people could prepare for a risk of disease and bear it in mind when planning their lives. This compares with a substantial damage potential: Individual distress and anxiety

caused by the results of predictive tests may be considerable. Even the mere knowledge that such tests exist may put major decision-making stress on a person. When people become fixated on excluding more and more risks from their lives, their *joie de vivre* may be considerablyimpaired. When they get into the hands of unauthorised persons, genetic data may hold a potential for discrimination. And finally, test results may have an adverse effect on the well-being and the right to self-determination of family members when these receive worrying or undesired information about their own predisposition.

The third relevant fundamental principle is the principle of **social justice**. Here, the possibilities of genetic testing mainly raise issues of discrimination, e.g. with regard to health and life insurance. In this context, progress in genetics confronts us with the need to reconsider issues of equal access, risk balancing and genetic discrimination. This also applies to the work place: Even though individualised protection driven by their genetic risk is in the employees' own best interest, there is also the possible problem that employees are selected on the basis of genetic criteria.

Other issues of social justice arise when it comes to covering the cost of genetic tests. So far, health insurance schemes have paid for tests for monogenic diseases and chromosomal disorders. But new and more differentiated considerations are called for when it comes to tests for multifactorial disorders or even lifestyle tests. Answers to such questions can only be found in the context of the complex considerations regarding general access to the health care system which is why they cannot be pursued further in this statement.

The above (legal and) ethical considerations lead to a number of consequences with regard to the appropriate handling of genetic tests and their results; these consequences will be outlined in the following.

5.4 Preventing damage and ensuring personal autonomy in dealing with genetic data

5.4.1 Tests performed on persons unable to give their informed consent

Predictive tests to be performed on a person unable to give their informed consent require the consent of that person's legal representative and may only be performed if they serve the person's own immediate and urgent health interest. In such a case, not only the legal representative, but also the person unable to give their consent must be educated to the extent that they are able to understand. The criterion of serving the person's own urgent interest is only complied with if without the test results important measures to prevent the future development of a disease were not taken (e.g. in the case of familial types of thyroid or colon cancer).

Especially in the case of minors or persons who are only temporarily unable to give their consent the mere wish of third parties (such as parents) to gain information about the genetic constitution of the person concerned that might be of future relevance must not be considered sufficient reason to perform a test. From the ethical perspective it is important to note that a potential later interest of the individual *not* to know their own genetic make-up might be irreversibly thwarted.

5.4.2 Restriction of the performance of genetic tests to the medical profession

The increasing possibilities of genetic diagnosis, as described above, trigger new supply and demand mechanisms whose order of magnitude can hardly be predicted. But in any case it is obvious that tests are increasingly also offered in the private non-medical market. Here the question arises whether and to what extent only medical professionals should have the right to perform genetic testing and diagnosis (cf. also the considerations outlined in section 4.5).

At first glance, such a barrier hindering the development of a "free market for genetic testing" seems to restrict the autonomy not only of the providers of tests on the supply side, but also of

patients or clients on the demand side who otherwise would be able to decide themselves whether they want to be tested by a medical or non-medical provider. But a closer look reveals that, conversely, a statutory limitation of the performance of such tests to the medical community will not only serve the well-being of citizens, but also enable them to exercise their right to self-determination.

In order to decide freely and independently for or against a test an individual must be able actually to judge the opportunities and risks of the procedure as well as the predictive power and individual consequences of possible results. Usually it will only be possible to educate people in individual counselling sessions with an expert or an interdisciplinary counselling team, because this requires theoretical, clinical and psychological experience which should be available to each individual person concerned. In particular, it has to be ensured that in the end the individual is free to exercise his or her "right not to know". Others must not simply assume – even it is done with the best of intentions - that the person concerned does not want to receive the information, nor can this be inferred from many other people's wish not to know. In order to exercise the right not to know in a concrete situation the person concerned must clearly signal this specific wish; this in turn requires this person to have at least basic knowledge of what he or she could learn in greater detail if they so wished. The basic information required to exercise the right not to know has to be offered in a gentle manner and, if necessary, step by step, because a complete one-step transfer of information might already violate the right not to know which the person concerned might have wished to exercise. These are difficulties that can best be handled and resolved by adequately trained physicians who in addition to having extensive medical knowledge also are experienced and skilled in individualised counselling. In compliance with the regulations on informed consent which have been established in medical practice and research, counselling and consent have to be documented in writing.

The result of an analysis should also be discussed with a competent physician. This would ensure that the tested individual would still have the opportunity to exercise his or her right not to know, while those who wish to know and understand the test result could be offered the competent education and counselling they need. To enable a non-expert to understand the significance and implications of a test result and draw free and independent conclusions, an expert is needed who in an individualised session explains in detail the special characteristics of the case in hand and describes what the test result may mean for the person tested and their

personal lifestyle (perhaps also pointing out that such results may only have limited predictive power). Furthermore, the person tested should receive a written report specifying the test result and highlighting the implications of these findings.

As a rule, only a triad of "counselling – diagnosis – counselling" will ensure that the persons concerned receive adequate information and can look after their personal concerns – which may be substantially affected by genetic analysis – in an informed and independent manner. Following the same line of argument, the Council of Europe's Convention on Human Rights and Biomedicine stipulates quite rightly that predictive genetic testing "may be performed only subject to appropriate genetic counselling".

Making genetic analysis contingent on counselling and making both contingent on medical expertise would not only protect the autonomy of the person tested, as described above. This also implies that the medical profession would be entrusted with the responsibility for defining indications and assuring the quality of genetic testing. In every single case there would have to be a medical indication and justification for performing a gene test which at the same time would prevent genetic diagnosis on a primarily commercial basis. Against this backdrop, the principle of excluding persons other than medical professionals from performing genetic tests would have to be complemented by prescription-only genetic test kits.

In addition, embedding gene analyses in the socially established system of medical care with its recognised principles and code of conduct would also provide protection for the individuals concerned by requiring the processes to comply with the criteria of ongoing quality assurance, integrity of the investigators, professional secrecy and data protection. These considerations apply not only to those tests which are directly aiming to establish a predisposition to a disease, but also to those that have only an indirect potential significance for the health of the person tested.

Established law which does not (yet) recognise the proposed limitation of performing DNA-based tests to the medical profession does not provide an adequate guarantee for the qualified performance of genetic tests that would sufficiently respect the rights of those concerned. Although some parts of genetic diagnosis are subject to the German law on naturopathy, the permission this law requires does not ensure the level of comprehensive quality and legal

security that should be provided by the legislator through introducing a law on the exclusion of persons other than medical professionals from performing genetic tests, supported by prescription-only test kits.

5.4.3 Quality assurance of genetic testing procedures

Genetic diagnostics, including appropriate test kits, are medical devices and products and as such are subject to the European Directive on in vitro diagnostic medical devices of 27 October 1998, the German Medical Products Act and the regulations supplementing this Act. But so far pertinent provisions have not addressed in sufficiently specific terms the issue of gene diagnostics and their special quality requirements. The same applies to the adequate *handling* of medical devices and products and hence also of gene diagnostics; section 2 para. 2 of the regulation concerning the operators of medical devices and products stipulates in a rather general way that medical devices and products may only be installed, operated, applied and maintained by persons who have the necessary training or know-how and experience. And finally the guidelines published by the German Medical Association for quality assurance in medical laboratories - to which section 4a para. 1 of the regulation concerning the operators of medical devices and products refers - do not so far contain any specific rules for cytogenetic or molecular genetic tests. Consequently, there is still a considerable need to specify the rules governing the quality assurance of genetic test procedures.

5.4.4 Data protection and professional confidentiality

As is the case with collecting, storing and using other kinds of personal data, a distinction needs to be made in genetics between (1) anonymised, (2) pseudonymised (or "encoded") and (3) personal data (i.e. data that can be assigned to a particular or identifiable person). In the first case a connection between the individual and associated data can only be established with extraordinary efforts in terms of time, cost and labour, or not at all. With pseudonymisation, however, the name and other identification characteristics are replaced by a code and thus rendered unrecognisable. In this way the identification of the person concerned is practically only possible if a key (reference list) is used.

When already anonymised genetic data are available anyway or when they are deliberately anonymised,improper use is almost certainly excluded. However, in medical research it is often important to be able to establish a connection between a person and their data.

Handling such personal (genetic) data is subject to the provisions of general and specific data protection laws which in Germany, however, vary slightly from state to state. In addition, there is the principle of professional confidentiality which – like data protection rules – prohibits the unrestricted disclosure of information even among persons who are subject to the same confidentiality rules (e.g. the medical community). The limits of the permissible disclosure of personal data must be observed especially strictly in those cases where the data are sensitive in nature. Based on the principle of data avoidance and data economy, it was also stipulated that personal data must be anonymised or pseudonymised where possible and where the effort entailed was proportionate to the interests sought to be protected (section 3a of the Federal Data Protection Act).

As a matter of principle, the use of personal data is limited to purposes that are covered either in a sufficiently clear form by the written informed consent of the person concerned or by a legal authorisation. Furthermore, legal research clauses permit the use and disclosure of personal data under a specific project - which otherwise could not be implemented - in those cases where public interest in the research project "prevails " or "prevails considerably" over the data privacy of the individual. These rather vague legal terms and the large number of pertinent norms lead to considerable legal uncertainty not only for the persons concerned, but also for the scientists involved so that counselling of scientists by their responsible ethics committee is of special importance. So far it has not yet been sufficiently clarified, either, how specific the consent of the person concerned to the use of their data must be and how general it may be (cf. section 5.5).

It is especially in the research sector that data are often pseudonymised. As a result, these data can no longer be connected with a particular person, even though it is still possible to link the data of an individual and re-identify them by applying the encoding key. As far as possible, the circumstances under which pseudonymised data may be decoded should be covered by the informed consent of the data subject. Subsequent decoding of the data may be in the data subject's own medical interest if the research results should reveal the possibility and necessity of treatment. In exceptional cases decoding might become necessary if the interest

of research prevails (just as the use of personal data – as outlined above – is generally permissible if public interest in the research project "prevails" or "prevails considerably" over the data privacy interest of the person concerned). In such a case the decision is primarily taken by a person or body ("data trustee") to be jointly appointed in the original consent procedure by the researcher and the data subject. The "trustee" could be a member of the research team, an ethics committee or, in the case of large data banks, also a notary public. But the undoubtedly necessary protection of the data subject by protecting the encoding key against any misuse must not lead to excessive bureaucratic or financial hurdles, thus hampering clinical research. It goes without saying that the dual role of the researcher-physician who, due to his personal knowledge of his patients, could identify their code must continue to be guaranteed.

5.5 Handling genetic specimen and data banks

5.5.1 Fundamentals

As outlined above, a major interest of medical research is to focus on the interplay of genetic predisposition and external factors in the development of clinical symptoms and the possibility to influence them. The knowledge hoped for should not only shed some light on the mechanisms underlying pathogenesis, but also help to develop new and individualised forms of treatment. Research projects of this kind require the collection of genetic specimens and data which, depending on the issue in hand, cover patient groups with a particular disease or representative groups of the population and which permit genetic data to be linked with other relevant data of the data subjects. By searching such specimen and data banks for the common presence of certain genetic marker patterns and characteristics, investigators can discover correlations between genotype and phenotype. Genetic specimen and data banks also make it possible to look specifically into the question of how a correlation between genetic markers and the phenotype found in patient cohorts affects members of the population at large. In some cases, existing specimen and data banks may be used or extended for such projects, but it is also intended to establish new large DNA collections. The large-scale banks which were established or are planned in some countries such as the UK, Estonia and Iceland are particularly spectacular. Hundreds of thousands of donated DNA specimens and many

other donor data relating to physical traits, lifestyle, diseases or environmental exposure are stored in these banks and, in some cases, even complemented on an ongoing basis. Of course, these banks are based on working hypotheses to be tested regarding the correlation between specific genetic traits and specific phenotypical characteristics. But it is in the very nature of such projects that the issues and hypotheses for which the collected and banked specimens and data may be of interest can hardly be grasped in their entirety at the time when the specimen banks or data collections are established.

The general view is that the donation of specimens and data for purposes of genetic research has to satisfy two requirements which are considered fundamental in all areas of bioethics and biolaw:

- First, the donation has to be objectively justifiable in terms of its harmless or beneficial nature. In clinical medicine, this is to be guaranteed by the standards governing medical indication and quality, in research a review by ethics committees is required. An intervention that is objectively considered to be too risky would not be legitimised, no matter how autonomous the person concerned is in giving their informed consent. Against this backdrop, suitable measures need to be taken – especially with regard to storing, linking and possibly complementing data - to ensure data and donor privacy. It must be guaranteed above all that data are not disclosed to third parties, in particular employers and insurers, nor must they be divulged in the context of forensic issues. It must also be ensured that unauthorised persons cannot access the encoding list which would help to identify pseudonymised data.

- Second, the donation must be based on the free and independent decision of the donor. To ensure this, potential donors must understand what this actually means. Above all, they must be informed of whether and, if so, how their specimens and/or data will be encrypted and protected and under which conditions and after what time the specimens and data should or can be destroyed. This may vary, depending on the type of collection concerned and the study design chosen. The same applies to decisions to be made by the legal representatives of persons unable to consent to the use of their specimens and data.

As a matter of principle, the data subject, in order to protect his or her privacy, must be entitled to stop a previously agreed prospective data input at a later point in time. The same holds for the destruction of tissue specimens and the deletion of his or her personal code. Subject to special legal provisions, the data subject may also declare, by subsequently withdrawing their consent, that data already collected must not be used any more or have to be deleted. However, it should be possible in the donation agreement to limit the period of time within which such a withdrawal is possible (e.g. to one to three years after taking the specimens). This would make sense because destroying specimens and/or deleting data at a later point in time may not only hamper the continuation of research activities already underway, but also – and this is important - jeopardise the validity and verifiability of previous research. In compliance with good research practices, data underlying scientific publications must be kept for 10 to 15 years for verification purposes. This means that when withdrawal is agreed upon, the legitimate expectations of researchers and the priority right to privacy of the data subject need to be balanced. Incidentally, it would not be justified from the scientific point of view to demand that genetic data and tissue specimens be invariably destroyed after a specific period of time, because as a result humanity would lose an essential part of its genetic knowledge potential. But on the other hand, it goes without saying that donors must be free to provide their own genetic data and specimens for scientific purposes only for a limited period of time to be determined *in advance*.

Apart from these restrictions which are relatively obvious genetic specimen and data banks raise three specific and intensively discussed (legal and) ethical sets of issues, i.e.

(1) issues concerning the permissibility of a general consent of donors regarding the future uses of specimens and data;
(2) issues as to whether and how donors should be informed of possible research results that may be of personal importance for them;
(3) issues concerning donor profit-sharing.

5.5.2 Scope of consent

The obvious approach would be to base the authorising consent of donors on the model of informed consent which has long since been firmly established to legitimise medical

interventions and medical research on humans. One of the requirements of any legitimising patient consent (non-compliance with which is subject to sanctions under criminal and civil liability law) is that, among other things, the persons concerned know, understand and approve of the exact scope, implications and objective of the intended medical intervention. According to recognised legal and ethical standards, any intervention exceeding the agreed scope would be prohibited. This restriction of legitimising consent to actions that have been exactly defined in advance can be convincingly justified in clinical and research contexts which entail immediate risks for body and health.

In the context of genetic and epidemiological research, however, it would be counterproductive for research to tie the donors' consent to specific projects and purposes. But above all, from the ethical perspective such an approach would lack the reasons applying to clinical conditions. As in this case only specimens are handled, immediate repercussions of this research on the donor are impossible. However, it would be conceivable that there are psychological and psychosocial effects as donors might receive unrequested information about their predisposition, or personal data might be disclosed to unauthorised persons (cf. sections 4.3 and 5.4). To respond to these risks suitable measures have to be taken to ensure donor privacy. Researchers, for instance, just like physicians, should be obliged to maintain "researcher confidentiality" regarding personal data and should be subject to sanctions in case of non-compliance. Data trusteeship issues (cf. section 5.4.4) have to be resolved and unwanted feedback of data to the donor which might violate the latter's right not to know must be prevented.

Provided these requirements are met and form part of the explicit and detailed information offered to the potential donor, it is indeed justifiable from the ethical point of view to relax the provisions stipulating that the donation of specimens and data has to be tied to a specific purpose. In principle, also decisions taken in a deliberate state of ignorance and uncertainty can be an expression of the donor's right to self-determination; institutions requiring such decisions may be considered acceptable, provided these decisions relate to "objectively" beneficial, low-risk measures. These requirements are satisfied if strict data and data subject protection is in place. Consequently, no overriding objections can be raised to a consent phrased in general terms which does not specify all possible uses of specimens and data, or even to an all-encompassing blanket authorisation. This applies all the more when the use of specimens is restricted to biomedical research which, moreover, is reviewed by a committee

appointed for this very purpose. But in any case it must be ensured that the individual concerned is adequately informed about the implications of his or her decision including the possibility that specific uses cannot be foreseen. It must also be ensured that the person concerned has the choice to decide whether they want to give specific (limited) or blanket consent. When such decisions are requested, they should always be clearly distinguished from a possible consent to enrolment in research projects which involve a risk for body and health. In order not to conceal the clear difference from the consent – tied to a specific purpose and specific means - of patients and data subjects enrolled in research schemes involving immediate risks for body and health, the consent discussed here should not be referred to as "informed consent", but rather be called a "permit to use specimens and/or data". A situation which is comparable in some respects exists in the medical sector when patients wish to give their free and explicit consent to a medical intervention *without* having been informed in detail about the risks involved. Such a waiver - which is not that rare in medical practice - is accepted as an exception in those cases where it is voluntary, documented and relates only to low-risk interventions. Again, this is not an "informed consent", but a free and independent decision taken in deliberate partial ignorance that is generally considered legitimate under clearly defined circumstances.

5.5.3 Informing the donor of research results

The second basic question regarding specimen and data banks which has to be answered and also covered by counselling and consent refers to the feedback of research results that in some cases might be beneficial for the donor. If new effective and necessary treatment procedures were to be developed for diseases which affect some of the donors, the latter should – if possible - be informed. Considering the possibly ambiguous benefits outlined above that genetic knowledge might bring the individuals concerned and the importance of their right not to know, one should refrain from automatically informing the donors of their genetic constitution and its researched implications for their health. Instead it might be conceivable to publish general interim reports on research results on the Internet. Based on this information, persons who are interested could then decide to undergo individual genetic testing embedded in the personalised counselling structures demanded above.

5.5.4 Benefit sharing

Finally, public attention is attracted by the question as to whether donors have to, or should, benefit financially or otherwise from the profits possibly generated with the help of their specimens and data (benefit sharing). This issue touches upon aspects of social justice which cannot be answered without looking at the same time into the general economic conditions prevailing in our society.

In terms of capital expenditure, risks and potential benefits of specimen donors on the one hand, and of researchers and/or investors on the other hand, research involving gene data – even if it is on a large scale - does not differ fundamentally from conventional research. Obviously, the collective contributions by donors of specimens or data to the various research projects they are enrolled in are as necessary as a basis as the clinical findings of patients whose diseases are made the object of research. On the other hand, individual donations involve only a minimum of effort, no stress and, provided adequate donor privacy is ensured, no personal risks. If scientific and medical knowledge or products should be created by using the specimens and data donated – which, as a rule, cannot be predicted –, the public at large and/or the group of patients concerned to which some of the donors may belong will benefit.

In any case, much more substantial contributions are required from researchers and investors, such as – to a varying degree - working hours, intellectual efforts, structural preparations and capital expenditure. Consequently, this involves – again to a varying degree – the severe risk of bad professional and economic investment. It is only in the positive cases of successful research that researchers can gain a scientific reputation and investors financial profits.

The view that such profits and the sale of expensive drugs not accessible to many patients are unjust cannot be limited solely to research and product development based on genetic specimen and data banks. Such a line of argumentation would equally question the fairness of national and international public policy which governs private-sector industry, fiscal policy and national and global health policies. There is no objective justification for describing, in the public debate, the distribution of potential profits derived from research based on gene data as a specific problem. Consequently, there are no convincing ethical reasons why the donors of gene specimens and data in particular should share possible profits. Provided adequate donor privacy is ensured, investors need not have a "guilty conscience", nor do they

have any special "redistribution obligations". But when it is argued that benefit sharing should in some way or other compensate for the fact that specimens and/or data were provided by the donors without any remuneration, in other words, that scientists got them "for free", this will inevitably lead to the question why each "donation" should not be paid for in the first place on a realistic and individual basis. This, however, will without fail lead to the commercialisation of scientific research right from its start, a development which usually meets with general opposition.

If private-sector research institutions nevertheless agree to make a certain percentage of revenues flowing from this research available for the medical care of all donors (because preferential treatment of those whose data happened to lead to research successes would obviously be unfair) or of specific patient groups, or for other non-profit purposes, then this is certainly a welcome policy decision that could contribute to public acceptance of this particular line of research. But in any case, the rule applies that potential donors must be informed of whether or not benefit sharing is intended.

5.6 Labour and insurance law issues arising from predictive genetic diagnosis

5.6.1 Issues involved

Legal issues relating to predictive genetic testing that are particularly obvious may arise when an individual wishes to take out a (non-obligatory) insurance policy or form an employment relationship.

Generally, these issues arise from a clash of different legal positions and interests: On the one hand, there is the interest of insurers or employers to minimise any risks within the framework of their constitutionally guaranteed contractual freedom and freedom of action. In the case of non-obligatory insurance there is, above all, the interest of the community of the insured in terms and conditions that are equivalent to the risk involved. On the other hand, there is the personal freedom and right to self-determination of the potential party to the contract as

guaranteed in Article 2 paragraph 1 of the German constitution. As the genetic constitution of an individual is indisputably part of the very core of their personality, the forced disclosure and use of data relating to the person's genetic make-up can only be constitutionally permissible if such an approach can be justified by overriding reasons of general welfare and if in the case concerned the principle of proportionality is complied with.

These issues rooted in constitutional rights are also of importance in the area of private law which is affected in this context. It is undisputed that basic or constitutional rights are at least indirectly valid also between private parties. It should also be taken into account that the general right to privacy is not only protected as a constitutional right, but also enjoys direct protection under the law of tort pursuant to section 823 paragraph 1 of the German Civil Code.

5.6.2 Predictive genetic testing for employment

Predictive genetic testing for employment may serve various purposes. On the one hand, it can help to protect the employee from health hazards that may arise during certain activities at the workplace as a result of his or her specific genetic predisposition; in other words, it can serve as an instrument of occupational safety. On the other hand, genetic analyses may be performed to serve also, or exclusively, the interests of the employer or third parties, e.g. to establish prior to employment whether an employee would be able to cope with specific occupational requirements, whether raised levels of absence for sickness have to be expected or whether other people might be put at risk as a result of the prospective employee's genetically induced failure to perform their job safely.

Specific legal provisions ruling whether and to what extent employees are obliged to tolerate genetic testing do not exist in Germany. This is why a legal assessment will have to be based primarily on general civil law clauses (which have to be interpreted in the light of the value system laid down in the constitution); it will be the result of a comprehensive process of balancing legal and other interests on the basis of that same value system.

It is generally recognised that, in principle, an obligation to consent to genetic analyses or to disclose an already established diagnosis cannot be derived from the employment contract or

the legal obligation arising during recruitment, failing any exceptions which require specific justification. This was already borne out in a 1984 ruling of the Federal Labour Court on the permissibility and limitations of an employer's right to information prior to concluding an employment contract. The Federal Labour Court ruled that the employer had a limited right to ask for information in a job interview only insofar as he had a justified and equitable interest warranting protection in having his question answered with regard to the employment relationship. This interest, the Court said, had to be so strong in objective terms that it prevailed over the employee's interest to protect their personal rights and over the inviolability of their personal privacy. According to this legal interpretation by the Court, questions and also tests whose results are not in this way linked to employment are a priori inadmissible.

Even regarding manifest diseases known to the person concerned, existing jurisdiction tends to be restrictive regarding a claim to information by the employer. This implies that an even more restrained attitude is called for when it comes to future diseases. It is also important to take into account that, apart from a few exceptions, most genetic tests can only identify a higher probability of the outbreak of a disease in the individual case, but cannot with any certainty predict the outbreak of a disease, especially not a multifactorial disease. Depending on the degree of probability cited in the diagnosis, the protection of the employer and/or third parties which consequently can only be potential and abstract in nature has to be given less weight when balancing the interests involved. This is all the more true, considering that the result of a possible test not only has an impact on the professional career of the individual concerned, but may also have consequences for the entire life of the employee in question; these consequences may be foreseeable, but their medical causes can perhaps not be influenced.

Consequently, the need for protection of the employee usually takes precedence over any business interests of the employer. Exceptions to this principle may only be admitted if the manifestation of a genetic disease which is immediately linked to employment can be safely predicted or if other persons are put at considerable risk due to the consequences of such a genetic disease which the employee concerned will probably develop. In view of advancing medical and diagnostic possibilities it will be even more necessary than before to develop specific criteria of protection which will permit an adequate reconciliation and balancing of rights and interests.

5.6.3 Predictive genetic testing for insurance

Problems relating to predictive genetic diagnosis may also arise when a person takes out an insurance policy. There are no legal problems involved with statutory health and social insurance schemes whose basis is laid down in detail in German social law. For both members of compulsory social or health insurance schemes and voluntary contributors, an insurance relationship becomes valid when the person entitled to insurance declares their intention to enter into such a relationship. Social security providers may only refuse persons seeking insurance in those cases that are enumerated in the law. From no legal perspective does knowledge of one's own genetic predisposition to a certain disease or the refusal to undergo genetic testing currently warrant an insurer's refusal to grant social insurance cover. Consequently, medical examinations or information to be provided by the insured are neither legally prescribed nor demanded in practice as a condition of social insurance. It is in keeping with the very nature of social insurance law which is based on the notion of solidarity that objective criteria only are decisive for granting insurance cover, irrespective of an individual's risk of disease. As a result, social insurance law must make sure that the minimum protection against health risks that is considered indispensable in a society is guaranteed, irrespective of genetic differences and predispositions of the persons concerned.

The situation is different under private insurance law which is characterised by the notion of risk equivalence of terms and conditions. When assessing risks with a view to developing exclusion clauses or when calculating premiums for a private health, accident or life insurance, the insurer may indeed have an economic interest warranting protection in predictive genetic testing of the person seeking insurance. This is above all in the interest of the community of the insured which the insurer represents.

Pursuant to section 16 of the Insurance Act, the person seeking insurance is bound by law to disclose all facts relating to their present or future state of health that are known to them and are relevant for the insurer's decision to grant insurance cover. The applicant must comply with this obligation without being asked to and especially so when asked to answer specific questions by the insurer. Otherwise he will run the risk of the insurer rescinding the contract at a later point in time. The obligation to disclose information applies irrespective of whether it is a genetic or any other disease.

Under present law the insurer is entitled to demand pre-insurance medical examinations. However, for insurance - just like for employment – it has to be taken into account that compulsory *predictive genetic* analysis represents a major encroachment on the applicant's general personal rights which might lead to the disclosure of previously unrecognised risks that – even though this has nothing to do with the insurance contract - could considerably distress the applicant and his family. This is why an insurer should not, as a rule, require a genetic test before concluding an insurance contract. The interests of the insurer and the community of the insured are sufficiently taken into account when the applicant has to disclose the knowledge he has at the time of application of any diseases that have already become manifest or will most probably develop at a later time. This applies independently of the causes of the disease concerned.

However, the situation is different when there is a concrete suspicion that statements made are false, when the sum insured is disproportionately high or when the insurance prospect asks for cancellation of the waiting period before the insurance cover attaches. In such a case the insurer cannot be denied the right to make the conclusion of the insurance contract contingent on a medical examination. This examination should also include predictive genetic testing if this seems to be medically indicated in the case concerned. Unjustifiable unequal treatment would be the consequence if under private insurance law information relevant for decision-making that was obtained by way of a traditional examination were considered and could be controlled by the insurer to prevent misuse of unilateral knowledge by the applicant (i.e. to prevent so-called anti-selection), while information that is equally relevant for decision-making, but was obtained through genetic analysis could not be used. Under insurance law, too, it may be the result of a medical examination alone that matters, and not the method employed.

By undertaking a voluntary commitment the German insurance industry has decided to exercise even more self-restraint regarding the use of genetic information than required by current law. In October 2001, the members of the German Insurance Association committed themselves not to make predictive genetic testing a condition of insurance. Furthermore, for private health insurance and all types of life insurance including occupational disability, total disability, accident and nursing insurance up to a sum of less than € 250,000 or an annuity of less than € 30,000, people are not required to disclose – prior to taking out an insurance policy

- the results of voluntary genetic tests previously performed for other reasons. Within these limits insurers waive the right - laid down in the Insurance Act - to be informed of any risks before insurance is taken out. In these cases insurers do not even make use of any information that customers have disclosed anyway. This voluntary moratorium is scheduled to end on 31 December 2006.

In view of this voluntary moratorium a *legal* restriction of the right of the insurer to require information is currently not considered appropriate. In fact, the legislator should only intervene if the moratorium threatens to turn out to be inadequate.

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7 Glossary

Allele: One or two of alternative forms (copies) of a gene or a DNA sequence occupying the same locus on homologous (identical) chromosomes. Often many different alleles can be found in the population. The differences in alleles are a result of DNA sequence variations which need not be important for the function of the resulting gene product. As a rule, a person inherits one allele from the mother and one from the father. If the alleles are identical, they are referred to as homozygous, if they are different, they are heterozygous.

Autosomal: The term autosomal refers to genes and chromosomes occupying autosomes. Autosomes are all chromosomes except for the sex chromosomes X and Y.

Carrier: Female carrier (heterozygote) of a recessive genetic disease; the term is usually applied in the case of X-linked recessive inheritance, e.g. haemophilia A: If a woman is a heterozygote for a mutant allele on the factor VIII gene, she is not clinically affected by the disease (she is phenotypically normal). But she transmits the diseases so that 50 per cent of her male offspring can develop the disease and 50 per cent of her daughters can be carriers.

Chromosome: Chromosomes are present in the cell nucleus and the carriers of genetic information; this information is passed on to the daughter cells each time the cell divides. Chromosomes consist of a threadlike DNA molecule with associated proteins. In humans each body cell has a total of 46 chromosomes, 22 pairs of autosomes and one pair of sex chromosomes (46, XX or 46, XY). Each human germ cell has only a single set of chromosomes (23, X or 23, Y).

Chromosomal aberration: Disorder of the structure or number of chromosomes.

Compound heterozygosity: Persons with a recessive genetic disease have different mutations in the same gene on both chromosomes.

Diploid: Describing somatic cells with a full set of genetic material consisting of paired chromosomes that contain one chromosome from each parent [Note: In males both sex chromosomes, including the Y chromosome, are represented only once].

DNA: **d**esoxyribo**n**ucleic **a**cid; basic chemical component of the hereditary material. DNA contains the information required to produce all proteins needed for the functions of the body.

Dominant inheritance: The effects of the information contained in a gene are already visible in the heterozygous state. The trait is dominant.

Epigenetic regulation: An "externally" regulated state of activity of the genetic material which is not anchored in the primary DNA structure. At the DNA level this includes the methylation (inactivation) of promotor segments on the gene and the modification (methylation, acetylation, phosphorylation) of histones of the chromatin matrix. Epigenetic processes, for example, are the mechanisms underlying imprinting.

Gene: A defined section of DNA along a chromosome which codes for a function, e.g. a protein. In addition to the coding sections (exons) the structure of a gene includes other regions such as non-coding sections (introns) and regulation elements (promoters). The human *genome* consists of about 30,000 to 40,000 genes.

Genome: A term not uniformly used to describe the total DNA of an individual or the total genetic information of a cell.

Genomic imprinting: An epigenetic process occurring at the early stages of embryonal development which is responsible for the phenomenon that in certain genes an allele is expressed only when it is inherited from the mother, or in other cases, only when it is inherited from the father.

Genotype: The genetic information of a cell or an individual underlying the observable characteristics (phenotype).

Germ cells: Gametes, oocyte and spermatozoon, egg and sperm. Mature germ cells are haploid, i.e. each contains a single set of chromosomes. After two germ cells (egg and sperm) have united during fertilisation, the resulting zygote is diploid, i.e. it contains a double set of chromosomes.

Haploid: Containing single copies of chromosomes and hence of genes (single set of chromosomes).

Heterozygous: Having two different alleles at a given DNA section or gene locus on homologous chromosomes.

Homozygous: Having identical alleles at a given gene locus on both homologous chromosomes.

HIV: **H**uman **I**mmunodeficiency **V**irus, i.e. the virus causing AIDS (**A**cquired **I**mmune **D**eficiency **S**yndrome).

Meiosis: Term describing the two special cell divisions occurring at the final stage of the formation of gametes. The first division which may lead to a recombination of genes is called reduction division; the second division is a normal (mitotic) division. During germ cell formation meiosis serves to reduce the chromosome number by half, i.e. from a diploid to a haploid set of chromosomes.

Mendel's laws: In 1866, Gregor Mendel published the fundamental laws of inheritance named after him. These rules are based on his studies of the inheritance of traits when breeding peas, for instance. Mendel's laws also describe dominant and recessive inheritance.

Mitochondria: Rodlike organelles which are several micrometers long and bounded by a double membrane; they have their own DNA (mitochondrial genome). Mitochondria are usually passed on by the mother (maternal inheritance). The enzyme complexes of the respiratory chain are located along the inner, richly folded membrane. Mitochondria generate energy and play a vital role in cell metabolism. An inefficient error detection and repair mechanism and the influence of oxygen radicals developing along the contiguous respiratory chain render the mitochondrial genome susceptible to mutations. This is reflected in the mitochondrial mutation rate which is 10 to 20 times higher than that of chromosomal DNA.

Monogenic: Affecting a single gene. A monogenic disease is caused by a mutation within a single gene.

Multifactorial: Caused by many factors and influences. A multifactorial disease is attributable to multiple genetic and environmental factors.

Mutation: If not corrected by DNA repair mechanisms, a persistent change in the genetic material of somatic cells or gametes (germ line mutation).

Oligonucleotide: Short, artificially produced DNA section.

Phenotype: The observable characteristics of a cell or an individual resulting from the genotype and environmental factors.

PGD: Preimplantation genetic diagnosis. Genetic testing performed on an early embryo produced by in vitro fertilisation which has not yet been implanted in the uterus.

PND: Prenatal diagnosis. Prenatal diagnosis comprises various examinations of a baby still in the womb, such as ultrasound, chorionic villus sampling (examination of egg membrane cells) or amniocentesis (examination of amniotic fluid). Amniotic fluid contains embryonic cells which are examined for possible genetic damage.

Recessive inheritance: Phenotypical manifestation only if the alleles are identical (homozygous).

RNA: **r**ibo**n**ucleic **a**cid. RNA is produced in the cell by transcription of the DNA sequence. It serves as a matrix for protein synthesis.

Round robin (test): A round robin is a process designed to control the quality of medical laboratory tests. The head of the round robin distributes selected samples (e.g. blood, DNA, plasma samples) to external participants in the test. These external laboratories determine the parameters required and return a test report including interpretations and raw data to be evaluated by the project leader.

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