

The future of genetic diagnosis – from research to clinical practice

OPINION

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1 INTRODUCTION

In recent years, methods of genetic analysis have developed at a rapid speed. The aim of the new techniques is to make it easier to identify causes of illness, to predict risks and to find new approaches to treatment. However, it is not yet clear how quickly and to what a degree these approaches will become part of clinical practice. Genetic findings have potentially far-reaching consequences. Thus, the current discussion on the non-invasive prenatal test for trisomy 21 has shown that new diagnostic procedures raise fundamental social questions, for example with regard to our attitude to people with a disability.

Against this background, the Federal Government has instructed the German Ethics Council to prepare an Opinion on the future of genetic diagnosis. In this task, the Ethics Council sees providing recommendations for political decision-makers as only part of its duty. It also wishes to describe the difficult and complex scientific and medical information on the new developments and methods of genetic diagnosis and the ethical questions arising from this, in order to encourage the social discussion and formation of awareness which is so important. At the same time the Ethics Council also wishes to show that a one-sided view of genetic variation, concentrating on deficits, is too short-sighted. It emphasizes that the definition of quality of life must not be reduced to medical or genetic findings.¹

¹ Translator's note: For convenience, the masculine form is used where applicable for both sexes throughout this translation.

2 SCIENTIFIC FOUNDATION

2.1 Basic concepts and facts

2.1.1 Genetics and epigenetics

Genetics is a field of biology which deals with the fundamental elements of inheritance, that is, with the transfer of genetic make-up either to the next generation of individual cells or to a new organism. In contrast, **epigenetics** is concerned with the patterns of *activity* of the genes in various tissues and biological situations and with the mechanisms which control this activity. The **genotype** is the totality of genes either in a complete organism or in individual localized gene segments in the genome. The **phenotype** is the totality of physical characteristics of a person, constituted of anatomical, physiological, biochemical and psychological elements. Individual characteristics (such as eye colour) may also be defined as phenotypes.

A person's genes are contained in the nucleus of every somatic cell in the form of 23 chromosome pairs. 23 chromosomes come from the father and 23 from the mother. There are also a small number of genes which are located outside the nucleus in the mitochondria², the cellular “power plants”, and all these originate from the egg. A chromosome consists of a DNA molecule in the form of a double helix which is “wrapped” in protein molecules. The genetic information is contained in a sequence of nucleotide building blocks, like a text whose alphabet uses only four different nucleotide “letters”.³ The

2 Mitochondria are structures (organelles) in the cytoplasm enclosed by a double membrane. They exercise important functions for the energy metabolism of the cell and have their own genetic material, although this codes for only part of the genetic information needed by the mitochondria themselves. The remaining mitochondrial proteins are coded for by the genes contained in the nucleus.

3 Chemically defined alphabet consisting of the letters G, T, A, C – that is, the structurally and chemically distinct nucleotide building blocks guanine, thymine, adenine and cytosine – arranged in a chain molecule. In order to

complete DNA of a human being consists of approximately 3.2 billion letters in the single (haploid) set of chromosomes⁴, that is, 6.4 billion letters in the double (diploid) set of forty-six chromosomes. The entirety of the DNA with its sequence of specific nucleotide building blocks is called the **genome**.

In 22 of the 23 chromosome pairs, the sequences of each of the two chromosomes inherited from the father and the mother are almost identical. These chromosomes are called **autosomes** and form homologous pairs. On average, the text of homologous chromosomes contains a variation approximately every 1,000 letters. These nucleotide variations are a measure of the genetic similarity of two homologous chromosomes.

The 23rd chromosome pair is the sex chromosome pair (**gonosomes**); here, the X chromosome and the Y chromosome, which is only found in males, are much more clearly distinguished from each other. Women have two X chromosomes, whereas men have one X chromosome and one Y chromosome in every somatic cell.^{5,6}

Since all somatic cells develop from the fertilized egg cell by way of cell division, they all have the same genome.⁷ It is therefore possible to obtain genetic information which is valid for

create a protein molecule, which is also a chain molecule, the four-letter text of the DNA is first transcribed into a four-letter RNA text (alphabet: G, U, A, C) ("transcription") and from there to a 20-letter alphabet of protein building blocks (amino acids) ("translation").

- 4 This is the equivalent of approximately 1.8 million pages of print or about 24,000 volumes of an encyclopedia.
- 5 This means that in the male sex, in contrast to the female sex, a considerable proportion of the genome (that is, the information on the X chromosome) is present in only one copy, not as a double copy. The Y chromosome is small, and although it contains important genetic information, this is small in quantity. This explains why some genetic defects (in the X chromosome) almost exclusively affect the male sex.
- 6 In rare cases, the correlation described between sex chromosomes and biological sex does not apply. There are also men and women whose biological sex is different as the result of a variation in the chromosome set or other physical features, and intersex persons who cannot be unequivocally classified as male or female (cf. on this German Ethics Council 2013, original German edition published in 2012).
- 7 With few exceptions, arising from "somatic" mutations acquired in the course of life.

the individual from every somatic cell with a nucleus at every stage of development.

Before every division of a somatic cell, an almost perfect copy of each of the 46 chromosomes is first created by new synthesis of the DNA strands. In order for a cell to be divided, therefore, the 46 chromosomes of the cell are first doubled. In the following division, every daughter cell then receives a complete diploid chromosome set. In the course of copying there may be errors in reading; these are called **mutations**. If this occurs in the formation of a somatic cell, it is referred to as a **somatic mutation**. If a mutation occurs in the formation of a germ cell (egg or sperm), the whole organism which is formed after a fertilization carries a **germ line mutation**; there is therefore a 50% likelihood that this will be passed on to its offspring. According to our present state of knowledge, the great majority of mutations are neutral for the individual, that is, they have no consequences. However, some of them are detrimental and others useful for the development of the body or of its functions. By being passed on to offspring, mutations, as different forms of the same gene, known as **alleles**, contribute to genetic variability in a population. The presence of different alleles at one **gene location** (*locus*)⁸ in a population is called **polymorphism**.

This means that although the genomes of all humans have the same basic structure, each person has a large number of individual alleles. In two people who are not related to each other, there are approximately five million single nucleotide polymorphisms (SNPs)⁹ and approximately 30,000 copy number

8 Gene locus: precisely located section in the genome's DNA sequence; may be addressed precisely (in a similar way to searching for a keyword in a text) by direct sequencing or by binding (hybridization) to a specific partial sequence.

9 SNP: Replacement of a nucleotide by one of the other three possible ones at a precisely defined position on the genome; usually the result of a copying error in DNA synthesis or during the repair of DNA damage.

variants (CNV)¹⁰. **Insertions or deletions** of long DNA sections are only occasionally found.

The term **gene** refers to a section of DNA which contains the **code**, the “construction manual” for a particular **gene product** (RNA, protein). But it should be noted in this connection that generally the code for a gene product contained in a gene is repeatedly interrupted by sequences of non-coding DNA. The coding DNA sections in a gene are called **exons** and the non-coding ones **introns**. By a complex mechanism, in the synthesis of the gene products the introns are removed (“spliced”). In the splicing process, several different combinations are often possible, resulting in different gene products, and therefore the actual number of functionally different gene products may be many times the number of genes in the DNA sequence.

It is estimated that the human genome contains approximately 25,000 genes. Together, they make up only about 2% of the total DNA sequence. The function of the remaining 98% of the genome, which is non-coding, is not yet fully understood. The current findings of the “ENCODE” Project (ENCyclopedia Of DNA Elements), whose aim is to characterize all the functional elements of the human genome, suggest that at least 80% of the non-coding DNA plays a role in the complex system of gene regulation.¹¹

Ribonucleic acid (RNA) is the primary product of transferring DNA. Some of the RNA molecules created serve as an intermediate station for protein synthesis (known as messenger RNA, mRNA). The sequence of nucleotides in DNA is first coded into mRNA, which in turn is coded into the amino acid sequence of the protein. Most RNA molecules, however, are not used as codes for protein synthesis. Instead, it has been

¹⁰ CNV: Individual differences in the number of repetitions of certain sequence segments at particular sites on the genome.

¹¹ Cf. Ecker et al. 2012; The ENCODE Project Consortium 2012; Thurman et al. 2012; Neph et al. 2012; Gerstein et al. 2012; Djebali et al. 2012. The term “junk DNA” which was formerly used is at all events unlikely to be appropriate for the majority of non-coding DNA.

found that a growing number of such non-coding RNA molecules have independent functions in many cell processes, giving them an important role in development, metabolism, gene regulation and the genesis of disease.¹²

The activity of the genome is regulated by **epigenetic changes**. These influence the reading of the genetic information without altering the DNA sequence itself. Biochemical and structural modifications of DNA and of the histone proteins around which the DNA strand is wrapped are a main mechanism of epigenetic changes.¹³ Particular gene products (RNA or proteins) may also have a permanent effect on the readability of genes. In this way, epigenetic changes determine whether and when genes are accessible to be read in a cell and thus can be translated into RNA molecules and proteins. Epigenetic changes are already present at the stage of embryonic development and are passed on to the daughter cells in every cell division. They are sometimes very stable and may influence gene activity for a person's lifetime, or even into following generations. On the other hand, some epigenomic patterns are changeable and may be changed, for example by diet, psychological stress or environmental influences. The totality of the epigenetic modifications of a particular type of cell are known as the **epigenome**.¹⁴

In addition to epigenetic modification, there are other processes which influence gene activity for a shorter period of time, including the *quantity* of a gene product which is formed in a

12 Cf. Li et al. 2012; Rederstorff/Hüttenhofer 2010.

13 The chemical epigenetic alteration of DNA is mainly caused by the process of DNA methylation. In this process, methyl groups are attached to particular bases in the genome. In the histones, some amino acids are sometimes affected: their physical structure is changed. The agglomeration of proteins on the specific methylation patterns of DNA and the modified regions of the histones then influences the accessibility of the gene regions affected.

14 The International Human Epigenome Consortium intends to decode 1,000 human epigenomes according to jointly agreed standards, seventy of them in the "German Epigenome Programme" (DEEP) started in September 2012 and sponsored by the Federal Ministry of Education and Research. The aim is to develop a complete map of all control mechanisms of the human genome.

given situation. These include the products of control genes in other locations (transcription factors, repression factors)¹⁵ as well as, for example, metabolic products or hormones.¹⁶

The complex interaction of these factors is also subject to a complex genetic-epigenetic regulation and determines the current effective **expression profile**¹⁷ and the permanent **epigenetic profile** of a particular cell type.

The genotype is hereditary in the classical sense of the term, that is, it is transferred proportionately from the biological parents to their offspring. The epigenetic profile of a cell, in contrast, is hereditary only in the narrower sense that it is passed on to the daughter cells in a cell division. When germ cells are formed, there is a “reprogramming” of the epigenetic profile to an original state. What epigenetic characteristics are passed on to the next generation is a subject currently being researched.¹⁸

2.1.2 Diagnostic, prognostic and predictive genetic analysis

The aim of a **genetic analysis** is to determine the genetic structure of an object (cell, tissue, organism). In particular, it establishes

>> the number and microscopic structure of the chromosomes (cytogenetic analysis) or

15 DNA-binding regulatory proteins which promote the conversion of a gene into its gene products (transcription factors) or prevent it (repression factors).

16 Messenger substances in the metabolism.

17 Totality of the (active) genes actually translated into gene products in a cell at a defined point of time.

18 For example, current research indicates that the parents' diet may leave epigenetic traces in the germ cells of the parents or in the somatic and germ cells of a developing child during pregnancy, with the result that the effects of this inherited gene activity may still have an effect on health in the grandchildren's generation (cf. Alam et al. 2012; Ferguson-Smith/Patti 2011).

- >> the molecular fine structure (sequence) of the DNA or
- >> the molecular fine structure (sequence) of gene products (RNA, protein).

Only the determination of details of the nucleotide sequence of an RNA or of the amino acid sequence of a protein is a molecular-genetic analysis. In contrast, the determination of the quantity of a protein present, which is made in a large number of biochemical laboratory tests, is not a genetic analysis.

The genetic analysis may relate to questions of widely varying scope and content. It may examine individual, precisely defined gene loci. But it may also pursue a variety of **genome-wide approaches**, each with different quantities of data. For example, a genome-wide analysis may be selective and may determine the individual spectrum of polymorphisms (usually SNPs or SNP haplotypes¹⁹) of a genome. In **exome sequencing**, all gene segments coding for protein molecules are completely included. **Whole genome sequencing** is designed to investigate the totality of the nucleotide sequences in all 23 chromosome pairs.

It is only through knowledge of its phenotypical significance that the findings of a genetic analysis become meaningful with regard to the individual or group examined. A genetic analysis may be conducted for **non-medical or medical purposes**. The non-medical area comprises both scientific purposes (for example, anthropological studies) and a large number of products, for example genealogical analysis or investigations to determine genetic factors relevant for a person's lifestyle, which are associated, for example, with particular abilities such as the digestion of food or talent in sports; these

19 Haplotypes: defined variants of short or medium-length defined sequence segments at a particular location on a particular chromosome; these are generally inherited without change. They may be identified and characterized by particular SNP patterns on one and the same chromosome.

are found in particular in the commercial area in the form of **direct-to-consumer tests** (cf. section 2.5.7).

In the clinical and medical area, on the other hand, the analysis is directly targeted at a **diagnosis**, for example when a medical consultation for a patient gives rise to a concrete question as to whether an inherited or acquired genetic deviation is present. For this purpose, either the chromosome spectrum or the sequence of letters at one or more gene loci is examined. In a **diagnostic panel**, all the gene loci which may be relevant for a particular diagnosis can be screened simultaneously. Genetic analyses for medical purposes may also be directed towards establishing gene variations in genes which are responsible for the effect or the decomposition of medicinal products (**pharmacogenetics**). In **cancer diagnosis** they target inherited or acquired mutations in genes whose variants may be carcinogenic (oncogenes) or anticarcinogenic (tumour suppressor genes).

Where an illness has been diagnosed, **prognostic genetic diagnosis** is intended to predict the further course of the illness. In this connection, particular importance may attach to the characterization of gene expression in particular tissues (**epigenetic analysis**). In some cases this permits a prognosis of therapeutic sensitivity and the future course of tumour growth, in particular in tumour tissue.²⁰

In **predictive diagnosis**, in contrast to the above purposes, as yet no relevant phenotype is present, that is, neither a manifest illness nor impaired function. Instead, the genetic screening aims to make a **prediction**, that is, whether and with what probability and under what other conditions a particular phenotype could develop in a person.

20 Cf. Hoheisel 2012.

2.2 Genetic influences on health and lifestyle

2.2.1 Introduction

Genes influence the organism through the patterns and the extent to which the information contained in them is read, that is, converted into gene products (RNA and protein molecules) in various cells. They provide blueprints for the structural and functional elements of the organism. In the totality of the genetic and epigenetic processes of an organism, the implementation of these blueprints forms a complex network of interactions which take place in a relatively stable equilibrium of the organism. Dependent on sex, age, diet, psyche, lifestyle and outward conditions, but also on genetic variants, there are a large number of possible different states of equilibrium. Some of these states of equilibrium, however, are experienced by individuals or their surroundings as a “deviation from the norm”, and possibly as a disturbance, as a disease or as a disability.

If a single specific gene variant (genotype) and a specific characteristic in the phenotype of an individual are present, this is initially nothing more than a **coincidence**. If this occurs cumulatively in a large number of individuals of a population group, this is referred to as **association**. This may occur purely by chance. A cause and effect relationship between the particular genetic characteristic and the particular somatic characteristic may only be concluded if there is additional evidence (for example molecular or cell biological).

In some cases, a particular genotype is the sole direct (“monogenic”) cause of a changed phenotype, for example where the phenotype is conditional on the impaired function of a protein coded by the related gene. An example of this is provided by defects in the beta globin gene which result in a lack in the body of functional hemoglobin, which is responsible for transporting oxygen in the blood. A person affected by this suffers from the disease beta thalassemia.

In other cases there is a complex structure of causes in which gene variants also play a role but are not the sole cause. Thus the ApoE4 variant of the gene, which codes the blueprint for the metabolic protein apolipoprotein E, increases the risk of suffering from Alzheimer's dementia, but it does not unavoidably result in the onset of the disease. Carriers of a copy of this gene variant have approximately double the chance of acquiring it, and carriers of two copies have up to ten times the risk, but many carriers never acquire it. Many known factors – other gene variants, ethnic origin or sex, and probably a large number of other unknown factors – influence the risk of developing the disease, and therefore at the present time experts do not recommend making a prediction on individual risk on the basis of the ApoE genotype.²¹

By comparing the findings of many participants, where the characteristics are strongly associated, it is possible to make a diagnostically useful statements on the basis of statistical probability even without knowing the active molecular chain. Thus, for example, even today it is not known with certainty how the ApoE4 variant influences the risk of Alzheimer's. The strongest form of association is found if, as in the case of beta thalassemia, biological plausibility and statistical association of genotype and phenotype are present at the same time.

In principle there are two possibilities for genetic factors to be particularly relevant for the phenotype. On the one hand, there may be spontaneous and rare alterations of genes whose functional consequences substantially distinguish an organism from the average and make equilibrium within the normal range impossible. On the other hand, patterns of behaviour or environmental conditions may change so greatly that an organism which is actually genetically “normal” can no longer function under these conditions.

The first possibility is caused by mutations to structurally important genes which result in essential proteins either not

21 Cf. Goldman et al. 2011.

being produced at all, or being produced only in a defective form, as is shown by the example of beta thalassemia described above. The body can then not function normally, regardless of the environmental conditions.

Typical examples of the second possibility are what are known as diseases of civilization. In this connection, evolutionary medicine assumes that the genetic and physical constitution of many humans was excellently adapted to the pre-civilization environmental conditions, but is no longer well adapted to the conditions of modern city living. For example, the industrial production of highly refined flour and sugar products, which has only been possible for a few decades, has so greatly changed the composition of foods that genetic controls, which had adapted to a completely different range of foods in the course of human evolution, no longer function smoothly. Gene variants, for example, which promote the effective storage of dietary sugar in the form of fat tissue as an energy reserve will have been a natural advantage for survival in periods when sweet things were only available during a short harvest period in the form of a surfeit of fruits. But in view of the fact that sweet foods are permanently available in civilized society, such a form of utilization of sugar may become a risk of civilization if it contributes to obesity and disturbed insulin²² metabolism. Consequently, the influence of genetic variation on health can often only be assessed in the context of the relevant environmental conditions.²³

2.2.2 Monogenically caused developmental disorders, illnesses and disabilities

A **monogenic** predisposition refers to a mutation which is located in a single gene and which is highly likely to result in

22 A hormone, produced in the pancreas, which regulates blood glucose.

23 Cf. Eaton/Konner/Shostak 1988.

a genetic developmental disorder, illness or disability in the carrier.

Such mutations may occur in a variety of inheritance patterns. In **recessive inheritance**²⁴ each parent carries a mutation in one of the two homologous chromosomes, but is not himself ill, because he has an unaffected copy of the gene on the other homologous chromosome, and the function of this is sufficient to compensate for the mutation. The parents are thus **heterozygous carriers** of the mutation. There is a probability of 25% that a child will inherit from both parents the chromosome which carries the pathogenic mutation. This situation also explains why recessive diseases are more common if the parents are closely related to each other, since there is a greater probability that they are both carriers of the same mutated gene.

In **dominant inheritance**²⁵ the characteristic develops even if only one of the two homologous chromosomes of an individual carries the mutation, and therefore usually at least one parent is already affected by the illness and there is a 50% likelihood that the mutation will be passed to the child.

In the case of X-linked (sex-linked) inheritance, the child inherits the mutated X chromosome from the mother (probability: 50%). Her second, non-mutated chromosome guarantees that the gene functions normally. A son lacks such a possibility of compensation, because he inherits no second X chromosome, but instead a Y chromosome. But a daughter has normally inherited from the father a non-mutated X chromosome and is therefore only a carrier of the predisposition to disease and not herself affected.

Both recessive and X-linked inherited diseases frequently have very severe symptoms and cannot be effectively treated. They are often fatal even in childhood or youth. In contrast, some of the dominant hereditary diseases are clinically

24 Recessive in this connection = hidden in the parents.

25 Dominant in this case = passing from one generation to the next.

manifested only in later years (e.g. Huntington's disease, the adult form of myotonic dystrophy).

In principle, hereditary mutations can arise in every gene as accidental copying errors in the new synthesis of DNA to form an egg or sperm cell. To date, detailed descriptions have been made of over three-and-a-half thousand gene mutations which have a causative influence on the development of phenotypes, in particular diseases. It is at least suspected that a similar number of phenotypes are caused in the same way.²⁶ It can be expected that there will be a further increase of the number of associations established between genetic mutation and disease. However, most gene mutations are only found in individual families and therefore play a very small part in the statistics for the population as a whole. Among monogenic disorders, the recessive ones are far more common than the dominant ones. In Europe, there are approximately twelve monogenic disorders for every 1,000 births. Overall, monogenic deviations which result in diseases are approximately three to four times more frequent than chromosome disorders. According to some estimations, every individual is on average a heterozygous carrier of from four to five pathogenic mutations.

If several genetic factors (e.g. mutations) exist which independently of each other may cause a particular characteristic (e.g. illness), this is called **heterogeneity**. If there are different mutations (alleles) in different individuals in a particular gene location on the two homologous chromosomes, this is termed **allelic heterogeneity**. One example is the CFTR gene.²⁷ More than one thousand different mutations have already been described which can cause the same disease pattern, cystic fibrosis, in different individuals; the course of this varies in severity

26 Retrieval of the statistics of the OMIM database (Online Mendelian Inheritance in Man) on 4 March 2013: 3,730 phenotypes whose molecular basis is known. Online: <http://omim.org/statistics/entry> [2013-03-04].

27 CFTR = cystic fibrosis transmembrane conductance regulator.

depending on the mutation involved. Allelic heterogeneity²⁸ is very common in monogenic genetic defects.²⁹

Locus heterogeneity refers to the situation where an identical (or similar) phenotype may have been caused, or caused in part, by mutations in the various gene loci. One example is *retinitis pigmentosa*, an inherited eye disease³⁰ for which mutations in a wide variety of gene loci, some with different inheritance patterns, are said to be responsible.

In many cases, the knowledge of a single gene change, even in disorders classified as monogenic, does not permit an unequivocal conclusion as to whether symptoms will occur or be marked. Some possible reasons for this are set out in the following:

There is **reduced penetrance** if a genetically caused phenotype is expressed clearly in some carriers of the mutation, but only weakly or not at all in other (often closely related) carriers. Examples of reduced penetrance are what are known as the breast cancer genes BRCA1 and BRCA2. Some of the carriers develop breast cancer or ovarian cancer in the course of their lives (50 to 80%, depending on the mutation), and others do not. At present it cannot yet be predicted which group an affected woman belongs to.

Variable expressivity³¹ refers to the situation where, although all the carriers of a genotype demonstrate the phenotype, this is manifested in a variety of forms, with the result that the severity of the illness varies (e.g. mild or severe form

28 Term for various mutations (alleles) in a particular gene locus which result in similar or identical phenotypes.

29 For this reason, for many phenotypes DNA chips are needed which can identify a large number of different mutations and despite this may result in false negative findings if a mutation is found which has not yet been described.

30 Disease of the retina which results in night blindness, cataracts and other visual impairments.

31 Expressivity: degree of expression of a phenotype where the genotype is the same.

of the Marfan syndrome³²). The variable expressivity of genes may result from epigenetic changes (cf. section 2.1.1).

In cases of variable penetrance and expressivity of a monogenically caused defect, it is also possible that the expressivity of the phenotype is further dependent on alleles in other gene loci which have not yet been described. However, if it is known that there is a causal connection with other gene loci, this is also known as an **oligogenetically** caused disorder.³³ Here, a disability or illness – often at first classified as monogenic – is in many cases only triggered in if two genes are affected at the same time. For example, the eye disease referred to above, *retinitis pigmentosa*, can be actuated not only by various individual mutations, but also by combinations of two³⁴ or three³⁵ gene mutations.

There are therefore fluid transitions between monogenically and multifactorially conditioned phenotypes.

A large number of monogenic defects present even before birth or in early childhood as syndromes which are characterized by greatly varying manifestations, from minor to serious malformations of various organs including the skin, the cardiovascular system, the musculoskeletal system and the nervous system. In only a few cases are these symptoms so typical that it is possible at the clinical stage to establish that a few genes or a single gene are the cause (e.g. brittle bone disease). In the majority of cases, the most varying gene loci may be responsible for a syndrome either monogenically or in conjunction with another or a few other genes.

The precise explanation of the genetic status of such patients may in many cases not provide any specific prospects of cure, but as an exact diagnosis it is valuable to those affected

32 Marfan syndrome: inherited defective structure of the body's connective tissue, with mild to severe symptoms of the stability of body organs, varying from case to case.

33 Cf. Badano/Katsanis 2002.

34 Cf. Kajiwara/Berson/Dryja 1994.

35 Cf. Katsanis 2004.

and those around them to enable them to deal with the resulting difficulties and disabilities in a self-determined way. Associations of persons affected can also organize themselves in order to advise and help each other in managing the problems entailed by the illness. Such self-help is the value of a precise diagnostic explanation even if no treatment oriented towards the causes is available.

2.2.3 Multifactorial disorders and diseases

In contrast to the causation of illnesses, described above, by individual or few genes, a large number of other factors in addition to a person's genetic constitution are involved in the development of widespread diseases and diseases of civilization (e.g. environmental influences, diet, lifestyle, the effects of medicinal products). This group includes arteriosclerosis, heart attack, obesity, type 2 diabetes, some forms of cancer (in particular lung, bowel and breast), and also high blood pressure and metabolic syndrome, bipolar disorder³⁶ and certain allergies and skin diseases. In contrast to monogenic illnesses, the structure of the gene constellation is much more complex. The same is true of the associated complex phenotypes. Between the complex genotype and the complex phenotype there is also an equally complex interdependency, which consists not simply in the summation of the factors involved, but in a non-linear interaction.

In the case of diseases with multifactorial causation, it is inadvisable to describe genetic variations across the board as (potentially harmful) mutations. Instead, they are often polymorphisms which are widespread in the population at large. It is only in the complex interaction with other genetic,

³⁶ Multifactorial psychological disorder in which the mood of the affected person alternates between mania and depression.

epigenetic and environmental factors that their possible influence on illness and health is revealed.

If the gene variants found in two or more or in numerous gene loci are understood as a combined genotype, this is called a **polygenic** genetic constellation, and it may be the cause of complex phenotypes. A distinction must be made here between a combination of genetic characteristics which have effects independent of each other, and a complex genotype, in which the influences on the phenotype of the existing gene variants interact, strengthening or weakening each other or controlling each other's activity.

2.2.4 Chromosome abnormalities

Chromosome abnormalities often result in serious harm to the unborn child. A distinction is made between numerical and structural chromosome abnormalities. A **numerical chromosome abnormality** (aneuploidy) is present if there are more than two copies of a particular chromosome in the genome (polysomy, e.g. trisomy 21) or only one copy (monosomy). These are defects which usually arise spontaneously, when the gametes are formed from their progenitor cells, as a result of disturbances in the distribution of the chromosomes.³⁷ All autosomal monosomies and most polysomies are fatal, that is, they result in miscarriages or death very shortly after birth. Some autosomal aneuploidies have a weaker effect on

³⁷ Chromosome abnormalities are among the "genetic characteristics" as defined by the *Gendiagnostikgesetz* (Genetic Diagnosis Act) (Section 3 no. 4). They are also "hereditary" within the meaning of no. 4, for they come into existence *before* fertilization. A chromosome abnormality may be "hereditary" in the genetic sense if there is a balanced translocation or a trisomy in all somatic cells of one parent and the developing gamete contains no normal set of chromosomes. But defective chromosome sets which arise spontaneously in the germ cell division are far more common. A large percentage of all sperm cells are aneuploid. In egg cells, the rate of aneuploidy is in the lower single-digit range, but it increases markedly as the woman becomes older.

viability.³⁸ Trisomy 21 (Down syndrome) is the most common chromosome abnormality of this kind in newborns. It results in retarded development, is usually accompanied by mental impairment and sometimes also by physical deformities, ranging from slight to severe, in particular of the heart, lungs and gastrointestinal tract. Today, as a result of improved treatment and social integration, the average life expectancy of people with Down syndrome is almost 60 years.³⁹

Some aneuploidies of the sex chromosomes (e.g. Klinefelter syndrome⁴⁰, Turner syndrome⁴¹) are not fatal and forms with mild symptoms are more common in the population than autosomal aneuploidies.

Structural chromosome abnormalities usually present as translocations. This means that particular sections of a chromosome are located in a different part of this chromosome from in the overwhelming majority of the population, and in some cases even on another chromosome. Such anomalies may be “balanced”; this means that the total amount of the genetic make-up is not changed, merely some sections have been moved. Carriers of such translocations (frequency in the population approx. 1:500) have no symptoms themselves, but there is a risk for their children: when the germ cells mature, this may result in an unbalanced chromosome status in which the genetic material is increased or reduced, which normally

38 Trisomy 13 and 18 may be compatible with surviving for several years. The same may apply to other autosomal polysomies and monosomies if only part of the chromosome is affected (partial aneuploidy) and/or if the aneuploidy does not appear until the embryonic development in a cell and is therefore passed on to only some of the somatic cells (genetic mosaic). People with Pallister-Killian syndrome, for example, have a tetrasomy 12p mosaic condition; in some of their somatic cells they carry four copies of the short arm (p) of chromosome 12. The life expectancy and health of people with such restricted aneuploidies depends on the extent of the cells affected or of the supernumerary or missing chromosome sections.

39 Cf. Glasson et al. 2002.

40 Numerical chromosome abnormality of the sex chromosomes which only affects men who have the Y chromosome and two X chromosomes.

41 Monosomy X; disorder arising from a gonosomal monosomy where only one X chromosome is present; results in infertility, short height and disturbances of organ systems.

results in severe and multiple deformities and severe disorders of the central nervous system. Such disorders are usually fatal and may cause multiple spontaneous miscarriages.

2.2.5 Genetic influences relevant to lifestyle

In addition to the above relations between genotype and health disorders, there is also increasing understanding of genetic factors which are relevant to a person's way of life, without direct relevance to diseases or health disorders (lifestyle tests). Tests of this kind are already offered, which for example examine individual genetic components for a tendency to dependency on nicotine, caffeine and alcohol, the disposition to increased readiness to take risks, the individual tendency to freckles or to hair loss⁴², a disposition to overweight, a talent for particular sports or special intellectual talents⁴³ and even to choose a partner⁴⁴.

While some of the examples given have purely curiosity value and often have a shaky scientific foundation, for example may be based on individual small studies, there are also efforts to use findings on genetic influences in areas which may have long-term relevance for lifestyle, wellbeing and – at least indirectly – also for health. The concept of nutrigenomics may be cited here: it is an umbrella term for attempts to understand the influence of genetic factors on the utilization of food.⁴⁵ Here too there are already commercial packages which on the basis of the individual genetic profile give recommendations, perhaps for diet or sports, for example to justify individualized

42 Here is an example of one "Lifestyle Gene Test Package". Online: <http://www.gentest-deutschland.de/factoid> [2012-03-04].

43 Cf. online: <https://www.23andme.com/health/Measures-of-Intelligence> [2013-03-04]. This company, on the basis of a study, reports the possible genetic influence of a single gene variant on up to six IQ points (cf. Gosso et al. 2006).

44 Cf. online: <http://www.genepartner.com> [2013-02-19].

45 Cf. Nielsen/El-Sohemy 2012.

weight reduction strategies.⁴⁶ It should be taken into account here that genetic influences on such complex aspects relevant to lifestyle always act in an equally very complex relationship with epigenetic factors and with the environmental and life circumstances of the person. It is therefore as yet not clear how informative the data identified are and what relevance they have for lifestyle.⁴⁷

The boundary between genetic influence of lifestyle and health is sometimes hard to draw, as is shown by the example of dyslexia. Approximately 5% of children of school age suffer from dyslexia. According to current research, genetic abnormalities play a marked role in its development. A research project is currently being conducted to develop a genetic test for preschool children which together with a specific measurement of brain activities is to make it possible to assess the risk of the development of this characteristic. Determining risk carriers at the earliest possible date would make it possible to undertake measures against the development of dyslexia as early as in the third year of life.⁴⁸ According to the definition of the World Health Organization, dyslexia comprises “developmental disorders of scholastic skills”.⁴⁹ This disorder concept is not identical with the disease concept in medicine.

46 Cf. for example online: <http://www.cogap.de> [2013-02-13].

47 Cf. de Roos 2013.

48 Cf. online: <http://www.legascreen.de/projektziel.html> [2012-10-30]; Grimm 2011.

49 Online: <http://www.dimdi.de/static/de/klassi/icd-10-gm/kodesuche/onlinefassungen/htmlgm2013/block-f80-f89.htm> [2013-02-06].

2.3 New developments in methods of genetic diagnosis

2.3.1 Principles of molecular genetic analysis

Methods of molecular genetic analysis make it possible to examine DNA sequences directly after genetic material has been isolated from a tissue sample. Since the 1980s, two principles of genetic analysis, in a large number of varying methods, have predominated in the genetic analysis of humans: oligonucleotide hybridization and polymerase chain reaction.

Oligonucleotide hybridization: This procedure makes it possible to identify in a cell or tissue sample a short DNA fragment whose sequence is *known* (called an oligonucleotide, with a length of up to approximately 100 base pairs). The hybridization approach is the basis of DNA microarrays, on which tiny quantities of specific DNA as probes (reporters) are applied to solid surfaces (chips) in order to identify specific complementary DNA sequences by ligation (hybridization) and marking.⁵⁰ In this way, a large number of different genes or gene variants can be closely analysed on the basis of a single sample. The procedure can also be used to show mRNA, non-coding RNA and other RNA samples in order to record DNA expression. For this purpose, the RNA to be identified in each case is usually first “transcribed” into cDNA⁵¹ and shown as DNA using the enzyme reverse transcriptase.

50 For each DNA sequence there is precisely one complementary sequence, in which A is exchanged for T and G for C, and vice versa, in the series of letters. In particular analytic conditions, the sequence and the complementary sequence show a strong tendency to bind to each other in a very specific way (sequence-specific hybridization). This is used to find sequences in which the letters are precisely matched. If an oligonucleotide is attached to a chip as a “probe”, it “fishes” the complementary sequence, if this is present in the sample, from a number of fragments. This bond can be shown by radioactive, fluorescent or other marking. The hybridization conditions can be designed in such a way that either only the precise complementary sequence is detected or partial sequences deviating by one or a few points are also found.

51 cDNA: complementary DNA; form of DNA which is synthesized from mRNA with the help of an enzyme.

PCR-based sequencing: This method makes it possible to identify the *unknown* sequence of DNA segments, extending as far as sequencing the whole genome of an individual. With the help of the polymerase chain reaction (PCR), the individual strand of DNA to be sequenced is made visible, using nucleotides marked in colour or radioactively, and the sequence of the nucleotides is made visible by this marking. This makes it possible to diagnose point mutations and to determine partial sequences of up to 1,000 base pairs.

PCR-based sequencing has long been an extremely important research instrument, but for a long time it was of limited importance for clinical application on account of the effort and expense involved. But this is currently changing because prices are sinking and because of new high-throughput methods (cf. section 2.3.2).

Nanopore sequencing: A new approach is taken by what is known as nanopore sequencing. Here, the sequence of DNA or RNA strands or even of proteins is identified by means of nucleotide-specific electric signals as they pass through molecule-sized pores.⁵² Since the sequence can here be read by a single molecule, it may be possible in future to use even faster and more precise analyses with even smaller material samples.

Detection strategy: For the ethical and legal assessment of the analysis of extensive individual genome segments, it is important to bear in mind the fundamental distinction between the hybridization method and PCR sequencing. In hybridization procedures, specified *known* sequences are deliberately and specifically searched for in a sample and either detected or excluded, whereas in PCR sequencing *unknown* sequences are analysed by the new synthesis of a complementary DNA strand. For medical application, this means that in the case of the hybridization principle the result can be restricted to answering a precisely defined question (for example for a

52 Cf. Bahrami et al. 2012; Luan/Stolovitzky/Martyyna 2012.

particular point mutation in a diagnosis based on a medical suspicion), whereas the new synthesis principle multiplies all existing sequence information and in addition to answering specific questions can provide a large amount of superfluous genetic information, and additional findings resulting from this which are unexpected or are not needed for the specific medical question.

2.3.2 New high-throughput methods to detect genetic data

For approximately ten years, there has been a rapid improvement in the efficiency of procedures of genetic analysis. The current further development of the above methods makes it possible to sequence the whole genome more rapidly and at the same time with high resolution. By the combined use of miniaturization, automation and parallel analysis of individual sequence segments on a huge scale, followed by integration of the use of bio-informatics evaluation methods, it is becoming increasingly possible to obtain more and more DNA information cheaply on the basis of smaller and smaller samples in an ever shorter period of time. Novel nucleotide markings and detection methods are also making it possible to determine the sequence of the nucleotides more rapidly and easily.

To obtain more extensive sequence information – culminating in information on the whole genome – the DNA to be examined must be “cut” by enzyme action into a large number of fragments and these must be individually sequenced (shotgun sequencing). The fragments, some of which overlap each other, are then put in the correct sequence by a computer programme in a process comparable to a game of dominoes (sequence assembly).

Further steps in extensive sequencing include the correction of errors, assembly and the allocation of partial sequences to the correct location in the relevant chromosome and thus

in the whole genome. Only at this stage of creating a genome sequence is it possible to meaningfully research and interpret functionally relevant genetic variants of the whole chromosome.⁵³ In this connection, there are particular challenges to the precision of sequencing of mass-produced DNA “snippets”. Errors may occur even before the actual sequencing, because the sample material has to be copied more than once. In addition, PCR is not completely free of errors. Further, when a sequence is read by the optical detection methods, errors or uncertainties may also occur. The assembly may also result in errors, because in the whole genome there are many very similar or even identical sections. Many errors can be identified and corrected if the DNA is sequenced more than once, but this entails appreciable extra cost.

The totality of all the methodic strategies named, targeted for high performance and high throughput, are called **next generation sequencing**; they open the prospect of determining the complete individual genome of individual persons with moderate effort and at a moderate cost.

It is currently estimated that in the coming years further technical progress is to be expected in today’s popular high-throughput sequencing methods, led by Roche, Illumina and Life Technologies, with the potential to reduce costs further still. At present, a complete genome can be sequenced with the necessary precision in a few days at material costs of approximately 10,000 US dollars. Whole genome sequencing within a few days for under 1,000 US dollars is regarded as a realistic goal for the next five to ten years.⁵⁴ However, these price forecasts take no account of the costs of interpreting the extensive and complex data. Despite corresponding progress

53 It must be taken into account that the overwhelming majority of gene variants (above all SNPs) which are found in an ethnically defined population are completely neutral. Filtering out the functionally relevant “signals” from this “noise” is a demanding task.

54 Cf. papers read at the hearing of the German Ethics Council on 22 March 2012 in Berlin. Online: <http://www.ethikrat.org/veranstaltungen/anhoerungen/multiplex-und-high-throughput-diagnostik> [2012-09-11].

in bioinformatics (cf. section 2.3.3), these are likely to remain high.⁵⁵

Advances in high-resolution DNA microarrays (DNA chips) also result in substantial savings in time and expense in many genetic questions. For example, it is now possible with the aid of chips to simultaneously determine the individual genotype (mutations, SNPs, CNVs) of millions of locations in the whole genome.

High-throughput methods can also be used to provide epigenetic profiles from special tissue samples (DNA markings; epigenome) or from RNA⁵⁶ (gene activity profiles; transcriptome⁵⁷).

The employment of high-throughput methods is fundamentally directed towards the rapid detection of large quantities of data; but the specific strategies and the extent of data detected by them may vary depending on the findings sought:

» Diagnostic panel: Search for a potentially very large number of different gene variants at any desired large number of gene loci, always specified in advance, for example to detect the relevant precise genetic causes of an unclear complex of symptoms (syndrome). The hybridization procedure with appropriate microarrays would be particularly suited for this purpose; the sequencing is then restricted in advance to the genetic locations selected. Today it is already

55 Cf. Mardis 2010.

56 The DNA spectrum realized in the cell is normally determined indirectly. For this purpose, the molecules are changed back into complementary DNA (cDNA) and this is sequenced with the usual procedures.

57 The totality of all transcribed RNA in a concrete cell type is called the transcriptome. It determines the state of development and function of the more than 200 varying cell and tissue types in the body. Developmental disorders, losses of function and even the development of tumours may probably also be triggered by quantitative shifts of relevant non-coding RNA molecules without this being readable in the genotype. However, for this potential to be used on a wide scale diagnostically, more information and extensive developments of methods are necessary. Currently, there are intensive investigations as to what epigenetic influences on the expression of genes are conditioned by DNA modifications, which by changes in the protein envelope and which, finally, by the effect of nc-RNA.

possible to detect hundreds of specific gene variants, and in the near future it is estimated that it will be possible to detect thousands, by means of DNA chips.

- >> Genome-wide chip analysis: In the same way as in the diagnostic panel, here too a potentially very large number of gene variants are simultaneously examined. The difference lies above all in the formulation of questions. Genome-wide chip analyses are used less to examine the individual genetic basis of a particular syndrome by taking into account all potentially relevant known gene variants. Instead, they are broader in design and usually restricted to only a few potentially involved gene variants in each case, in view of the multiplicity of characteristics which may be relevant to health or lifestyle.
- >> Exome sequencing: Here, all exomes are sequenced, that is, only the sections of the genome which code for proteins. The totality of exons is the exome, which comprises only 50 million of the total of 4.6 billion letters of the genome. An exome sequencing is therefore cheaper and less error-prone than the sequencing of the whole genome. This restriction is achieved by “fishing” the exons out of the whole genome before the analysis, using specific “molecular fishing rods”, then hybridizing them and only then sequencing them. In this process, normally from 10,000 to 50,000 gene variants are found in a person, depending on the technology used.⁵⁸ In order to identify pathogenic mutations relevant to disease, prioritization strategies are developed in order to be able to restrict the final analysis to from 150 to 200 individual variants.

Current experience from clinical studies indicates that the possibilities of diagnosis of rare monogenic diseases are improved. Exome sequencing offers a substantial diagnostic potential to explain monogenic diseases with a largely identical phenotype, but which may result from mutations

58 Cf. Neveling/Hoischen 2012.

in different genes (e.g. Fanconi anaemia⁵⁹ or Bardet-Biedl syndrome⁶⁰). Exome sequencings have also been used to make a molecular diagnosis of some diseases whose causes have not been clearly clinically identifiable to date, for example in the case of patients with unexplained mental disability⁶¹. Studies have already identified new relevant genes for more than fifty diseases.⁶² There are early examples indicating that such diagnoses can definitely hold potential for new approaches to treatment.⁶³ The gene variants in the exome are considerably less complex to analyse than those in the rest of the whole genome. They can therefore provide better evidence than a sequencing of the genome, above all on monogenic predispositions to illnesses.

- >> Whole genome sequencing: The aim here is to identify the “textual sequence” of the whole genome, that is, the haploid nucleotide sequence in all 46 chromosomes. Whole genome sequencing is at present conducted above all in basic research, but it has already been used in individual clinical pilot projects in order to make it possible to identify genetic causes in patients with an unidentified clinical phenotype. Here, whole genome sequencing, unlike exome sequencing, also makes it possible to identify disease-related gene variants in the non-coding sections of the genome.⁶⁴

In the past two years, first steps have been taken in the direction of large clinical research projects. At the end of 2011, the National Human Genome Research Institute commenced its multidisciplinary programme Clinical

59 Autosomal recessive inherited form of an anaemia which results *inter alia* in short stature and malformation of the kidneys.

60 Autosomal recessive inherited malformation syndrome which *inter alia* may result in disorders of kidney function or in obesity and mental disability.

61 Cf. de Ligt et al. 2012; Rauch et al. 2012.

62 Cf. Neveling/Hoischen 2012, 10.

63 Thus, for example, the ACAD9 mutation in patients with Complex 1 deficiency, a form of damage to the mitochondria caused by gene mutation, was identified and as a result of this riboflavin treatment (a vitamin of the B complex) was successful (cf. Haack et al. 2010).

64 Cf. Gonzaga-Jauregui/Lupski/Gibbs 2012.

Sequencing Exploratory Research in the USA.⁶⁵ In December 2012, a decision was taken in the United Kingdom that up to 100,000 patients with cancer and rare diseases should be sequenced.⁶⁶ In October 2012, at the conference of the European Society for Medical Oncology, the results of a large French study were presented, in which the whole genome of 402 breast cancer patients was sequenced in order to improve the foundations for deciding on a personal treatment.⁶⁷

Currently, the sequencing costs and in particular the difficulties and costs of data interpretation still put a considerable brake on using whole genome sequencing. If at some future date the sequencing of the individual genome becomes relatively easy for large groups of the population together with a large number of phenotype characteristics, however, it is conceivable that a multitude of bioinformatics algorithms could be developed from the growing databases of genome-phenotype profiles, and these could be applied to the genome of the individual patient (customer) for prognoses of a great variety of natures: medically relevant and irrelevant prognoses and prognoses from the grey intermediate area.

2.3.3 New bioinformatics methods to analyse genetic data

In comparison to older methods, the new methods produce such huge amounts of data that they can no longer be handled, processed, stored and interpreted using traditional methods.

65 Online: <http://www.genome.gov/27546194> [2013-03-04].

66 Cf. announcement of the British Prime Minister of 10 December 2012. Online: <http://www.number10.gov.uk/news/dna-tests-to-fight-cancer> [2013-03-04].

67 Cf. press release of the European Society for Medical Oncology of 30 September 2012. Online: [http://www.esmo.org/about-esmo/press-office/esmo-2012-press-releases/view.html?tx_ttnews\[tt_news\]=1625](http://www.esmo.org/about-esmo/press-office/esmo-2012-press-releases/view.html?tx_ttnews[tt_news]=1625) [2013-03-12].

Consequently, in the field of genome research, **bioinformatics** has in the last two decades become a strategic discipline of molecular genetics, without which the progress in findings would not be possible.

With the help of bioinformatics methods, an extensive software library which has developed through international competition can be accessed. It is only with bioinformatics that gathering primary data from the sequencing and the hybridization techniques by means of high-throughput design is even possible. The assembly of large genome sections from the “fragmented” primary data (DNA segments) calls for precisely working statistical and combinatorial algorithms. In addition, these procedures also perform important diagnostic analyses of the validity check and the detection of errors. Finally, bioinformatics software also makes a contribution to personal data protection in the extensive databases, including reliable algorithms for pseudonymization and if appropriate decoding when it is urgently necessary to contact the data donors.

A further, extremely important area of application of bioinformatics is **annotation**, with which relevant information on the patterns of the genome data is recorded. This includes, for example, finding coding segments and the control signals and the beginning and the end of gene sections, the identification of regulatory sections and of exons and introns, the detection of splice signals or the cell-biological characterization of the function or the loss of function of mutations.

After the primary analysis of the data there follows the actual molecular-genetic interpretation, which is based on high-performance mathematical/statistical and combinatorial methods of mathematical linguistics and text analysis. Its aim is to link various kinds of biological information. Thus, analyses may be carried out of the different segments in a genome, or of the architecture of different physiological and biochemical partial areas of an organism, or comparing different organisms, or even of cross-species interconnections. In this process, bioinformatics endeavours to go beyond its inherent area of

mathematical gene analysis and also to integrate various levels of the phenotype in the examination.⁶⁸

However, this summary must be qualified by the statement that many findings of bioinformatics have the character of a hypothesis reached by induction and need to be specifically re-examined and validated by means of the traditional experimental methods. In addition, it is as a general rule a challenge if conclusions for the specific individual medical case (including a risk prognosis) are to be made on the basis of general epidemiological findings.

The possibilities of using bioinformatics to link very extensive data quantities from different biological levels and in this way to analyse genetic information in context are also the main emphasis of the new discipline of **systems biology**, which has existed for ten years. An urgent problem of modern genomics, in view of the enormous volume of data (with accompanying intensive statistical noise) is the multi-dimensionality of the non-linear links between the various biological levels. Systems biology aims to integrate these fragmented partial aspects in the computer modelling of biological systems.

In the medically relevant area of these developments, dynamic models of the material processes occurring in cells and tissues⁶⁹ are mathematically aligned to the regulation level, which is organized in signal networks with extensive forward, backward and cross-linking. Until now, this concept was predominantly successful in the analysis of less complex biological systems (bacteria; (yeast) fungi). It is hoped that in future

68 On this, cf. for example the bioinformatics approach to genome analysis involving other clinically relevant data, which is at present being developed at the Hasso Plattner Institute and is being tested in cancer diagnosis at the Charité university hospital in Berlin. Online: <http://epic.hpi.uni-potsdam.de/Home/HigProject> [2013-02-19].

69 In cells and tissues of the organism there is a permanent dynamic equilibrium, in which all molecular elements are constantly being renewed, material is separated at membranes, genetic material is transported between organs and through cell membranes, and the process of conversion of the cell components is catalytically accelerated. These processes are controlled by signal cascades and signal networks, which intervene to regulate them.

the systems biology approach will enable progress in the understanding of multifactorial diseases.⁷⁰ But in this respect, this research area is still at a very early stage of development.

2.3.4 Consequences of high-throughput analysis for genetic diagnosis

None of the rapidly developing approaches to genetic diagnosis testing goes substantially further than the basic methodic principles developed in the 1990s. Most procedures are still based on detecting sequences by hybridization by oligonucleotide probes or by an artificial multiplication of the sample sequence (PCR). All further developments are based on constant acceleration, on extreme miniaturization and on mass parallelism of the long familiar detection procedures, complemented by a bioinformatics which has become enormously efficient.

The new methods may have consequences for medicine and society which will present new challenges to ethical evaluation. The ultra-high-throughput principle significantly changes the nature of the findings of genetic analysis:

- » Production of a mass of elementary genetic data. This results in particular in new challenges to data protection.
- » A tendency to unspecific “search procedures” in place of a targeted test. The procedure directed towards a particular mutation – for example in a family – is replaced by a broad diagnostic panel or even by genome-wide analyses, extending as far as whole genome sequencing. This broad, less specific approach leads to more complex demands on explanation and advice for patients or customers.

70 On this, see for example the funding priorities of the Federal Ministry of Education and Research with regard to systems biology. Online: <http://www.bmbf.de/de/1140.php> [2012-09-12].

- » A tendency to make comprehensive statements on probability. These are derived from the genetic data profile by the use of statistical population data (databases) on the basis of belonging to risk groups; they are used alongside targeted genetic studies, which take account of the individual phenotype of the person examined.⁷¹ This too makes it difficult to give comprehensive, comprehensible explanations and obtain correctly informed consent before and after the test – both for advisers and for the person examined.

2.3.5 Collections of genetic samples and data

In the interpretation of genetic analyses, databases play an increasingly large part. Thus, for a further validation of exome analyses extensive genotype and phenotype databases are necessary.

In order to achieve further progress in the analysis and interpretation of sequence data, increasingly complex collated and internationally networked biobanks are needed, which collect data from various sources, including data from broad medical practice, and make these available for genetic research. In this connection, a questionable monopolization by private enterprises may develop: one example serves to illustrate this. The company Myriad Genetics has developed a patent in breast cancer diagnosis and has systematically enforced this in the USA. When the sequencing findings are interpreted, it is important to distinguish clearly pathogenic variants from variants whose clinical relevance is unclear. Over the years, Myriad Genetics has been able to create a large database containing

71 The statement on probability is based on comparing the individual genetic constellation with the constellation of a control group (population). The individual features are defined against the background of the population and not primarily on the basis of the person. The tendency is that a personal profile can only be derived from the limited number of profiles already defined which are in the database.

the clinical information from the samples submitted and the results of many diagnostic examinations, and this database improves the classification of the pathogenicity of variants. It does not provide this information either for medical research or for clinical application. This means that this database gives the company a monopoly for the virtually exclusive conduct of the diagnosis in question.⁷²

Another problem is that genetic diagnosis is increasingly being carried out in a few large non-university laboratories, since the investment costs for the analytical equipment and bioinformatics programmes are high and continue to accrue on account of the constant further development of the technology. As a result, the data of outpatients at least, whose genetic diagnosis is no longer carried out in university hospitals, are decreasingly available to university medicine. This has an ongoing adverse effect on clinical research.

2.3.6 Methods of non-invasive prenatal genetic diagnosis

In order to determine genetic characteristics, biological material is needed; this is obtained either non-invasively (e.g. saliva sample), with a low degree of invasiveness (e.g. blood sample) or invasively (e.g. tumour biopsy). Previously, specifically for prenatal genetic studies, only invasive methods have been available to obtain fetal tissue samples (chorionic villus sampling, amniocentesis). Obtaining these samples carries a miscarriage risk of from 0.5 to 1%.⁷³ In contrast, non-invasive methods (e.g. an ultrasound examination of the embryo or fetus) have until recently been able to give only indirect evidence of the genetic constitution of an embryo or fetus⁷⁴; these

72 On this, cf. Cook-Deegan et al. 2012.

73 Cf. Tabor/Alfirevic 2010.

74 Until the organs are fully formed, the developing unborn child is called an embryo, and afterwards – from the ninth week of development – fetus.

are often followed by more thorough genetic diagnosis. But a more far-reaching, differentiated ultrasound examination⁷⁵ gives important information on the phenotypical status of particular characteristics such as malformations of the brain, heart and inner organs.

Today, it is technically possible to carry out genetic studies of embryonic or fetal DNA from maternal blood. Such non-invasive examinations can be used as early as in the first trimester.⁷⁶

Non-invasive prenatal genetic diagnosis is based on the fact that although the placenta separates the blood circulation of mother and fetus, a small quantity of cell-free DNA and RNA and a small number of cells of the fetus enter the mother's blood. After a blood sample is taken from a pregnant woman (minimally invasive for her, non-invasive for the fetus), the blood serum gives not only her own DNA but also always fragments of embryonic or fetal DNA. These fragments are sequenced and it is determined which parts are from the mother and which from the fetus.⁷⁷

Fetal DNA can be found in the woman's blood serum as early as from the fourth to fifth weeks of pregnancy, in the form of short fragments (approximately 140 base pairs). The further the pregnancy progresses, the greater is the concentration of

75 Cf. Merz et al. 2004; Merz et al. 2012.

76 The first trimester of pregnancy (trimester) is medically defined as the period of the first twelve weeks from the first day of the last menstrual period. Since the actual fertilization takes place on average two weeks after this date, the fetus is in fact only ten weeks old at the end of the first trimester. In gynaecology, this is nevertheless counted as the end of the twelfth week of pregnancy. German law uses a different definition, which is oriented towards the weeks of development after fertilization. Section 218a of the *Strafgesetzbuch* (Criminal Code) counts the weeks "since conception" (*post conceptionem*). In the following, the gynaecological counting method is followed, except where "post conception" is added.

77 The DNA of the offspring originally comes from the mother *and* the father. The paternal part can be distinguished from the maternal part. It is more difficult to distinguish between maternal DNA and the child's DNA inherited from the mother.

fetal or embryonic DNA in the woman's blood serum, from 9% in early pregnancy to 20% in the second trimester.⁷⁸

One technical difficulty of the procedure is that the blood always contains not only the fetal DNA traces, but also a surplus of up to twenty times of DNA fragments of the mother. Half of these maternal sequences are also found in the fetus, by inheritance, and depending on the purpose of the test (cf. below) the sequences in mother and fetus must be distinguished. In order to distinguish the genetic make-up of the embryo/fetus from that of its mother, epigenetic and genetic markings are used to identify and count sequences of child and mother.⁷⁹ Here, the high-throughput sequencing described above is increasingly used in order to examine maternal and embryonic/fetal DNA and in doing so to determine even the most subtle quantitative differences.⁸⁰

Once the fetal DNA has been identified or quantified, the presence or absence of particular gene sequences or their relative frequency can be examined. Several scenarios suggest themselves for diagnosis:

Search for aneuploidies: A numerical chromosome anomaly can be detected if the blood sample contains a significantly greater number of fetal sequence fragments of the relevant chromosome than expected.

In Germany, a test is available for trisomy 21, 18 and 13 (PraenaTest), according to its supplier currently from the twelfth week of pregnancy⁸¹; comparable tests outside Germany are sometimes available from as early as the tenth week

78 Cf. Hill et al. 2012, 640.

79 An epigenetic differentiation may be based, for example, on the fact that the placental DNA methylation pattern is different from the maternal one. At present, a large number of variations of these measuring and evaluation principles are being tested (cf. for example Chim et al. 2008; Tong et al. 2010).

80 Studies have shown that this approach is suitable for clinical practice (cf. Chiu/Lo 2012, 405).

81 Tests for further trisomies are as yet not available in Germany, but for example in the USA they are also offered for aneuploidies of the sex chromosomes. Cf. online: <http://www.verinata.com/providers/provider-overview> [2013-03-05].

of pregnancy⁸². It has now been shown that this method also makes it possible in principle to diagnose subchromosomal anomalies such as double or missing chromosome parts.⁸³

Diagnosis of characteristics which are not present in the mother: If the fetal DNA is examined for characteristics which are exclusively inherited from the father or have newly arisen in the fetus, the problem of distinguishing between maternal and fetal DNA does not occur. Hereditary diseases and other genetic deviations which are not present in the mother can therefore potentially be more easily identified by non-invasive prenatal genetic diagnosis.

This is the case, for example, when the method is used to determine the sex of the fetus. Here there is a search for sequences which are specific to the Y chromosome and therefore do not occur in the mother. Since precise quantification is not necessary here, this test needs less material and can technically be carried out from the seventh week on.⁸⁴ However, under the Genetic Diagnosis Act the pregnant woman may only be informed of the sex of the unborn child after the end of the twelfth week of pregnancy, unless the prenatal diagnosis relates to a sex-linked hereditary disease such as, for example, Duchenne muscular dystrophy⁸⁵.

By the same principle it is possible to use non-invasive prenatal genetic diagnosis to test the fetus for individual genetic defects which are not present in the mother. This is the case, for example, in the case of autosomal dominant diseases (such as Huntington's disease or myotonic dystrophy⁸⁶) if they are passed down in the family in question on the father's side or result from *de novo* mutations⁸⁷ (as in the case of achondroplasia,

82 Cf. online: http://www.panoramatest.com/patients_faqs [2013-03-08].

83 Cf. Srinivasan et al. 2013.

84 Cf. Hill et al. 2012, 640.

85 An X-linked recessive inherited disease which is usually fatal and which results in muscle weakness and muscle degeneration.

86 Autosomal dominant inherited muscular disease which may result in progressive physical and mental disability and is fatal in middle age.

87 This is a mutation which is not inherited from the parents but arises anew in the individual affected.

a growth disorder which predominantly results from new mutations).

In the case of recessive hereditary disease, for example cystic fibrosis, beta thalassemia and sickle-cell anaemia⁸⁸, it is also possible to show that the fetus is not affected if the paternal mutation can be clearly distinguished from the maternal variant, for example by logically following SNP. If the paternal mutation is then not found when the fetal DNA is examined, it can be assumed that the fetus is at most heterozygous and therefore not affected.

Diagnosis of characteristics inherited from the mother: New technologies have recently made it possible to diagnose gene variants inherited from the mother non-invasively too. In contrast to the above scenarios, in which it is only necessary to examine whether the allele mutated in the unborn child is present in the mother's blood or not, for positive diagnosis of a recessive mutation inherited homozygously from both parents or a dominant mutation inherited from the mother it is necessary to unequivocally separate the maternal DNA from the fetal DNA in order that it can be determined whether the unborn child has inherited the maternal genetic characteristic. For this purpose, it is necessary to compare the fetal DNA with the mother's DNA or even with the DNA of both parents.⁸⁹

Prenatal whole genome analysis: First pilot studies have now shown that even the sequence of the whole fetal genome can be determined by the comparative analysis of the DNA fragments from the woman's blood with the separately sequenced genome of the mother⁹⁰ or of both parents⁹¹. Technically, this also opens the future prospect that broad non-invasive genetic diagnosis can be carried out prenatally and can simultaneously

88 Recessive inherited blood disease with a pathological change of red blood pigment (haemoglobin) which results in sickle-cell-shaped red blood corpuscles (erythrocytes); frequent in Africa and among the population of the USA of African origin.

89 Cf. Lam et al. 2012.

90 Cf. Fan et al. 2012.

91 Cf. Kitzman et al. 2012.

search for aneuploidies and all possible dispositions to illness that are found in individual gene loci and at the same time additionally finds a large number of characteristics of the future child which are not directly medically relevant.

Prediction of complications in pregnancy: The non-invasive prenatal methods of diagnosis also make it possible to find indications of potential complications during pregnancy, for example preeclampsia⁹², premature labour and restricted growth of the fetus. The reason for this is that in pregnancy complications the number of fetal cells in the mother's blood increases if the pathologically altered placenta is more porous. In this connection, therefore, the comparison of the number of fetal DNA fragments as opposed to maternal DNA fragments is crucial.⁹³

Methods which require a precise identification and quantification of fetal DNA are at present, with exception of the tests for selected trisomies, not so far advanced that they could be employed in clinical practice. But it can be predicted for the future that with the use of high-throughput procedures both chromosome abnormalities and also monogenic defects and the risks of immunological pregnancy complications (e.g. Rh incompatibility⁹⁴) can be detected non-invasively even in the first trimester of pregnancy. For many characteristics of the child, however, such an early diagnosis has no therapeutic advantage, but at best an early improvement of knowledge; often, though, it also reports probabilities of deviations from the norm which are difficult to interpret and which may give occasion for further examinations. However, there are also characteristics in the case of which treatment could begin early in pregnancy (for example in the case of genetic disorders of hormone balance).

92 A condition (also known as pregnancy poisoning) which occurs in late pregnancy and can only be treated effectively by delivery of the child.

93 Cf. Kavanagh et al. 2010, 1906.

94 Blood group Rh factor incompatibility between an Rh-negative mother (Rh-) and an Rh-positive child (Rh+).

2.4 Validity of genetic tests

Genetic tests and their validity are of great importance, not only in research but also in clinical application. While the prime concern in research is to assess how well a test functions on the technical level, the medical application of genetic tests gives rise to further challenges. There are three factors to take into account in this area: firstly, the technical reliability of a test; secondly, the application of epidemiologically validated findings regarding the statistical risks to individuals; and thirdly, the reliable interpretation of the test results based on complex linkages between genotype and phenotype.

2.4.1 Technical reliability

The validity of a test depends on how sensitively and how reliably the test provides correct information in the specific case.⁹⁵ Even if a test is conducted very carefully, it can still contain small and minute errors, which sometimes produce an objectively false result.

The technical quality of a test is indicated by its **specificity** and its **sensitivity**.

A genetic test is 100% specific if it reports only carriers, and no non-carriers. The less specific a test is, the greater is the risk of erroneously reporting a non-carrier as a carrier; this is known as a **false positive** test result.

A genetic test is 100% sensitive if it captures every carrier. The less sensitive a test is, the greater is the risk of missing a carrier; this is known as a **false negative** test result.

⁹⁵ There are also additional criteria to describe the technical reliability and validity, such as precision, robustness and, for example, linearity in quantitative determinations.

A false positive diagnosis may have harmful consequences if it leads to invasive preventive or therapeutic measures which are totally unnecessary.

A false negative diagnosis may have harmful consequences if it means that necessary or beneficial therapeutic or preventive measures are not carried out.

Both false positive and false negative test results can be due to technical problems, for example copying errors in cloning steps, which are often necessary for DNA analysis in order to obtain sufficient examination material for the test.

Both specificity and sensitivity can be expressed in quantitative terms. In order to assess the validity of a test, it is necessary to know not only its sensitivity and specificity, but also the expected prevalence in the population sample being examined – that is to say, the proportion of carriers (positives). Using this information it is possible to calculate the expected rate of false positive and false negative test results from a random sample that is representative of the prevalence of a characteristic (e.g. a disease).⁹⁶

In practice, even with very sensitive and highly specific tests, there is still a residual risk of false positive or false negative results; this is generally in the range of low single-digit percentages.

96 The following formulae are used for this calculation:

- sens (%) = frequency (%) of positive test results among carriers
- spec (%) = frequency (%) of negative test results among non-carriers (This definition may not be immediately obvious because of the casual use of the word "specific" in everyday language. However, it is easy to see that a test which is 100% specific can only produce true positives, and no false positives, so that the formula produces a value of 100% for spec (%).)
- prev = relative proportion of carriers in the random sample (prevalence; value between 0 and 1)
- Rate of false positive test results (%) = $100 * (1 - \text{prev}) * (100 - \text{spec}) / \{(1 - \text{prev}) * (100 - \text{spec}) + \text{prev} * \text{sens}\}$
- Rate of false negative test results (%) = $100 * \text{prev} * (100 - \text{sens}) / \{\text{prev} * (100 - \text{sens}) + (1 - \text{prev}) * \text{spec}\}$
- Ratio of false positive to true positive test results = $100 * (1 - \text{prev}) * (100 - \text{spec}) / (\text{prev} * \text{sens})$

If the disease is very rare, the validity of the test is reduced because, by dint of the large number of unaffected test subjects, there may be considerably more false positives than true positives. If the disease is prevalent and the test not specific enough, the test tends to classify a large number of risk-carriers as unaffected.

If a test or a group of tests is used for screening in the general population, it is necessary to bear in mind that most genetically conditioned pathological characteristics are very rare in the population as a whole. Consequently, such a screening test tends to produce more false positive than true positive diagnoses.⁹⁷ If a complex test is used to search for a large number of different rare mutations in many gene loci (conceivable in the future by way of whole genome sequencing with an untargeted search for all possible genetic deviations), then a large number of false positive results will be found. Added to this is the fact that, in the case of monogenic defects (because a large number of rare alleles are not reported), it is hard to test their allelic heterogeneity exhaustively. In this case, there would also be a large number of false negative diagnoses, as the test does not pick up carriers with rare causative alleles.

If whole genome sequencing were to be widely used in the population in future, as seems likely, such clusters would be expected to cause considerable problems, both in terms of epidemiological analysis and also in the assessment of specific cases. As already outlined, both types of false diagnosis turn the screening process into a guessing game, if the tests are not extremely specific and sensitive and, in the case of genetic characteristics with heterogeneous causation, do not reliably cover the whole spectrum of genetic causes.

Tests can be repeated or their results validated by the use of other methods, which may help to prevent misinterpretations

97 By way of an illustrative example, section 2.5.3 shows a calculation for non-invasive prenatal diagnosis.

due to technically generated false diagnoses. However, this entails substantial expense.

2.4.2 Predictive transfer of statistical risks to individuals

When genetic tests are used for prognosis and prediction, the technical uncertainty described in 2.4.1 is compounded by the fact that a personal risk is derived for the **individual** patient or customer from the findings obtained from an anonymized random sample comprising many people. This personal risk indicates the probability that a link between a certain genotype and a certain phenotype, observed in some of the random sample, will apply to the individual in the future. To do this, values are estimated from the frequencies in the representative random sample to give the probability of this link in the population as a whole, and these values are then applied to the individual in question. What is provided for the individual is therefore not a **diagnosis**, but a **risk assessment**. This gives rise to an additional danger of false *predictions*.

The predictive use of tests is intended to provide predictions based on characteristics, which can indicate the possibility of a disease manifesting at a later stage. In most cases there is no 100% certainty of subsequent manifestation of a disease, because additional (still unknown) characteristics must be present, or because unforeseeable factors may occur before the disease manifests to influence or even prevent it. For the same reason, even though the test may correctly indicate the **genotype**, an individual prediction is merely a statement of risk.

If the disease *risk* determined for a particular section of the population is translated into a *prediction* for a specific person, that is to say that he will *probably* acquire the disease, and this does not happen, then in retrospect this may be called a “false positive *prediction*” in this particular case, in the same way as for the technical test quality described above. Just like

a technically generated false positive test result, a “false positive” prediction can have harmful consequences if the person in question chooses to undergo extreme therapeutic or preventive measures (e.g. mastectomy and oophorectomy where a high probability of contracting breast cancer is predicted).

By analogy, there may also be “false negative predictions” where a specific person is *not* predicted to have a high probability of contracting a disease, but goes on to do so. The “false negative” prediction may have serious consequences if measures could have been taken to prevent the disease (e.g. regular medical checkups).

A simple fictitious example may illustrate the problem of the predictive application of statistical risks to individuals:

600 female subjects undergo a BRCA gene test for breast cancer mutations. A record is then kept of the women who develop breast cancer in later life. The following figures are found⁹⁸ for the distribution of genotype (BRCA mutations or normal genotype) and lifetime incidence of breast cancer (that is, the total number of breast cancer cases).

	Breast cancer	No breast cancer	Total
BRCA mutation	20	10	30
Normal genotype	57	513	570
Total	77	523	600

Table 1: Incidence of breast cancer as a function of genotype

This is therefore a disease which develops in 13% (77/600) of the group in their lifetimes. In cancer sufferers, the mutated genotype is found in 26% (20/77) of cases, but only in 2% of healthy women (10/523).

⁹⁸ For the sake of simplicity, absolute numbers are used. All the entries can be converted into estimated probabilities by dividing by 600.

The table shows that the BRCA mutation is **statistically associated** with the occurrence of breast cancer, that is to say that it is more frequently found in women suffering from breast cancer than in healthy women. There are a number of possibilities to describe such an association quantitatively. One example is the **odds ratio**. It is defined as a cross product ratio⁹⁹ – in the table:

$$\frac{20 \times 513}{57 \times 10} = 18$$

The resulting value expresses how much greater the risk of developing breast cancer is for mutation carriers compared with non-mutation carriers – in this case eighteen times greater.

From the data in the table, the following predictions can be made for an **individual** from the same group of the population as the women studied in the random sample:

Prediction of disease risk: Women who carry the mutation have a 67% (20/30)¹⁰⁰ probability of developing breast cancer. On the other hand, women who carry the normal allele only have a 10% (57/570)¹⁰¹ probability.

If one were to derive from these figures the prediction “will probably develop the disease” for carriers of the mutation and “will probably not develop the disease” for carriers of the normal allele, then this prediction would be accurate in 88% (533/600) of cases.

However, this still means that for 12% of those tested the expectation of developing or not developing the disease based

99 In order to calculate a cross product ratio, the diagonally opposite “crossover” entries in the table are multiplied and the results are then divided. In this case the product of breast cancer sufferers *with* gene mutation (20) and healthy women *without* gene mutation (513) divided by the product of breast cancer sufferers *without* gene mutation (57) and healthy women *with* gene mutation (10).

100 Proportion of the total number of gene mutation carriers who are suffering from breast cancer.

101 Proportion of the total number of women *without* gene mutation who are suffering from breast cancer.

on the results of the genetic test was *not* met, because the prediction later proved to be false:

For carriers of the normal allele, who are therefore classified as “free from disease risk”, the prediction is a false negative prediction in 10% (57/570) of cases; they develop breast cancer, even though they do not carry the mutated gene. This is because the vast majority of cases of breast cancer are caused by something other than a BRCA mutation. So, even if it is possible to rule out any risk from a mutated BRCA gene, the remaining 10% risk of developing the disease is nearly as high as the overall risk for the female population (13%) – because the test only excludes the specific partial risk of developing the disease due to a BRCA mutation.

On the other hand, the test indicates a high probability of developing the disease for the carriers of the mutated allele from the same population and this proves to be a false positive in 33% (10/30) of cases. Invasive preventive measures (e.g. prophylactic mastectomies) would be totally inappropriate for these people.

Therefore, the essential problem with all predictive tests is that a statement of probability which is valid for the reference population can be completely wrong in an individual case.

Consequently the assessment of a predictive test and its potential errors largely depends upon the level of the risk of developing the disease¹⁰² and the test quality as well as the negative impact of incorrect (false positive or false negative) test results upon those affected.

¹⁰² Here the spread ranges from the low single-digit range, if, for example a particular gene variant only increases the risk of developing a multifactorial disease by a few per cent, up to the high two-digit range in the case of monogenic hereditary diseases with diminished penetrance, if a gene variant is associated with a considerable risk of developing the disease, as in the case of hereditary breast cancer.

2.4.3 Interpretation of complex linkages

Because of the uncertainties described above, genetic risk prognoses are difficult, even if there are many monogenic characteristics. The difficulties are exacerbated where there are complex linkages between genotype and phenotype.

Over the last decade, many studies have been conducted with very large numbers of participants for numerous complex, genetically co-determined characteristics, especially dispositions to a disease. For this purpose characteristic symptoms and findings were recorded for the phenotypes (diseases) under investigation and the genome-wide spectrum of individual SNP variants or SNP haplotypes¹⁰³ determined. These studies have been published under the collective designation of genome-wide association studies (GWAS) on the statistical correlation between genotypes¹⁰⁴ and phenotypes of various medical conditions. They have provided an extensive database, from which numerous hypotheses about gene loci involved in the development of complex phenotypes have been mathematically deduced. There has also been an attempt to use genotypical-phenotypical associations to predict risks of developing a disease.¹⁰⁵ For example, this is the idea behind some direct-to-consumer (DTC) testing services, which try to calculate a customer's risk of selected diseases from their individual genomic data (cf. section 2.5.7).

Genome wide association studies are mapping processes. They are not used to investigate the whole DNA sequence but to map as “markers” DNA patterns that occur with statistical

¹⁰³ Haplotypes are characteristic SNP patterns on a given chromosome, which occur in certain population groups and are usually passed on unchanged from generation to generation. The international haplotype mapping project (HapMap Project) is determining the SNP haplotypes in different population groups throughout the world to provide a basis for more accurate marking and mapping of segment sequences of the genome that are consistently passed down.

¹⁰⁴ Specifically: between suspected gene variants at associated gene loci identified by the mapping process.

¹⁰⁵ Cf. Manolio 2010; Pearson/Manolio 2008; Roberts et al. 2012.

frequency in a person affected by a phenotypical characteristic. Usually, it is not the marker (SNP or haplotype) itself that gives rise to the genetic deviation but a mutation adjacent to the marker, which would have to be identified by more accurate sequencing. However, the basic assumption of an association between markers and causative variants is not necessarily valid in every case. For example, if a mutation is very “old”, then the coupling of marker and mutation can be lost after many generations. It will only be possible to systematically check the hypothesis of a strict association between markers and the cause of the disease in a few years’ time when there are sufficiently comprehensive direct genotype-phenotype studies, which do not use the intermediate device of markers as orientation aids, available for comparison.

The initial high expectations for a direct clinical application of the results of genome-wide association studies have now given way to disillusionment, at least for the time being.¹⁰⁶ The insuperable conceptual difficulty is that, when dealing with characteristics influenced by multiple factors, there are a large number of possible gene loci, and an even greater number of interactions between these gene loci, to consider. This inevitably gives rise to a tendency to statistical (overfitting)¹⁰⁷ of the linkages, which means that random linkages between DNA sequence and phenotype are interpreted as supposedly causative. In the same way there might be (underfitting)¹⁰⁸, in which actually relevant genes or interactions between several genes are not recorded or are incorrectly recorded and so escape identification.

Large population studies are necessary to understand the complex relationship between certain gene variants and a

¹⁰⁶ Cf. Buchanan/Weiss/Fullerton 2006.

¹⁰⁷ Random effects are modelled as supposedly causative factors, but they cannot be verified amongst other volunteers.

¹⁰⁸ The genotype influence is incorrectly represented in the mathematical model so that systematic deviations remain between the model and the data, thus falsifying the prediction.

multifactorially conditioned phenotype. In addition to genetic markers, these studies record thousands of parameters to describe personal circumstances, neurological and behavioural psychology profiles, health status (blood values, blood pressure, hormones etc.) and physical attributes (height, weight, imaging data). The totality of all these findings is very variable and specific to each individual. Extremely large random samples are required in order to be able to make statements from the huge number of all possible combinations about individual parameters and, where appropriate, about cause-effect relationships. Since, on top of all this, the interplay of all these factors changes over the course of a person's lifetime, long-term studies are also required. A prospective national cohort study is currently being prepared in Germany and, starting in 2014, this will follow 200,000 people over the course of twenty to thirty years, in order to investigate unanswered questions regarding the genotype-phenotype interaction.¹⁰⁹

The larger population studies published to date have yielded a plenitude of "candidate genes" with their notable polymorphisms, which are possible partial causes of the disease in question, albeit usually only to a very limited extent. In most cases, there is no satisfactory correlation between the heritability of the disease characteristics statistically modelled on the basis of known genetic factors and that actually measured in real family studies. This is referred to as missing heritability¹¹⁰; often, no satisfactory predictive significance of the mathematical models created can be found. Often, too, it is not known whether this is due to the failure to consider the heterogeneity of causes of the disease in question or whether the population sample was not sufficiently homogeneous.

109 Cf. online: <http://www.nationale-kohorte.de/informationen.html> [2013-02-14].

110 This term describes the phenomenon that in the investigation of the influence of genes, it may transpire that the identified gene variants individually explain only a few per cent and together only a small proportion of the heritability of the phenotype, determined not from the genome but, for example, from twin and other family studies (cf. Maher 2008).

At present, it is not possible to predict for which multifactorial diseases it will be possible to develop a valid systems biological model of causation which is powerful enough to be used for predictive purposes (prevention, preventive therapy). Because of the uncertainties outlined above, there is currently still a considerable amount of scepticism about the potential for the predictive application of genetic diagnosis for diseases with complex causes.¹¹¹

2.5 Areas of application of genetic diagnosis

2.5.1 Preconception genetic diagnosis

Preconception genetic diagnosis is a genetic test before conception. Its aim is to determine the genetic makeup of father and/or mother in order to exclude a genetic predisposition, either as an undirected test or because a genetic anomaly was manifested in an early pregnancy or has occurred among relatives. Suspicion may also arise less specifically where there have been several miscarriages.

Depending on the situation, a targeted search is carried out for mutations in a particular gene, for chromosomal translocation or for predispositions for recessive defects or X-linked defects. Where the findings are positive, the parents must decide what consequences to draw, whether, for example, they will decide not to have a child, or to have artificial insemination (in-vitro fertilization) followed by preimplantation genetic diagnosis of the embryos, or a natural pregnancy with prenatal diagnosis.

111 Cf. papers read at the hearing of the German Ethics Council on 3 May 2012 in Berlin. Online: <http://www.ethikrat.org/veranstaltungen/anhoeerungen/praediktive-genetische-diagnostik-multifaktorieller-erkrankungen> [2012-09-11].

Up to now, preconception predisposition tests were offered largely for one or a few specific hereditary diseases and only for persons with an increased risk of this disease which lies either in the history or the family (with relatives already affected) or in membership of a population group in which the risk is higher overall (e.g. Tay-Sachs disease¹¹² among Ashkenazi Jews or beta thalassemia in the Mediterranean area).

As a result of the development of the new high-throughput techniques for genome analysis and the expected reduction of costs resulting from this, however, preconception genetic diagnosis increasingly offers the possibility of searching for many possible genetic risks at the same time before conception.

It can be foreseen that test possibilities will increase; a test for nearly 600 predispositions is currently being clinically examined.¹¹³ Several companies already offer genetic carrier tests for from approximately twenty to over 100 hereditary diseases at the same time and in some cases market these direct to interested persons without the intervention of a doctor.¹¹⁴

With the number of gene loci examined, the probability increases that genetic changes will be found which might be manifested in the child as hereditary diseases or genetic risks. If in future the analysis of frequent alleles with consequences which have less drastic effects on health or a low to moderate risk of disease is available, this might result in new challenges

112 Autosomal recessive inherited fat metabolism disturbance which results in death in the first years of life and is accompanied by blindness and seriously delayed physical and mental development; particularly common in people of East European Jewish descent.

113 Cf. Kingsmore 2012.

114 In Germany, the company bio.logis provides such tests for over twenty diseases direct to customers, including tests for cystic fibrosis and beta thalassemia (online: <https://www.bio.logis.de/pgs/produktnutzen/carrier-status> [2013-02-20]). In addition, a genetic carrier test for forty diseases can be ordered online from 23andMe (online: <https://www.23andme.com/health/carrier> [2012-09-12]). In the USA, Pathway Genomics offers preconception tests for over seventy recessive hereditary diseases (online: <https://www.pathway.com/dna-reports/carrier-status> [2012-09-12]); Counsyl's "Universal Genetic Test" tests for over 100 hereditary diseases (online: <https://www.counsyl.com/diseases> [2013-02-20]). These tests may be ordered through a doctor.

for dealing with such information and for advising couples who make use of such a diagnosis.

2.5.2 Preimplantation genetic diagnosis

In preimplantation genetic diagnosis (PGD), genetic diagnosis takes place after in-vitro fertilization on the embryo outside the womb. Under current law, PGD is permissible only to determine the danger of a serious hereditary disease or serious damage to the embryo which is highly likely to result in a still-birth or a miscarriage (Section 3a of the *Embryonenschutzgesetz* [Embryo Protection Act]). Several embryos are fertilized in order that embryos which do not manifest the feared genetic predisposition can be selected for transfer to the woman's uterus. Technically it will be increasingly possible as part of a PGD to go beyond this limited indication and in addition to generate large quantities of further genetic data on the *in vitro* embryo. Theoretically, the analysis could in future be extended to the sequencing of the whole genome.

2.5.3 Prenatal genetic diagnosis

In prenatal genetic diagnosis, the test is carried out before birth on genetic material from the developing child. Both chromosome abnormalities and also changes in specific genes can be diagnosed in this way. At present this is usually done either after a chorionic villus sampling or after an amniocentesis. Both methods carry a risk of miscarriage of from 0.5 to 1%¹¹⁵, and for this reason they are recommended only for risk pregnancies in the Maternity Directive¹¹⁶ of the *Gemeinsamer Bundesausschuss*

115 Cf. Tabor/Alfirevic 2010.

116 Directive concerning the medical care for insured persons during pregnancy and after birth (*Gemeinsamer Bundesausschuss* 2012).

(Federal Joint Committee). In addition, a chorionic villus sampling is generally only carried out after the 11th week of pregnancy and an amniocentesis only after the 16th week of pregnancy.^{117,118}

The newly developed non-invasive procedures described in section 2.3.6, in which fragments of fetal DNA from the mother's blood are examined, offer the possibility of avoiding the risks of the invasive approach of chorionic villus sampling and amniocentesis, although it must be taken into account that invasive diagnosis is still required to clarify further genetic changes apart from trisomy 21, 18 and 13. But in future, more comprehensive possibilities of non-invasive chromosomal and molecular genetic analysis are expected to be available. In addition, with the increasing possibilities of genome analysis, there is a prospect that in future it will be possible to examine the fetal genome independently of the method of obtaining DNA more broadly and unspecifically for all genetic characteristics than at present.

By reason of the non-invasive nature of the new testing methods, it is possible that the demand for prenatal genetic tests will increase in future. In this connection, account should be taken of wrong diagnoses, which may be expected to occur, in particular false positive test results, which might result in an invasive follow-up test or a termination of pregnancy. In the case of a non-invasive test for trisomy 21, 18 and 13, as currently offered in Germany as PraenaTest by LifeCodexx, it is currently assumed that there is a false-positive rate of approximately 0.3%.¹¹⁹

117 Cf. Directive on prenatal diagnosis of diseases and disease predispositions (*Bundesärztekammer* 2003).

118 Weeks of pregnancy counted from the first day of the last menstrual period.

119 0.2% according to the manufacturer's latest information for medical experts of February 2013, on the basis of a study of 468 cases; 0.3% as the mean value of large international studies (cf. Benn et al. 2012). In this connection it should also be noted that the actual rate might vary between 0.2 and 0.7 by reason of statistical fluctuations and can only be calculated more reliably on the basis of much more extensive studies.

The significance of such a rate can be demonstrated by the following model calculation: the probability of conceiving a child with trisomy 21 in the group of women with increased risk for whom the test is at present exclusively recommended is approximately 1%.¹²⁰ If one assumes that there are 30,000 pregnant women with this risk¹²¹, all of whom request a non-invasive test for trisomy 21 with a false-positive rate of 0.3%, then in addition to 300 pregnancies which are actually affected by trisomy 21 (1% of 30,000), there are expected to be an additional 89 cases with false positive results among the remaining 29,700 unaffected pregnancies (0.3% of 29,700). Of a total of 389 test results which suggest trisomy 21, in this case almost one quarter would be false positive.

A still higher proportion would be expected if in future sinking test costs and the possibility of early non-invasive access to a test would mean that the test was also used on pregnant women with a lower trisomy risk. In the case of a trisomy 21 risk of approximately 1:700¹²², for example, it could be expected that approximately two-thirds of the trisomy 21 diagnoses would be false positive and only one-third correct.¹²³

Companies offering the test therefore recommend that if there is a suspicion of trisomy, the PraenaTest should only be used as an (additional) screening method and specifically if the test is positive to follow it up with an invasive procedure to confirm the diagnosis.

120 Average probability for pregnant women aged 40; threshold value for which a follow-up invasive test is often recommended in first-trimester screening.

121 Based on the number of children born alive in 2011 whose mothers were 40 or more years old: 28,470. Cf. online: <https://www.destatis.de/DE/ZahlenFakten/GesellschaftStaat/Bevoelkerung/Geburten/Tabellen/LebendgeboreneAlter.html> [2013-03-07].

122 Average for all pregnant women.

123 This applies if the false-positive rate of the test is equally high for this group as for cases with a greater risk; in practice, non-invasive prenatal diagnosis has as yet not been sufficiently tested on pregnant women with a low risk. The model calculation with 30,000 pregnant women, for a risk of 1:700, shows 43 unborn children with Down syndrome and 90 unborn children not affected whose mothers nevertheless receive a wrong diagnosis of trisomy 21.

However, the possibility cannot be excluded that in particular in the early use – which is technically possible¹²⁴ – of non-invasive prenatal genetic diagnosis in the tenth week of pregnancy some of the pregnant women who receive a positive test result will refuse to have the diagnosis confirmed by an invasive test and will attempt to have an immediate termination of pregnancy (e.g. under Section 218a (1) of the Criminal Code). If such a reaction of pregnant women to making decisions should become widespread, the number of terminations of pregnancy after a false positive test result would be approximately as high as the number of miscarriages which would occur if all pregnant women had undergone invasive prenatal diagnosis from the outset.¹²⁵

2.5.4 Postnatal genetic diagnosis for the purpose of prognosis and treatment planning

In these examinations, the aim is to detect individual characteristics or qualities which, for example where a particular illness is present, may indicate the future course of the illness. Test results may give early evidence of a particularly serious type of progression or particular complications or may allay fears by predicting a milder progression.¹²⁶

There is also increasing success in selecting appropriate treatments or even developing them on the basis of better knowledge of the genetic and molecular mechanisms for the genesis of a disease. In these cases, genetic diagnosis may make it possible to allocate the patient to a particular group of cases

124 In Germany, the LifeCodexx PraenaTest is only offered from the twelfth week of pregnancy on; but comparable tests outside Germany are already available from as early as the tenth week of pregnancy. Cf. online: http://www.panoramatest.com/patients_faqs [2013-03-08].

125 The risk of miscarriage after invasive prenatal diagnosis is currently estimated to be between 0.5 and 1%, and the risk of a false-positive result in non-invasive prenatal diagnosis 0.2 to 0.7%.

126 This may be the case, for example, for certain alleles for cystic fibrosis.

which can be successfully treated with a targeted medicinal product. The aim may also be to spare patients for whom a medicinal product has no effect from being treated with this medicinal product, to avoid the side effects.

Such pharmacogenetic tests are currently used for the detailed diagnosis and planning of treatment above all in cancer treatment. But there are now also specific blood tests for clinical pharmacotherapy in a limited group of other diseases, for example for treatment with statins in the cases of disorders of fat metabolism.

The standard treatment of breast cancer includes taking the anti-oestrogen¹²⁷ Tamoxifen daily. This medicinal product is taken by thousands of women in compliance with the guidelines. Known side effects included hot flushes, liver enzyme elevations and joint pains. In just under 10% of the women, this medicinal product has no effect at all, and in approximately 20% its effect is weak. In such cases, pharmacogenetic studies could help avoid wrong treatment.

2.5.5 Predictive genetic diagnosis of monogenic diseases

The classical area of application of genetic studies for monogenic hereditary diseases is the differential diagnosis and prognosis of potential deformities, metabolic defects and organic syndromes. A predictive use may be considered if the genetic findings precede the development of the physical finding. A well-known example is Huntington's disease. In the gene which causes this, whose base sequence is responsible for the development of the disease, the nucleotide sequence CAG is repeated several times in a particular location. The disease manifests in every carrier of more than forty repetitions of this

127 Oestrogen: hormone which has regulatory functions, particularly in the female organism.

base triplet¹²⁸; all individuals who clinically suffer Huntington's disease have these changes in the gene, in some cases as multiple mutations.

Monogenic predispositions to diseases may be examined at different times, *inter alia* in the preconception and prenatal tests described above and in newborn screening, but also later after birth or in adulthood. This can be done on the basis of a specific medical indication or as an undirected search procedure. The latter will be available for large population groups with the use of high-throughput procedures.

In general it can be said of predictive molecular genetic tests for monogenic diseases that in all cases in which the cause and effect relation between genotype and disease is incomplete as described above (cf. section 2.2), the result does not lead to a **diagnosis** of the illness or disorder, but only to a statistically derived **risk**, that is, that a disease *might* develop on the basis of a "positive" genetic finding. As a result of this, in genetic advice on monogenic disorders in such cases there are similar problems to those described below for multifactorial diseases.

2.5.6 Predictive genetic diagnosis in multifactorial diseases

In the case of multifactorial diseases, determining a particular genotype is in most cases not capable of resulting in a certain diagnosis. Instead, the diagnosis is only determined clinically by evaluating the symptoms and by classical laboratory examinations or with the use of imaging. Nevertheless, there is the hope that additional diagnostic and above all predictive

128 Admittedly, this happens only at an advanced age, which is why this disease is an elementary model for the discussion of predictive genetic diagnosis as opposed to symptomatic genetic diagnosis. The more CAG triplets are present, the earlier and more severely the disease manifests itself. If there are from 36 to 40 CAG repetitions in the Huntington gene, the disease cannot be predicted with certainty; fewer than 36 repetitions are regarded as normal.

information can be obtained by genetic analysis. The knowledge of a genetically based higher risk of disease is intended to increase the motivation to take preventive measures at an early date.

Until now, several hundred genome-wide association studies (GWAS) have been carried out using DNA chips, and in the process several thousand candidate gene loci have been shown to be statistically significant for an influence of the genotype on the respective phenotype in a large number of multifactorial characteristics (cf. section 2.4.3). As yet, this does not usually create a consistent picture for predictive genetic diagnosis.

The use of genetic diagnosis for widespread diseases, in contrast, is already producing results where the subject is rare family variants of a widespread disease, that is, if a genetic variant with a clearly causative role in the disease is determined whose influence in the person affected is suspected on the basis of family heredity.¹²⁹

2.5.7 Direct-to-consumer tests

Tests in some of the above areas of application have also been offered for some years as what are known as direct-to-consumer tests (DTC tests). Genetic tests are in principle offered for purchase without restrictions – usually on the internet – to the whole population¹³⁰; without the need for a doctor as intermediary, the customer may order them direct from the seller or through third parties (e.g. fitness studios or nutritionists) by sending in a genetic (saliva) sample. The test results may generally be downloaded from the seller by the customers themselves using a personal code.

129 Fewer than 5% of Alzheimer patients, for example, suffer from a monogenically caused variant of the illness. These cases arise from mutations in one of three genes (presenilin 1 gene, presenilin 2 gene, amyloid precursor protein gene) (cf. Bertram/Tanzi 2008).

130 Cf. *Deutsche Gesellschaft für Humangenetik* 2011.

One of the best-known suppliers of DTC tests is the US company 23andMe. In Europe, one example of a company offering tests is easyDNA¹³¹ and in Germany, one example is bio.logis¹³²; they currently offer a range of test combinations with lists of the genetic predispositions to be diagnosed, directly accessible on the internet.

Most other companies, in contrast, concentrate on offering tests where selected genetic characteristics are sequenced, with accompanying analysis and interpretation. The range of tests includes above all tests relevant for health in relation to family planning (genetic carriers), prevention (determining risk factors for health disorders) and for the optimization of medicinal therapy (pharmacogenetics).

Test results on genetic characteristics which are very highly likely to be monogenic or to result in a serious impairment of health are also sometimes reported to the customers without a doctor being involved, even though the impairment can either not be treated or can be treated only with the aid of invasive measures.

In addition, many companies also offer tests to analyse descent and tests for characteristics which have no direct relevance to health but are to supply information for a person's lifestyle. 23andMe, for example, tests fifty-seven characteristics which are not directly medically relevant. The findings cover a broad spectrum of predictions; this extends from specific sensitivities of taste and smell, nutrition recommendations and reactions to certain sports programmes to predicting memory, intelligence, breast size or hair density.¹³³

How far the enormous financial expectations of the DTC test sellers and the fears of politicians that the demand for

131 Online: <http://www.easydna.ch> [2013-03-04].

132 Online: <https://www.bio.logis.de> [2012-03-04], for example the "carrier" package, which tests a list of genetic variants with significance for family planning and offspring, the "pharma" package (metabolization of particular medicinal products) or the "complete" package, which comprises all the other packages.

133 Cf. online: <https://www.23andme.com/health/all> [2013-03-04].

these tests will drastically increase are realistic has yet to be seen. The original expectations of an expanding DTC market have not yet been fulfilled. In the USA, the interventions of the Food and Drug Administration have resulted in DTC sellers voluntarily stopping genetic tests whose predictions are dubious or which can diagnose predispositions for serious diseases. The DTC pioneers deCODE Genetics and Navigenics stopped trading in 2012 after being taken over by other companies.¹³⁴ Other companies such as Pathway Genomics¹³⁵ or Counsyl¹³⁶ (whose main focus is on preconception tests) now offer their services only through doctors, following an original DTC phase. Concentrating on scholarship and on healthcare institutions is clearly seen as considerably more advantageous from the economic point of view.

134 Navigenics was bought by Life Technologies, deCODE Genetics by Amgen. Cf. online: <http://www.genomicslawreport.com/index.php/2012/12/10/implications-of-amgendecode-deal-for-genetic-testing-consumers> [2013-02-14]; Allison 2012.

135 Online: <https://www.pathway.com> [2013-02-04].

136 Online: <https://www.counsyl.com> [2013-03-04].

3 THE LEGAL FRAMEWORK

The legal system has an important controlling function for the use of genetic diagnosis procedures.

3.1 Constitutional foundations and criteria

Within the national legal system, constitutional law functions as the central criterion. Particularly in its section on fundamental rights, the *Grundgesetz* (Basic Law) contains many provisions that apply (*inter alia*) to the practice of genetic diagnosis. By way of defining the structure of the problem, the following distinctions may be made:

(1) The primary emphasis is on the objects of protection of constitutional law of the persons on whose human samples genetic diagnosis is carried out. Article 1 (1) of the Basic Law guarantees that human dignity is inviolable, but the protective function of this provision takes effect only in the case of serious violation of elementary rights of personality; in addition, the following constitutional guarantees must be taken into account:

- » the fundamental right to life and physical integrity (Article 2 (2) sentence 1 of the Basic Law);
- » the general right of personality guaranteed by Article 2 (1) in conjunction with Article 1 (1) of the Basic Law with its varying areas of application. These include
 - the protection of the intimate and private sphere,
 - the right to informational self-determination as the competence of individuals fundamentally to decide for themselves whether to reveal personal life circumstances,
 - the right to knowledge and equally the right to lack of knowledge as the conditions of self-determined conduct of one's life;

- » the general principle of equality (Article 3 (1) of the Basic Law) and the prohibitions of discrimination of Article 3 (3) of the Basic Law including the prohibition of disadvantaging disabled persons;
- » in addition, for particular constellations, the right to reproduction (Article 6 (1) of the Basic Law) and the parental right (Article 6 (2) of the Basic Law).

(2) In addition, account should be taken on the part of those who offer and carry out genetic diagnosis of the freedom to choose an occupation (for example the freedom of doctors to choose their profession) under Article 12 (1) of the Basic Law and in the context of research the freedom of scholarship (Article 5 (2) sentence 1 of the Basic Law).

The above fundamental rights take effect on different functional levels:

- » They are rights of defence against interventions by state powers.
- » They create protective rights and in this respect the duty, above all of the legislature, to protect the objects of protection of fundamental rights against encroachments by private third parties.
- » Finally, in some circumstances they may also create rights to benefits and in this respect they are supplemented by the principle of the social state.

With regard to the practice of genetic diagnosis, multipolar legal relations are often characteristic. Several subjects of fundamental rights, some of whose interests conflict, are involved, and on the basis of the varying fundamental rights functions, the state has to react to them. This is obvious in the case of prenatal genetic diagnosis, where the obtaining of information serves to make a decision on a possible termination of pregnancy. But the same also applies to several sets of circumstances in postnatal genetic diagnosis – for example in the

relationship of children to their parents or in connection with the (lack of) knowledge of the heterozygous status. However, multipolar fundamental rights relationships in general result in serious questions on the weighing of rights. If the state attempts to achieve “protection through intervention”, it must do equal justice to the requirements of the prohibition of excessive measures¹³⁷ and of the prohibition of insufficient measures¹³⁸. Because this challenge is so complex, parliament, which has to pass legislation governing the essential questions of fundamental rights, has a particularly large margin of assessment.

3.2 Provisions of law below the constitutional level

The areas of life and subject areas for which genetic diagnosis is important are very varied. German law has not codified this material in a single set of provisions. Instead, there is a “main statute” which covers some important areas, the Genetic Diagnosis Act, but this is supplemented by further sets of provisions which are either more general or more specific. As a result, there is an overall legal framework which subjects individual important areas of life to thorough provisions specific to particular areas, but on the other hand largely excludes other areas which are also important, such as research (unless this takes place as part of medical treatment), and which sometimes reacts to still further problem constellations with selective special rules, and finally provides general provisions too (that is, provisions which are not bound to a specific area). The contents of the most important pieces legislation are set out below. This legislation is supplemented by further primary and secondary legislation consisting of specific and general

137 This requires it not to disproportionately restrict the defensive rights position of the subjects of fundamental rights affected.

138 This calls on it to provide sufficiently effective protection of the objects affected by private encroachments.

provisions on federal and Land level; where necessary, reference will be made to these in context in the Opinion. At this point, for example, mention should be made of medical professional ethics and the legally relevant professional standards of the professions involved.¹³⁹ General non-codified medical law, as put into specific terms and developed by court decisions, also continues to apply, unless otherwise provided by statute.

3.2.1 The Genetic Diagnosis Act

Since 1 February 2010 the Genetic Diagnosis Act has been in force.¹⁴⁰

Area of application

The area of application of the Act is laid down in Section 2, in terms which are not easy to summarize, as follows:

- » On the one hand, the Genetic Diagnosis Act applies “to genetic studies and to genetic analysis carried out as part of genetic studies on persons born and also on embryos and fetuses during pregnancy and to the treatment of genetic samples and genetic data obtained in this process in genetic studies for medical purposes and to clarify descent”.
- » On the other hand, the Act – independently of a medical purpose – covers genetic studies “in the area of insurance and in working life”.
- » In addition, the prohibitions of discrimination of Sections 4 and 21 of the Genetic Diagnosis Act link directly to the concept of genetic characteristics and thus under the

¹³⁹ On this, cf. Taupitz 2009, 63 ff.

¹⁴⁰ *Gesetz über genetische Untersuchungen bei Menschen* (Human Genetic Examination Act) of 31 July 2009 (BGBl. I, 2529, 3672); for more details on the entry into force of the individual provisions of the statute with different arrangements as to time for individual provisions see Section 27 of the Genetic Diagnosis Act.

definition in Section 3 no. 4 they also include genetic qualities which are not obtained through genetic studies within the meaning of Section 3 no. 1 of the Genetic Diagnosis Act.¹⁴¹

But Section 2 of the Genetic Diagnosis Act does not define its area of application only in positive terms. Subsection 2 of the provision, instead, excludes negatively conditioned areas of life and subject areas from the application of the Act. It provides that the Act does not apply to genetic studies and analyses and the treatment of genetic samples and data for research purposes (no. 1) on the basis of provisions of criminal procedure and police law (no. 2a) and on the basis of provisions of infection protection law (no. 2b). It was originally intended that the area of research should also be governed, but in the course of the legislative procedure it was dropped.¹⁴² The Genetic Diagnosis Act therefore applies in research projects only if genetic diagnosis serves not only the use of the data for research, but also medical treatment or compassionate use for an individual person. The provisions of the Genetic Diagnosis Act apply to persons born and to embryos and fetuses during pregnancy. They do not apply to genetic studies carried out on a dead person. A further restriction of the area of application arises from the fact that “genetic characteristics” within the meaning of the Genetic Diagnosis Act are “genetic information of human origin inherited or acquired during fertilization or before birth” (Section 3 no. 4). The genetic testing for genetic characteristics

¹⁴¹ Stockter, in: Prütting 2012, Section 2 para. 3; Kern 2012, Section 4 para. 26. This is supported by the fact that Section 1 emphasizes that the purpose of the Act is to govern discrimination on grounds of genetic characteristics but does not link this to genetic studies. And it would be absurd if the prohibition of discrimination were to differentiate according to genetic characteristics which are obtained in a genetic test under Section 3 no. 1 of the Genetic Diagnosis Act and those obtained in a different way.

¹⁴² In the legislature’s statement of intention, this is explained as follows: genetic research is general research into the causative factors of human characteristics which is not directed toward concrete measures for individual persons.

acquired after birth, such as the genetic testing of tumour tissue, for example in order to determine responsiveness to treatment or to make a prognosis on the future course of the disease, is not subject to the requirements of the Genetic Diagnosis Act. However, in these cases the inherited genome of the patient's tissue that is not changed by the tumour is also examined, and consequently the provisions of the Genetic Diagnosis Act apply to giving the patient an explanation and obtaining consent to a diagnostic genetic test. Genetic studies and analyses which do not serve medical purposes or the clarification of descent and are not undertaken in the insurance field or working life are not covered by the Act. Consequently, they are also not prohibited. The same applies to genetic tests which are intended to help improve lifestyle (lifestyle tests, cf. section 2.2.5).

Definitions

Part 1 (General Provisions) defines both the area of application in Section 3 and the important definitions of the statutory terms. Particular emphasis should be given here to the definitions of "genetic test" and "genetic analysis", which put the area of application of the Act into more concrete terms and distinguish them from other measures. "Genetic analysis" is an analysis intended to determine genetic characteristics of a) the number and structure of the chromosomes (cytogenetic analysis), b) of the molecular structure of DNA or RNA or c) of the products of nucleic acids (Section 3 nos. 2a to c).¹⁴³ "Genetic

¹⁴³ It is often claimed that since the Genetic Diagnosis Act entered into force, all medical examinations which analyse not only genetic makeup itself but also genetic products, including for example examinations of blood for proteins, which are common in practice, are now genetic analyses satisfying the strict requirements of the Genetic Diagnosis Act. This is not correct. The Bundestag Committee on Health explained this in the legislative procedure as follows: "By the introduction of the words 'directed towards determining genetic characteristics', it is made clear that all analyses named in no. 2 are only covered by the Act if they serve to determine genetic characteristics. The determination of cholesterol values in a person at risk in whose family familial hypercholesterolemia occurs is an analysis of genetic products which is intended to determine genetic characteristics which

test” is genetic analysis with the purpose of determining genetic characteristics or clarifying prenatal risks (comprising phenotype analysis and ultrasound) including the assessment of the results in each case (Section 3 nos. 1a and b)

Requirement of involvement of a doctor

The Genetic Diagnosis Act makes it a mandatory condition for a genetic test for medical purposes¹⁴⁴ (that is, in diagnostic and predictive genetic tests to clarify causes of disease, predispositions to disease, the effects of medicinal products and predispositions to a genetic disease) that a doctor orders the genetic test and the genetic analysis, that they are carried out in accordance with the current state of science and technology by personnel qualified to carry them out and that the organizational and technical measures necessary for the preservation and destruction of the genetic data collected are observed (Section 5 (2) in conjunction with (1), Section 12). The explanation for the patient and the counselling must be given by a doctor. The mandatory requirement of the involvement of a doctor is intended to ensure that this diagnosis, which has particular effects on fundamental rights (right to informational self-determination, right to know and not to know one’s own genetic

are causative of the illness. It is therefore a genetic analysis. In contrast, the determination of cholesterol values in a health check or for general clarification of a risk of cardiovascular disease is a genetic product analysis which is not directed towards the determination of genetic characteristics, and is therefore not a genetic product analysis” (BT-Drs. 16/12713).

¹⁴⁴ In genetic studies for medical purposes, the Act distinguishes between diagnostic and predictive examinations (Section 3 no. 6). A diagnostic genetic test is a genetic test with the aim a) of clarifying an existing illness or health disorder, b) of clarifying whether genetic characteristics are present which together with the effect of particular external factors or foreign substances may actuate an illness or health disorder, c) of clarifying whether genetic characteristics are present which are capable of influencing the effect of a medicinal product or d) of clarifying whether genetic characteristics are present which may in whole or in part prevent the occurrence of a possible illness or health disorder (Section 3 no. 7). A predictive genetic test is a genetic test with the aim of clarifying a) an illness or health disorder which will only occur in future or b) a genetic predisposition for illnesses or health disorders in issue (Section 3 no. 8).

constitution) takes place only under expert medical competence for the protection of those affected.

Information and consent

Before obtaining consent to a genetic test for medical purposes, the responsible doctor must explain to the person affected the nature, meaning and scope of the genetic test. Section 9 (2) lays down the contents of the explanation in detail. The explanation must above all cover the purpose, nature, scope and validity of the results to be obtained by the planned genetic test and their significance for a disease, and health risks which are associated with the knowledge of the results.¹⁴⁵ The informed consent must include both the decision on the scope of the genetic test and also the decision as to whether and how far the results of the test are to be notified or destroyed. The doctor must be convinced that the person affected has understood the explanations and is clear about the nature, meaning and scope of his decision (Sections 8, 9 of the Genetic Diagnosis Act). The consent, which is (only) effective in this way (informed consent) is a condition for all diagnostic and preventive genetic studies for medical purposes on human beings.

As a result of the further development of genetic diagnosis, it will be possible to analyse an ever greater amount of genetic information of a person simultaneously by the use of DNA microarrays on chips and to use search procedures to search the individual genome without a concrete medical question, culminating in sequencing the whole exome and genome (cf. section 2.3). On the legal level it must be resolved how, in view of this development, the provisions of the Genetic Diagnosis Act are to be applied or how far they are to be amended. In particular, it should be determined how to deal with the superfluous genetic information which is likely to be collected in

¹⁴⁵ On this, see also the guideline for the requirements of the content of patient information in genetic studies for medical purposes (*Gendiagnostik-Kommission* 2012a).

ever greater quantities, that is, information which goes beyond the genetic test covered by the concrete medical question. Under the Genetic Diagnosis Act, in the case of genetic studies for medical purposes it is necessary to inform the patient of all information on genetic characteristics that is obtainable with the means of examination chosen, and the person affected must decide when consenting which parts of the obtainable information are to be included in the test and notified to him and which are to be destroyed.¹⁴⁶ In view of the scope of the genetic information to be obtained with the new methods, it will often no longer be possible to give the subject an explanation of every possible piece of information that may be uncovered, especially if the method of complete exome or genome sequencing is chosen. The question arises as to how the explanation is to be designed in these cases, what matters are to be specifically laid down in the consent or whether and if so what restrictions on the obtaining of information should be made in advance on the technical level to protect the person affected. It also needs to be laid down how explanation and consent should be structured in the case of genetic studies which are not subject to the requirements of the Genetic Diagnosis Act because they are not made for medical purposes, but which by reason of the

¹⁴⁶ The legislature's statement of intention states as follows on Section 8, Consent: In compliance with the right of informational self-determination, the person affected must himself decide both on the undertaking of a genetic test for medical purposes and on its extent. The decision of the person affected also extends to what information on genetic characteristics is obtainable with the intended genetic test methods and whether and if so what possible unexpected test results named in the information are to be included in the genetic test. On the information before consent, the statement of intention states on Section 9: The information on the results obtainable with the intended test methods is restricted to the purpose of the test, that is, the genetic characteristics to be clarified by the test. Insofar as the intended means of testing, for example a multichip, provides further genetic characteristics in the genetic analysis in addition to those to be clarified in the genetic test, the person affected must both be fully informed about this and also be informed that the superfluous genetic information is destroyed under Section 8 (1) sentence 2. In this way the person affected is at the same time given the possibility of deciding whether, and if so to what extent, the information on genetic characteristics which can be obtained with such genetic testing means is to be included in the test.

method chosen (for example genome sequencing) may also provide information on genetic predispositions to illnesses. A further question is what notification requirements arise for the medical person if there are additional findings which were not the subject of the explanation and consent and which may possibly have serious effects on the health of the person in question or of the person's offspring.

Genetic counselling

Section 10 lays down the requirements for genetic counselling, which since 1 February 2012 may only be made by doctors qualified for genetic counselling (Section 7 (3), Section 27 (4)).¹⁴⁷ Whereas when the test results of a **diagnostic** genetic test are available genetic counselling is merely to be offered, and a mandatory obligation without exceptions to make such an offer only applies where an untreatable disease or health disorder is present, before a **predictive** genetic test and when the test results are available, there must always be such genetic counselling, unless the person affected, after prior information in writing on the contents of counselling “in an individual case” has waived the counselling in writing. The genetic counselling must be made in a generally comprehensible and open-ended form. It should take the form of a personal conversation.¹⁴⁸ It must in particular include a thorough discussion of the possible medical, psychological and social questions in connection with making or not making the genetic test and its actual or potential test results and the possibilities of support in the case of physical and psychological burdens on the person affected as a result of the test and its results. The aim is to attain a responsible way of dealing with the decision on a genetic test and

¹⁴⁷ On this, see also the guideline for the requirements of the qualification for and contents of genetic counselling (*Gendiagnostik-Kommission* 2011a). In the opinion of the German Ethics Council, there are no radical competence objections against the power of the Federal Government to legislate (Article 74 (1) no. 26 of the Basic Law).

¹⁴⁸ Cf. *Gendiagnostik-Kommission* 2011a.

with the results. If it may be assumed that genetic relatives of the person affected are carriers of the genetic characteristics to be examined with significance for an avoidable or treatable illness or health disorder, the genetic counselling also comprises the recommendation to recommend that these relatives undergo genetic counselling (Section 10 (3) sentence 4). This also applies in the case of a test on an embryo or fetus.

The results of a genetic test may only be communicated by the doctor who was responsible for the genetic test or gave the counselling, and only direct to the person affected (Section 11 (1) of the Genetic Diagnosis Act).¹⁴⁹ Section 11 (3) permits this information to be given to third parties only with the express consent of the person affected in writing. This provision is sometimes felt to be too restrictive and there are calls for the doctor to be given an independent right to inform relations of the person affected, who may also be affected by the genetic illness diagnosed, of their risk and to recommend them to have genetic counselling.

Storage and destruction of genetic data

Under Section 12, the findings of genetic studies and analyses which are conducted for medical purposes are to be kept in the study documentation. They must be destroyed without delay when the storage period of ten years has expired or where the patient affected has decided not to have knowledge of the test results. Insofar as there is reason to believe that the destruction would negatively impact concerns of the patient affected which merit protection or insofar as the person affected has consented in writing to long storage, the findings are to be locked. Under Section 12 (2), these provisions also apply to the institutions (laboratories which carry out the genetic analysis and usually store it) instructed by the doctor to carry out the genetic

¹⁴⁹ 11.4 of the guideline for the requirements of the content of patient information in genetic studies for medical purposes (*Gendiagnostik-Kommission 2012a*) governs the details of this, such as powers of representation in exceptional cases on notifications of findings.

analysis. However, it is as yet not clear whether or not superfluous genetic information and additional findings¹⁵⁰ on genetic characteristics which are not connected to the concrete medical treatment but which the patient under his consent to the genetic test has taken notice of and which are therefore not to be destroyed without delay are to be included in the test documentation. Such additional information may accrue in large quantities in the course of technical development where the corresponding study method is chosen. Clarification is needed here. The more simply, rapidly and economically genetic analyses can be conducted in future, the more it will be necessary to answer the question as to whether under the requirements of data privacy law of data reduction and data economy (Section 3a of the *Bundesdatenschutzgesetz* [Federal Data Protection Act]) the data which are not required for a concrete medical question should be omitted from the test documentation, since if medical treatment becomes necessary later a new genetic test may be made.

Genetic tests of patients incapable of consenting

Section 14 governs the genetic test for medical purposes of persons who are incapable of consenting.¹⁵¹ It is permitted only for the direct benefit of the person affected, or exceptionally in order to assess risks in family planning. Genetic tests, of such persons may only be made where this is necessary to treat, avoid or prevent a genetically conditioned illness or health disorder or if in the case of a genetically related person with regard to a planned pregnancy there is no other way of determining whether a particular genetically conditioned illness or health disorder may occur in the future offspring of this related person. Consent is given by the person's legal representative, who must be given information

150 Superfluous genetic information means information generated by a genetic analysis which is not needed for the concrete question of the study or which accrues unexpectedly or unwantedly. Additional findings are findings which are generated from superfluous genetic information and which go beyond the medical purpose of a concrete genetic study.

151 On this, see also the guideline for genetic studies in persons incapable of consent (*Gendiagnostik-Kommission* 2011b).

and if necessary counselled in the same way as an affected person capable of consent. Under Section 14 (3) only the studies of the genetic sample necessary for the relevant test purpose may be made. No other findings may be made. There are no such specifications in the provisions on other genetic studies.

Prenatal genetic studies

Section 15 deals with prenatal genetic studies. It is regarded as a special feature here that the definition of genetic studies is widened to include also non-invasive screening tests to clarify risks, for example measuring nuchal transparency by ultrasound or first-trimester screening and the triple test. Under Section 15 (1), a genetic study before birth may be made only for medical purposes and only to the extent that the test is directed to particular genetic characteristics of the embryo or fetus which under the generally recognized standard of science and technology adversely affect its health during pregnancy or after birth, or if a treatment of the embryo or fetus with a medicinal product is intended whose effect is influenced by particular genetic characteristics, and the pregnant woman has been informed under Section 9 and has consented under Section 8. However, a genetic test for a hereditary disease also gives the information as to whether a mere genetic predisposition is present in the fetus which does not adversely affect its health. The question arises here as to how far this information on genetic predisposition, not covered by the purpose of the study, may be communicated by the doctor. Before a prenatal genetic test and after the results are available, the pregnant woman must be given genetic counselling; in addition, she should be informed of the right to counselling under Section 2 of the *Schwangerschaftskonfliktgesetz* (Conflicted Pregnancy Act) (Section 15 (3)).¹⁵² Under this, the test known as the PraenaTest (cf. section 2.3.6) may also be

152 On this, see also VI.3 of the guideline for the requirements of the qualification for and contents of genetic counselling (*Gendiagnostik-Kommission* 2011a, 1250).

used in prenatal diagnosis – subject to comprehensive information, counselling and the consent of the pregnant woman. As currently defined, it serves medical purposes and the clarification of an existing or future illness or health disorder of the embryo or fetus.¹⁵³ The test has now been put on the market as a medicinal product.¹⁵⁴ If on the occasion of a prenatal test the sex of an embryo or fetus is established, this may be communicated to the pregnant woman with her consent after the end of the twelfth week of pregnancy post conception. Under Section 15 (2), a prenatal genetic test which aims to establish genetic characteristics which according to the generally recognized state of medical science and technology do not manifest until after the person reaches the age of eighteen may not be made. This is intended to serve the protection of the child's right not to know. Special rules apply for genetic studies on a pregnant woman who is incapable of consent.

Mass screenings

Section 16 contains special provisions for genetic mass screenings.¹⁵⁵ They may only be undertaken if the test is to clarify

153 A different conclusion is reached by Gärditz in his expert opinion on the permissibility of the PraenaTest of 28 June 2012 for the Federal Government Commissioner for Matters relating to Disabled Persons. According to Gärditz, there is no medical indication for informing the patient of the existence of a disability, which like trisomy 21 cannot (and should not) be treated by reason of its genetic cause and whose consequences can be reduced by targeted measures only after birth. He argues as follows: "methods of diagnosis which as a general rule serve to terminate pregnancy where a disability is established, should with regard to Article 3 (3) sentence 2 of the Basic Law [which governs the prohibition of discrimination of disabled persons] be classified as not medically indicated, in conformity with the Basic Law" (Gärditz 2012, 15 f.). In this connection, it should be noted: even if one assumes that the area of application of Article 3 (3) sentence 2 of the Basic Law extends to the prenatal area (which is disputed), it does not follow from this that there is a – constitutionally required – verdict of the impermissibility of a single prenatal diagnosis intervention. There is an opposing standpoint to Gärditz in the legal opinion by Hufen 2013 drafted on the instructions of LifeCodexx AG.

154 The Freiburg regional government council, which is responsible for reviewing the PraenaTest, did not object to the test with regard to the requirements of the law of medicinal products, and it may therefore be marketed.

155 On this, see also the guideline for the requirements for conducting genetic mass screenings (*Gendiagnostik-Kommission* 2012b).

whether the persons affected have genetic characteristics which are important for an illness or health disorder which according to the generally recognized state of science and technology is avoidable or treatable or can be prevented. A mass screening may only be undertaken after the *Gendiagnostik-Kommission* (Genetic Diagnosis Commission) has assessed the test in writing, reviewing whether the statutory requirements are satisfied and the test is ethically defensible in this sense.

An example of a mass screening is the newborn screening with which a number of illnesses or illness risks of a newborn which can be influenced at an early date can be detected. Until the Genetic Diagnosis Act came into force, the screening was generally carried out by midwives, who were also responsible for explanation and obtaining the consent of those entitled to custody. But since the Genetic Diagnosis Act came into force, the rule is that where the test is made with the use of genetic diagnosis, here too there is a mandatory requirement of a doctor. Since it is feared that this could result in fewer newborns or their parents with competence to decide being reached for screening, in practice the statute is currently reinterpreted in a provision in the Paediatrics Directive¹⁵⁶ which in particular cases still allows the midwives to carry out the screening.¹⁵⁷

156 Directive concerning the early detection of diseases in children up to completion of the 6th year of age (*Gemeinsamer Bundesausschuss* 2010).

157 See announcement of a resolution on a change to the Paediatrics Directive of 16 December 2010 (BAnz 2011 (40), 1013). Here, the Federal Joint Committee expresses the following opinion on the permissibility of newborn screening by midwives with regard to the mandatory involvement of a doctor of the Genetic Diagnosis Act in Section 7: "If the birth was conducted under the responsibility of a midwife, then by mutual agreement she should name a responsible doctor. If, exceptionally, a doctor cannot be named, the midwife shall carry out the screening on her own responsibility if it is guaranteed that she can consult a doctor." This is a "solution praeter legem" (outside the law), according to Henning Rosenau (2011, 80), the vice-president of the Genetic Diagnosis Commission. But legally this is problematic, since a statutory amendment of the unfortunate provision of the Genetic Diagnosis Act is necessary for such an arrangement.

Guidelines of the Genetic Diagnosis Commission

Finally, the sixth Chapter (Section 23), which deals with the competence of the Genetic Diagnosis Commission to issue guidelines, is of particular importance. It was the intention of the legislature that the provisions of the Genetic Diagnosis Act should be put into specific terms by guidelines of the Committee, which was founded for this special purpose (Section 23). Under Section 23 (1) sentence 3, the rules of procedure of the Genetic Diagnosis Commission require the consent of the Federal Ministry of Health. According to the statement of reasons of the Act¹⁵⁸, the guidelines are in each case to “lay down” the state of science and technology for the areas named in Section 23 (2) for doctors and non-medical experts. In this, the statement of reasons of the Act defines the guidelines as more than merely declaratory in nature. The Genetic Diagnosis Commission assumes that its guidelines are binding; at all events it always names a date when the guidelines it issues enter into force.

The competence of the federal government to legislate on the authority to issue guidelines follows from Article 74 (1) no. 26, and this also applies where the content relates to the practice of the medical profession.¹⁵⁹ Other federal special statutes¹⁶⁰ also contain far-reaching provisions on the qualification and work of doctors and content of patient information conversations.¹⁶¹ In addition, the *Bundesverfassungsgericht* (Federal Constitutional Court) has expressly emphasized that the legal basis of Article 74 (1) no. 26 of the Basic Law is to be interpreted broadly in order to avoid the fragmentation of law.¹⁶²

158 BT-Drs. 16/10532; BT-Drs. 16/12713, explanatory statement on Section 23 (2), nos. 1, 2, 3, 4 and 5.

159 No. 26 gives the federal government concurrent legislative competence *inter alia* for the medically supported creation of human life and the testing and artificial alteration of genetic information.

160 Such as the *Medizinproduktegesetz* (Medical Devices Act), the *Arzneimittelgesetz* (Medicinal Products Act) and the *Transplantationsgesetz* (Transplantation Act).

161 Cf. Kern 2012, Section 23 para. 11.

162 Federal Constitutional Court's judgment of 24 November 2010, ref. 1 BvF 2/05 (BVerfGE 128, 1, 33 f.).

Section 23 (2) of the Genetic Diagnosis Act contains a list of topics on which guidelines should be issued, but makes it clear in the word “insbesondere” (including but not limited to) that this list is not exhaustive. The Genetic Diagnosis Commission has already issued a large number of guidelines, some of them very detailed, for example on the requirements for genetic counselling, on quality assurance for genetic analyses for medical purposes, on the assessment of genetic characteristics with regard to their significance for illnesses and health disorders, on genetic testing on persons incapable of consent and on reports on ancestry.

It is sometimes disputed whether the Genetic Diagnosis Commission has sufficient constitutional legitimation to issue guidelines for all the matters set out in Section 23 (2) of the Genetic Diagnosis Act.¹⁶³ This relates above all, because it is so essential to human rights, to a guideline under (2) no. 1d on the assessment of genetic characteristics with regard to their significance under Section 15 (1) sentence 1 for an adverse effect on the health of the embryo or the fetus during pregnancy or after birth.¹⁶⁴ It is claimed that in this connection, in parallel to the provisions of Section 4 (5) of the *Gentechnikgesetz* (Genetic Engineering Act) and Section 8 (4) of the *Stammzellgesetz* (Stem Cell Act), there is a need for a greater statutory structuring of procedural law.

In addition to this, the Maternity Directive¹⁶⁵ of the Federal Joint Committee supplement the provisions on genetic diagnosis of the unborn child with regard to the benefits of statutory health insurance (cf. section 3.2.5).

¹⁶³ Cf. Taupitz 2013; Winkler 2011.

¹⁶⁴ The guideline on Section 15 (1) exists only in draft at the present time (*Genodiagnostik-Kommission* 2012c). In this, the Genetic Diagnosis Commission restricts itself to citing the statutory wording of Section 15 of the Genetic Diagnosis Act in a structured form, including the other related provisions of the Genetic Diagnosis Act, and states as grounds for this that all the essential points are already adequately defined in the Genetic Diagnosis Act and there is no point in putting them into more concrete form.

¹⁶⁵ Directive concerning the medical care for insured persons during pregnancy and after birth (*Gemeinsamer Bundesausschuss* 2012).

Direct-to-consumer tests

What are known as direct-to-consumer genetic tests (cf. section 2.5.7), which also detect significant quantities of illnesses and dispositions to illness, are not capable of satisfying the above standards of the Genetic Diagnosis Act for genetic tests for medical purposes. The genetic diagnosis is ordered by the consumer direct from the seller by sending a (saliva) sample; the seller informs the customer of the results directly, and the customer can usually download the results digitally using a personal code. There is no involvement of a doctor in explanation, taking the genetic sample, counselling and informing of the results. At best, explanation is made in the form of customer information in writing in general terms or by reference to particular internet portals. There is no examination as to whether the person affected is capable of consent; it is equally impossible to examine whether the genetic sample comes from the person who orders the genetic diagnosis. Further legal questions arise from the fact that DTC tests are available across national borders and it is not necessary for internet sellers abroad to comply with domestic provisions.

3.2.2 The law of medical devices and genetic diagnosis

Genetic testing methods are *in vitro* diagnostic devices within the meaning of the European Directive on In Vitro Diagnostic Medical Devices (IVD Directive)¹⁶⁶ and medical devices within the meaning of the Medical Devices Act¹⁶⁷. The Directive with

¹⁶⁶ Directive 98/79/EC of the European Parliament and of the Council (OJ L 331/1 of 7 December 1998). It serves to harmonize the legal provisions of the Member States on product requirements for *in vitro* diagnostic devices.

¹⁶⁷ Section 3 no. 4 of the Medical Devices Act: An *in vitro* diagnostic medical device is a medical device which is intended to be used, alone or in combination with others, as a reagent, reagent device, calibrator material, control material, kit, instrument, apparatus, equipment or system, according to the intended purpose specified by the manufacturer, for the *in vitro* examination of specimens derived from the human body, including blood

its annexes lays down the product requirements of *in vitro* diagnostic devices; these must be complied with in order to put an *in vitro* diagnostic device on the market. The Medical Devices Act implements the Directive in German law. It governs the manufacture and the marketing¹⁶⁸ of medical devices, the avoidance of risks in their use and the requirements for the performance, safety and quality of medical devices, that is, protection against risks and dangers which result direct from the device itself or its use. The Medical Devices Act does not govern the medical requirements for the use and interpretation of the readings of the *in vitro* diagnostic devices; it therefore in particular does not govern the conditions under which a genetic test may be carried out. With regard to the legal provisions on the use of *in vitro* medical devices for genetic testing, it is therefore necessary to distinguish between the technical performance of the *in vitro* device – this is governed by the Medical Devices Act – and its use on human beings, that is, the requirements for arranging and conducting a genetic test on a person including the evaluation of the genetic analysis and assessment of the results with regard to the aim of the genetic test – this is governed by the Genetic Diagnosis Act.

In vitro diagnostic devices do not require approval to be placed on the market. They may be placed on the market if they carry CE marking. They may carry this marking if they satisfy the fundamental requirements under Section 7 of the Medical

and tissue donations, purely or mainly with a view to providing information a) on physiological or pathological conditions, b) congenital abnormalities, or c) to investigate the safety of or tolerance by potential recipients, or d) to monitor therapeutic measures. [Translator's note: Adopted from the non-official translation provided by the Federal Ministry of Health, online: http://www.bmg.bund.de/fileadmin/dateien/Downloads/Gesetze_und_Verordnungen/GuV/M/MPG_englisch.pdf (2013-10-02).]

168 Section 3 no. 11 of the Medical Devices Act: Placing on the market is any act of supplying medical devices to others, [...]. The following is not considered to be placing on the market for the purposes of this Act: a) the making available of medical devices for the purpose of clinical investigation, b) the making available of *in vitro* diagnostic medical devices for performance evaluation studies, [...]. [Translator's note: Adopted from the non-official translation provided by the Federal Ministry of Health.]

Devices Act in conjunction with Annex I of the IVD Directive and the *Medizinprodukte-Verordnung* (Medical Devices Order)¹⁶⁹ and have undergone a conformity assessment procedure, which must be conducted by the manufacturer itself. In the conformity assessment, the compliance of the *in vitro* diagnostic device with the legal requirements of the Directive are reviewed and assessed.¹⁷⁰ In particular, *in vitro* diagnostic devices must be suitable¹⁷¹ in accordance with the generally recognized state of technology for the intended use determined by the manufacturer.¹⁷² Under Section 19 (2) of the Medical Devices Act the review of the suitability of *in vitro* diagnostic devices for the intended use must be evidenced by a performance appraisal, for example data from the scientific literature.¹⁷³ Where the manufacturer makes statements on “clinical

169 *Verordnung über Medizinprodukte* (Order on Medical Devices) of 20 December 2001 (BGBl. I, 3854), most recently amended on 10 May 2010 (BGBl. I, 542).

170 Sections 7, 37 of the Medical Devices Act in conjunction with Annex I of the IVD Directive and Section 1 of the Medical Devices Order.

171 Section 3 no. 10 of the Medical Devices Act: The intended purpose is the use for which the medical device is intended according to the data provided by the [manufacturer] in the labelling, the instructions for use or promotional materials. [Translator’s note: Adopted from the non-official translation provided by the Federal Ministry of Health.]

172 Section 7 of the Medical Devices Act in conjunction with Annex I A.3. of the IVD Directive: They must – where applicable – comply with the performance parameters in particular with regard to the following matters as stated by the manufacturer: analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity, correctness, repeatability, reproducibility, including controlling the known interferences and limits of detection. On the recognized state of science and technology for genetic analyses, see III.1 of the guideline for the requirements of the quality assurance of genetic analyses for medical purposes (*Gendiagnostik-Kommission* 2012d).

173 The performance evaluation study is the study of an *in vitro* diagnostic device to determine the suitability and reliability or performance of the *in vitro* diagnostic device with regard to the performance figures given by the manufacturer in the expected conditions of use. If there is an invasive sampling of test persons in the performance evaluation study, the provisions on clinical tests of medical devices must be complied with (Section 24 (1) in conjunction with Sections 20 ff. of the Medical Devices Act and *Verordnung über klinische Prüfungen von Medizinprodukten* [Order on Clinical Trials with Medical Devices] of 10 May 2010 [BGBl. I, 555]). However, the provisions do not apply to saliva sampling from the oral cavity (Section 1 (2) of the Order on Clinical Trials with Medical Devices).

validity”, these must be correct.¹⁷⁴ However, clinical validity is not the subject of the provisions of the IVD Directive and the Medical Devices Act. The clinical validity must be assessed by the doctor using the test as part of the specific diagnostic question, and the doctor must take responsibility for it. This is important above all for the interpretation of findings with regard to multifactorial illnesses, possible false positive and false negative results and in general for the question as to how far the result of a genetic analysis is important for the prognosis of a patient’s physical and psychological constitution.

The Member States of the European Union may not prevent the placing on the market of *in vitro* diagnostic devices which have undergone a conformity assessment procedure and carry CE marking. However, the placing on the market may be prohibited or restricted by a Member State if this is necessary to avoid compromising the health or safety of patients or users (Article 8 of the IVD Directive). The Member States may take transitional measures for this purpose (Article 13 of the IVD Directive). In Germany, placing an *in vitro* medical device on the market is prohibited if there is a justified suspicion that if used properly and for an appropriate purpose it will directly or indirectly endanger the safety and health of patients, users or other persons in excess of a defensible degree (Section 4 (1) no. 1 of the Medical Devices Act). The competent Land authorities are authorized to take measures to remove violations (Section 26 (2) of the Medical Devices Act).¹⁷⁵ In addition, under Article 1 (6) of the IVD Directive

174 The clinical validity of a genetic test measures how suitable the test is to diagnose the presence of an illness or health disorder in a target population (“diagnostic test”) or to predict that it will occur later (“predictive test”); see III.1 of the guideline for the evaluation of genetic characteristics with regard to their importance for illnesses or health disorders and for the possibility of avoiding them, preventing them or treating them (*Gendiagnostik-Kommission* 2012e).

175 According to Gärditz 2012, the PraenaTest endangers other persons – that is, disabled unborn persons – within the meaning of Section 4 (1) no. 1 of the Medical Devices Act, and under Section 26 (2) of the Medical Devices Act it should be prohibited from being placed on the market. For a different opinion, see Hufen 2013.

national legal provisions under which medical devices may only be used if medically prescribed are permissible. Section 37 of the Medical Devices Act authorizes the Federal Ministry of Health to issue statutory orders subjecting medical devices subject to prescription where they could directly or indirectly compromise human health if used for their intended purpose or are frequently used contrary to their intended purpose, if this compromises human health directly or indirectly (Section 37 (2) no. 2, (3) of the Medical Devices Act). Channels of distribution may also be laid down where it is necessary to maintain the necessary quality of the medical device or to satisfy the requirements for the patient's safety which are necessary on supply or use.

The provisions of the Medical Devices Act are supplemented by the *Medizinprodukte-Betreiberverordnung* (Medical Devices Operator Ordinance) and the provisions on quality assurance in Section 5 and Section 23 (2) no. 4 of the Genetic Diagnosis Act in conjunction with the guidelines of the Genetic Diagnosis Commission, medical professional ethics and international DIN standards.¹⁷⁶

On 26 September 2012, the EU Commission adopted a proposal for a Regulation on *in vitro* diagnostic devices.¹⁷⁷ The Regulation is to replace the Directive in order to create a uniform legal framework for *in vitro* diagnostic devices in the European Union. The Regulation defines more clearly which products are *in vitro* diagnostic devices within the meaning of the Regulation. There is explicit reference to genetic tests providing information about the predisposition to a medical condition or a disease or on treatment response or reactions (companion diagnostics). Medical software is explicitly mentioned in the definitions of *in vitro* diagnostic devices. The legal obligations on manufacturers are graduated in four risk

¹⁷⁶ See Table 1 in the guideline for the requirements of the quality assurance of genetic analyses for medical purposes (*Gendiagnostik-Kommission* 2012d).

¹⁷⁷ Proposal for a Regulation of the European Parliament and of the Council on *in vitro* diagnostic medical devices (COM/2012/0541 final).

classes (A to D). All manufacturers must have a quality management system in place to ensure that their products meet the regulatory requirements. A new element is provisions on clinical evidence, on identification, registration and traceability of devices. A central database is to be created collecting information on the *in vitro* diagnostic medical devices on the market, economic operators involved, certificates, vigilance cases and market surveillance. The aim is, *inter alia*, to enable the public to be adequately informed about devices on the market.

Genetic tests on humans and tests on fetuses to determine genetically conditioned disorders are in Class C, with the result that the conformity assessment which reviews conformity with the requirements of the Regulation must in future be carried out by an independent notified body.

The placing on the market of genetic tests on humans is in future to be governed by the following procedure:

1. Key documents for the manufacturer to demonstrate compliance with the legal requirements are the technical documentation and the EU declaration of conformity. The conformity assessment is to be made with the collaboration of a body appointed by the national authorities in each case (Article 40).
2. The manufacturer must prepare a summary of the safety and performance of the product. The demonstration of conformity with the general safety and performance requirements must be based on clinical evidence (Article 47). The clinical evidence comprises all the information to support the scientific validity, the analytical performance (Annex 1 II: *inter alia* precision, repeatability, analytical sensitivity and specificity and, where the clinical performance of the product is stated by the manufacturer in the intended purpose, the diagnostic sensitivity and specificity, positive and negative predictive value, probability, expected values in affected and unaffected population groups). These data must be regularly updated throughout the whole life cycle

of the test. The Regulation also contains instructions on the performance of clinical performance studies in order to obtain the clinical evidence and reliable data to ensure the intended purpose stated by the manufacturer.

3. The complete documentation is submitted to the notified body involved in the conformity assessment and is validated by that body (Article 24)
4. In the case of companion diagnostics, which test whether a medicinal product is suitable for a patient, in the course of the conformity assessment the national authority which is competent for marketing authorization of medicinal products or the European Medicines Agency must be consulted.
5. After verification and assessment, the notified body issues a certificate on the design if the requirements of the Regulation are satisfied. This certificate contains the results of the assessment and the conditions for its validity, and also the information necessary to identify the assessed design, and if appropriate a description of the intended use of the product.

To support the implementation of this Regulation, the European Commission may name “EU reference laboratories”, which *inter alia* give scientific advice on the state of technology and collaborate in the development of suitable test and analysis procedures to be used in conformity assessments and market surveillance. For this purpose, instructions are also given for the product information which the manufacturer must supply to the users.

The Regulation is to apply directly in the Member States five years after it is passed.

3.2.3 Genetic diagnosis in the Embryo Protection Act

In the year 2011, on the impetus of a decision of the *Bundesgerichtshof* (Federal Court of Justice)¹⁷⁸, legislation was passed governing an area of genetic diagnosis which is particularly ethically disputed, preimplantation genetic diagnosis (PGD), by way of supplementing the Embryo Protection Act.¹⁷⁹ The German Ethics Council had previously presented a comprehensive Opinion on this topic.¹⁸⁰ In certain circumstances, Section 3a of the Embryo Protection Act permits the genetic testing of cells of an embryo *in vitro* in the course of bringing about a pregnancy. If as the result of a genetic disposition of the woman and/or the man there is a high risk that their offspring will have a serious hereditary disease, the embryo *in vitro* may be genetically tested for this disease. In addition, preimplantation genetic diagnosis is permissible to detect serious damage to the embryo which would be highly likely to result in a stillbirth or miscarriage.

PGD may only be carried out after an ethics commission has checked that these requirements are fulfilled and has given an approving assessment. The Act also governs the giving of information to the woman and the quality requirements for the licensing of the centres which carry out PGD. However, the Act governs neither the method of genetic analysis to be used in PGD nor the nature of the technical testing means to be used. The question as to how far superfluous genetic information and additional findings have to be avoided even on the technical level when the genetic analysis generates the genetic data and how superfluous genetic data, if they are collected in the genetic analysis, are to be treated, and in particular whether

178 Federal Court of Justice's judgment of 6 July 2012, ref. 5 StR 386/09 (BGH, NJW 2010, 2672).

179 *Gesetz zur Regelung der Präimplantationsdiagnostik* (Act Regulating Preimplantation Genetic Diagnosis) of 21 November 2011 (BGBl. I, 2228).

180 German Ethics Council 2012, original German edition published in 2011.

the woman may be informed of them, remains unclear. Nor are there any provisions on the decision as to choice of embryo and how to deal with the embryos after the results of the PGD are available. On the contrary, it is within the woman's competence to decide whether and which embryos she will have transferred after the PGD. The PGD Order, which puts the Act into concrete terms, will enter into force on 1 February 2014.

3.2.4 Genetic Diagnosis in the Conflicted Pregnancy Act

The Conflicted Pregnancy Act was amended in the year 2009 – after an intensive debate on the problems of late terminations of pregnancy – by the addition of a special provision on information and counselling after prenatal diagnosis.¹⁸¹ In Section 2a, the duty of a doctor to counsel the pregnant woman was introduced if on the basis of the prenatal diagnosis there were urgent reasons to assume that the physical or mental health of the child has been harmed. This relates both to impairment on the basis of genetic characteristics and other impairment. This counselling obligation applies irrespective of the stage of the pregnancy and irrespective of the question of a termination of pregnancy. It applies to the doctor who informs the pregnant woman of the diagnosis, and it comprises advice on the medical and psychosomatic aspects which follow from the finding, the involvement of doctors who have experience of this health impairment among born children, the discussion of the possible medical, psychological and social questions and the possibilities of support for physical and psychological burdens, the information on the entitlement to further and deeper psychosocial counselling by a conflicted pregnancy counselling centre

¹⁸¹ *Gesetz zur Vermeidung und Bewältigung von Schwangerschaftskonflikten* (Act on Assistance to Avoid and Cope with Conflicts in Pregnancy) of 27 July 1992 (BGBl. I, 1398), amended by the Act of 26 August 2009 (BGBl. I, 2990).

and providing contacts to support groups, associations for the disabled and counselling centres which are familiar with the disability which the child is expected to have.

3.2.5 Provisions on the coverage of test costs by statutory health insurance

In considering whether the costs of genetic testing are to be borne by the statutory health insurance scheme, a distinction must be made between genetic testing for the planning of treatment and other genetic testing. In addition it should be taken into account that treatment by a statutory health insurance doctor (outpatient treatment) is subject to different financing arrangements from inpatient treatment in a hospital.¹⁸²

Genetic testing for the planning of treatment by statutory health insurance doctors

Genetic testing for the planning of treatment (companion diagnostics) is a service for medical treatment under Section 27 (1) of Book V of the *Sozialgesetzbuch* (Social Code). If the method applied, at the date when the service is rendered, is listed as a separate item in the *Einheitlicher Bewertungsmaßstab* (EBM – statutory health insurance doctors' fee scale), it may be assumed that it is part of treatment by statutory health insurance doctors and may be applied at the cost of the statutory health insurance scheme.¹⁸³

¹⁸² On reimbursement of costs of genetic diagnosis in the statutory health insurance scheme and on the following, in detail and comprehensive, Huster 2012.

¹⁸³ See Section 87 (1) and (2) sentence 1 half-sentence 1 of Book V of the Social Code; the EBM is agreed between the *Kassenärztlicher Bundesvereinigung* (National Association of Statutory Health Insurance Physicians) and the *Spitzenverband Bund der Krankenkassen* (National Association of Statutory Health Insurance Funds) by assessment committees. It determines the contents and amount of the reimbursable services in a points system. For a medical service by a statutory health insurance doctor to be reimbursable, it must be included in the EBM.

In the case of a genetic test for which there is not yet a fee item in the EBM, it must be clarified whether this is a new method of testing and treatment within the meaning of Section 135 (1) of Book V of the Social Code. A method is new within the meaning of the case law of the *Bundessozialgericht* (Federal Social Court) if it is a new medical procedure which is based on an individual theoretical and scientific concept which differs from other forms of treatment and whose systematic application is to be justified in the treatment of particular diseases.¹⁸⁴ If the genetic test as part of companion diagnostics is part of a new testing and treatment method, then before it is included as a fee item in the EBM of the Federal Joint Committee, guidelines must have made a recommendation permitting the method to be used as part of the statutory health insurance system. For in statutory health insurance doctors' care, unlike in hospital care, new methods of testing and treatment may only be carried out at the cost of the health insurance funds if the Federal Joint Committee has declared its recognition of the diagnostic and therapeutic use of the new method and its medical necessity and economic efficiency – also in comparison to methods already applied at the cost of the health insurance funds – in the current state of scientific knowledge in the relevant treatment area (Section 135 (1) sentence 1 no. 1 of Book V of the Social Code).

New examination and treatment methods which are carried out in inpatient treatment in hospital may be reimbursed without the consent of the Federal Joint Committee; in this case, the services will be financed from the flat-rate payment for the case and if applicable will be taken into account when the flat-rate fee is newly assessed. Within inpatient treatment, the Federal Joint Committee may exclude a method from

¹⁸⁴ If it is a case of testing and treatment methods which were already part of the services of health insurance doctors before 1 January 1989, they are not subject to the application of Section 135 (1) sentence 1 of Book V of the Social Code, since they are not a new treatment within the meaning of this provision.

reimbursement if an assessment shows that in view of the generally recognized state of medical knowledge it is to be regarded as unnecessary for adequate, appropriate and cost-effective hospital care (Section 137c of Book V of the Social Code).

If a new examination method is considered in isolation, then in the general case it will not be a new method within the meaning of Section 135 (1) sentence 1 of Book V of the Social Code, because in itself it does not constitute a service of medical treatment. In conjunction with a medicinal product to be administered, however, it may be an indispensable part of a new treatment. If a finished medicinal product is to be licensed and it is prescribed that there must first be a genetic diagnosis which takes place before the medicinal product is administered, then the licensing of the medicinal product will automatically entail the licensing of the prescribed diagnosis.¹⁸⁵ No decision by the Federal Joint Committee is necessary. But there may be conflicts if although the medicinal product is licensed, the genetic test is not (yet) listed as a separate fee item in the EBM. The medicinal product may then be given at the cost of the statutory health insurance scheme, but there will be no reimbursement of the costs of the prior genetic examination necessary to administer the medicinal product, because it is not an EBM fee item. It is true that the evaluation committee is required to review the specifications of services in the EBM at regular intervals, but in the prevailing legal opinion it does not follow from this that there is a duty for it to act immediately after the medicinal product is licensed, and therefore some time may pass before the genetic test is included in the EBM. In this period, the new method will as a rule not be applied at the cost of the statutory health insurance scheme. In this time, the patient may only claim it by way of reimbursement of costs or assumption of costs if it can be shown that the system has failed – the requirements for this are strict – or that the patient has a life-threatening illness.¹⁸⁶

185 Cf. Huster 2012, 19.

186 In detail, see Huster 2012, 22 ff.

Conflicts may also occur in the case of prescribed medicinal products which have previously been licensed for health insurance doctors' care. Sometimes new methods of testing make it possible to determine more precisely the patients for whom the prescription medicinal product works and those for which it either does not work or works only with particularly serious side effects, and consequently the medicinal product is to be used only on the patients whose genetic disposition indicates that its effect will be positive; here, the Federal Joint Committee also has to make a decision. But patients who have previously been treated with this medicinal product may not be deprived of this method of treatment unless the Federal Joint Committee has carried out an adequate evidence-based review.

Other genetic tests

If the other genetic tests have diagnostic purposes, they are qualified as medical treatment within the meaning of Section 27 (1) of Book V of the Social Code and may be charged, provided there is a fee scale item in the EBM.

In addition, predictive genetic tests may also be treated as reimbursable health benefits or early diagnosis benefits if they have been appropriately validated in clinical studies. There should be no problems classifying them as these types of benefit, provided that there are relevant fee items in the EBM.

3.2.6 Data protection law

The Genetic Diagnosis Act governs data protection in the area of genetic diagnosis for medical purposes with regard to the keeping and destruction of the results of genetic tests and analyses and genetic samples (Sections 12, 13). Where the Genetic Diagnosis Act contains no provisions, then in addition to the provisions of criminal law on medical confidentiality, federal and Land data protection law also apply. Data protection law is

therefore of direct importance for the area of genetic research, since this is not covered by the Genetic Diagnosis Act.

The Federal Data Protection Act governs the whole area of federal activity under public law and also non-public agencies, where these process data with the use of data processing systems (Section 1 (2) no. 3, Section 2 (4)). The public authorities of the Länder are subject to the respective Land data protection Act.

Only personal data are covered by the data protection Acts. Personal data are particulars concerning the personal or material circumstances of a natural person. Anonymized data are therefore not subject to the provisions of data protection law. For special categories of personal data (Section 3 no. 9 of the Federal Data Protection Act) – this includes health data and thus also genetic data – the data protection Acts contain special provisions.

In addition, the data protection Acts cover only the data of living persons. However, the data of deceased persons may also at the same time be the data of living persons where inheritable characteristics are concerned. They are then subject to the data protection Acts in this respect.

Fundamental principles of data protection law

Data reduction and data economy, Section 3a of the Federal Data Protection Act. Section 3a sentence 1 of the Act provides that collecting, processing and using personal data and the selection and design of processing systems are to be in accordance with the aim of collecting, processing and using as little personal data as possible. It follows from Section 3a sentence 2 of the Act that personal data are to be rendered anonymous or aliased insofar as this is possible in view of the purpose of their use and does not require disproportionate expense and effort in view of the purpose of protection sought. What is meant by “rendering anonymous” and “aliasing” can be seen in the statutory definitions in Section 3 (6) and (6a) of the Federal Data Protection Act. This provides that rendering anonymous

means the modification of personal data so that the information concerning personal or material circumstances can no longer or only with a disproportionate amount of time, expense and labour be attributed to an identified or identifiable individual. In contrast, aliasing means replacing a person's name and other identifying characteristics with a label, in order to preclude identification of the data subject or to render such identification substantially more difficult.

Principle of prohibition with reservation of the right to permit, Section 4 (1) of the Federal Data Protection Act: Under Section 4 (1) of the Federal Data Protection Act, the collection, processing and use of personal data is prohibited unless it is specifically permitted by a legal provision or the data subject has consented.

Principle of limitation of use to specific purposes, Section 14 (1) of the Federal Data Protection Act: Under Section 14 (1) of the Act, the storage, modification or use of personal data is permissible only for the purpose for which the data were collected. However, Section 14 of the Act contains a large number of exceptions from the principle; these will be referred to in more detail in relation to research below.

Principle of transparency: A further fundamental principle of data protection is the principle of transparency of data collection, which can be found in many provisions of the Federal Data Protection Act. Only as a result of this is the data subject placed in a position to assert the rights granted him by law.¹⁸⁷

Privileges of research

Under Section 13 (2) no. 8 and Section 14 (1) of the Federal Data Protection Act, even without the consent of the data subject, the collecting, storage, modification and use of special types of personal data – that is to say, including genetic (health) data – is permissible where this is necessary to carry out scientific research, the scientific interest in carrying out the research project

¹⁸⁷ Cf. Gola/Schomerus, in Gola et al. 2012, Section 33 para. 1.

substantially outweighs the interest of the data subject in the exclusion of collection and use, and the purpose of the research cannot be attained otherwise, or can be attained otherwise only with disproportionate effort. In addition, under Section 14 (5) no. 2 of the Federal Data Protection Act, subject to the same requirements, the data may be used for other purposes, or a change of purpose of the use of the stored data is permissible. In these cases, in the public interest, in the weighing of the concerns of research and the interest of the data subject in excluding the change of purpose, particular account must be taken of the scientific interest in conduct of the research project.

Similar provisions apply to data processing by non-public agencies and public-law competitor enterprises under Section 28 (2) no. 3 and (6) no. 4 of the Federal Data Protection Act.

The data protection statutes of the Länder and the hospital or health data protection primary and secondary legislation which sometimes exists on the Land level, in contrast, contain greatly varying provisions governing how far it is permitted to deviate from the principle that personal data may only be collected and used for a purpose laid down in advance. In some Länder, the data subject's consent may be dispensed with only for research carried out by the relevant hospital itself, but in others, it may also be dispensed with for research outside the institution in question. Some legislation attaches weight to ensuring that concerns of the affected person which merit protection are not adversely affected. Other legislation, on the other hand, also permits data to be used for research purposes if public interest in carrying out the research project outweighs or substantially outweighs the concerns of the data subject which merit protection; in some cases, it is also required that the research purpose can otherwise either not be achieved or be achieved only with disproportionate expense and effort. Some data protection Acts refer indiscriminately to "research", while others permit data processing only "for a specific research project". Some legislation additionally requires data protection officers or authorizing agencies to be involved.

A question connected to the principle of limiting use to specific purposes is how specifically the donor's consent must relate to the later use of the sample and data material. Opinions on this differ substantially. Some require that the donor knows the specific research project for which his sample and data material is to be used. Others hold it sufficient if the donor is informed of the research field (e.g. cancer research, dementia research). Others still are satisfied with an even broader consent ("medical research"). On the one hand it is pointed out that the donor cannot give *informed* consent if he does not know exactly what he is consenting to. The purpose "medical research", it is argued, is also not precise enough to show the donor the scope of his consent. This is countered by the argument that it is part of a person's right of self-determination, when he is aware that a situation is uncertain, to be able to accept this very uncertainty. Consequently, the argument continues, it is only necessary for the donor to be informed that the concrete future use is uncertain and to agree to accept this situation.

In international research cooperation, an additional problem arises as a result of differing data protection provisions. In some countries, the publication of data from research projects is a requirement for them to be publicly subsidized. But when personal reference material¹⁸⁸ is available, then even if there is complete anonymization the problem of re-identification remains.

3.3 The international legal framework

The German legal system is supplemented and overlaid in complex ways by European Union law and international law. Under European Union law, the bodies of the European Union, and the Federal Republic of Germany, insofar as it implements

¹⁸⁸ Cf. Gymrek et al. 2013.

European Union law, are bound by the fundamental rights guarantees of the Charter of Fundamental Rights of the European Union and the other EU fundamental rights. Article 21 (1) of the Charter of Fundamental Rights of the European Union lays down an express prohibition of discrimination on the grounds of genetic features.

On the international law level, it is necessary to distinguish between international law in the narrow sense (hard law) and “soft” international law (soft law). Important provisions of international law in the narrow sense for the practice of genetic diagnosis are the human rights guarantees of the European Convention on Human Rights and the UN covenants on human rights. The scope of the relevant guarantees (above all of dignity, integrity and the protection of the private sphere) overlaps to some extent with the fundamental rights of the Basic Law, although the protection of human dignity under international law and the protection of the freedom of scholarship are far less extensive than in the Basic Law.

But the protection of the genetic code, for example, is guaranteed by Article 17 of the International Covenant on Civil and Political Rights and also by the European Convention on Human Rights. Article 17 of the Covenant protects the identity – also determined by the genetic code – and in addition the integrity, intimacy and autonomy of the persons affected against encroachments they have not consented to. Here, private encroachments give rise to a state duty of protection. The Council of Europe Convention on Human Rights and Biomedicine and its Protocols, on the other hand, was not signed by the Federal Republic of Germany.

The soft law provisions and principles of the UNESCO declarations of 1997 (Universal Declaration on the Human Genome and Human Rights), 2003 (International Declaration on Human Genetic Data) and 2005 (Universal Declaration on Bioethics and Human Rights) also have a de facto binding effect for the Federal Republic of Germany. The respective UNESCO parties in principle agree to make the contents of

a declaration the benchmark for action for national measures and provisions. If and to the extent that the declaration provides for this, however, the states may pass legislation going beyond the standards of a declaration and where applicable may deviate from the provisions of a UNESCO declaration if legitimate reasons are present. The Genetic Diagnosis Act largely corresponds to the contents of the relevant UNESCO declarations. However, the UNESCO declarations also contain specific provisions on the areas of genetic diagnosis which are at present not yet legislated for in the Federal Republic of Germany by the Genetic Diagnosis Act and other statutes. This applies, for example, to the whole area of research in the field of genetic diagnosis, in particular on whole genome sequencing. The UNESCO declarations contain detailed provisions here on the requirements for the consent of patients and test persons. In addition, the important prohibition of commercialization of the human genome is contained in the UNESCO declarations. The following provisions of the 2003 UNESCO declaration must be emphasized as important requirements for the treatment of human genetic data in research:

Persons concerned must be informed of their right to choose whether or not to be informed on research results. This right does not apply to data irretrievably unlinked to identifiable persons or to data that do not lead to individual findings concerning the persons who have participated in research (Article 10). According to one possible interpretation, the information must also comprise the possibility of superfluous genetic information and additional findings. With regard to relatives, the following applies: Only as far as appropriate, the right not to be informed (and the information on this) should be extended to relatives (Article 10 sentence 3). Withdrawal of consent is possible and entails neither a disadvantage nor a penalty for the person concerned unless the data are irretrievably unlinked to an identifiable person (Article 9). When a person withdraws consent, the person's genetic data may in general no longer be used (Article 9b). Individuals therefore remain

in charge of their data, specifically in the area of research work. They also have the right (Article 13) to access their own genetic data, if this is technically possible. Exceptions are however possible on the basis of domestic law, in the interest of the health of the population, of public order or national security. In principle, data should also be anonymized; exceptions may only be made if and as long as this is necessary for research (Article 14c). In the 2005 declaration, there are special provisions for research on persons incapable of consenting. However, Germany has made a restrictive declaration in this consent; this prohibits the implementation of these provisions where this is incompatible with Article 1 (1) of the Basic Law.

4 ETHICAL CHALLENGES

4.1 Starting points and distinctions

The return of old questions in the light of new technologies and specific fears and hopes in face of new possibilities of genetic diagnosis present ethics with central challenges.

Two aspects in particular need to be taken into account in connection with the new developments in genetic diagnosis: firstly, the rapidly growing quantity of collectable genetic information on individuals and groups of persons through exome and whole genome sequencing, and secondly the increasingly low threshold of access to this information, for example through DTC offers or non-invasive prenatal diagnosis.

They impinge on three central ethical problem areas: firstly, questions of the understanding of illness and health (cf. section 4.2.1), secondly, the issues of autonomy, self-determination and responsibility (cf. section 4.2.2), and thirdly, social aspects, in particular justice and solidarity (cf. section 4.2.3). In the discussion of these questions, not only moral principles but also ideas of the good life and fundamental convictions on the image of humanity play a role. In the ethical consideration of the subject, it is just as important to name these elements and make them available for public discussion as to endeavour to distinguish justified and unjustified expectations and fears from one another.

The ethical challenges which arise from the use of genetic diagnosis methods present themselves in different way in the case of prenatal diagnosis and in connection with born persons. The prenatal collection of genetic characteristics of the unborn child may result in a pregnancy conflict and in a decision against the life of the unborn child. The ethical questions with regard to the use of postnatal genetic tests, that is, of the information on the born person, in contrast, at least relate to a person's own concerns or the concerns of close relatives.

Although they may be of existential significance, they do not result in a decision on a unborn life. The ethical problems of prenatal and postnatal genetic diagnosis procedures are therefore treated separately below; in addition, in the postnatal area, it is necessary to distinguish between persons capable of giving consent and persons incapable of giving consent.

Throughout all areas of application of genetic diagnosis there is a need to make differentiations with regard to the following aspects:

- » **the nature of the information:** Genetic information may be disease-related or health-related. In addition, beyond health aspects, it may have effects on lifestyle (e.g. in the case of genetic information on sports or cognitive talents, cf. section 2.2.5). Finally, it may have no relevance to lifestyle (e.g. the “earwax type test”¹⁸⁹).
- » **the probability of occurrence** of a phenotype if a particular genotype is present
- » **the probable time** when a particular phenotype will occur
- » **the severity of the health disorder** in the case of disease-related information
- » **the possibility of influencing the health disorder** in the sense of a **prevention or treatment**
- » **the time of the genetic test**
- » **the individual significance** of the prognosis for the affected person
- » **the technical reliability and validity** of the genetic test

The following observations take up the above differentiations and relate them to a variety of problem areas. In this process, above all the purpose of the test is shown to be ethically significant in a medical or non-medical sense. Another ethically relevant point is the distinction between genetic diagnosis

189 Cf. online: <https://www.23andme.com/health/all> [2012-11-21].

measures which are to serve research purposes and those which are to benefit only the patient/consumer.

4.2 Postnatal genetic tests

4.2.1 Understanding of disease and health

Recent development in genetic diagnosis may have a far-reaching effect on our understanding of disease and health. This relates in particular to the attitude as to what role the genetic makeup plays in the genesis and development of diseases and how, on this basis, research and medical care are designed. In addition, in view of the increase in genetically based investigations of disease risks, there is discussion of a new interim status between health and illness which may be termed the new “latently sick person”.

Genes as determinants of illness?

The increasing knowledge of genetic factors in the genesis and development of diseases and disabilities may lead to varying effects. On the one hand, there may be emotional relief, because a disease is better understood and for example genes replace the patient’s own fault as an explanation, and no one is held responsible for genes. Thus, for example, exome sequencing makes it possible to reveal the genetic foundations of syndromes whose genesis was previously not understood. If a genetic mutation has been found, affected families feel in part relieved that they know at least one cause of these abnormalities and restrictions, often after having consulted many doctors over a long period of time in order to find an explanation. Especially when the persons affected are children with unexplained symptoms, the knowledge that the cause is a genetic defect may reduce worries and feelings of guilt, for example that mistakes made during pregnancy might have caused the impairment. In addition, parents can make better informed

decisions on future family planning if it is clear whether the genetic defect is inherited from them or is present for the first time in the child.

It is also hoped that the knowledge of a mutation and a following explanation of the pathophysiological paths of the genesis of symptoms give starting points for a targeted therapy. In the field of what is known as pharmacogenetics, it is already possible for the knowledge of genetic peculiarities to enable more effective treatment, since in some cases the effectiveness of a medicinal product depends decisively on a person's genetic constitution. This is the case, for example, with malignant melanoma or particular forms of lung cancer; here, the genetic nature of the tumour is relevant for the choice of treatment.¹⁹⁰ Other genetic predispositions may influence the effect and metabolization of medicinal products, and for this reason it is possible to optimize treatment and avoid side effects on the basis of such knowledge.

On the other hand, an exclusive concentration on genetic factors in the genesis in particular of multifactorial diseases may lead to neglecting other biological and psychosocial magnitudes of influence. The result would be too narrow an understanding of disease, in which the complex connection between genotype, phenotype and environment, as well as lifestyle factors, would be excluded from consideration. If genetic and biological aspects are allowed to dominate the interpretation of disease processes, there is the danger that efforts to find treatment strategies will relate one-sidedly to the genetic dimension. Such a one-dimensional approach is often called genetic determinism.

The above risks may also be accompanied by a one-sided promotion of genetic and biological research, neglecting the scientific examination of complex processes and interconnections. In addition, in face of such a narrowly directed understanding of illness, medicine might lose sight of the patients

190 Cf. Chapman et al. 2011.

in their many dimensions. This is problematical, because the fundamental understanding of the duty and subject of medical care is reflected in the structures of the health system and also in basic and advanced training and career advancement courses training in the health professions. Ultimately, important elements of treatment might be neglected which are oriented not primarily to biological and genetic findings, but to psychological and social standards.

Interim status between health and disease?

An important argument against the broad use of predictive genetic diagnosis is the claim that as a result of progress in genetic diagnosis a new interim status between health and disease is created, and this has destructive effects not only on self-perception, but also on social relations: it is claimed that a conception of examination that is not indication-based, which proceeds from molecular changes in order to inform the person in question of his genetic disease risks, creates an artificial status between the healthy person and the sick person. The “latently sick person” is *not yet* a patient, because no disease can be detected, but also *no longer* completely healthy, since an increased risk of particularly diseases has been diagnosed. This development, it is claimed, introduces a kind of harbinger status before disease in which no one knows whether it will ever develop into a disease whose symptoms can be detected with current medical procedures. One is then no longer ill on the basis of subjective feeling or currently measurable disease values, but because one is put on a kind of metaphorical waiting list as a result of the capturing of the genetic risk profile.

In such a scenario, three problems stand in the foreground: firstly, precisely in the case of predictions which suggest a high risk of illness, the person affected may be made extremely insecure and fearful. Possibly the person will perceive quite normal and transient phenomena as the first signs of disease, will organize his life on this basis and give up future plans which he would otherwise have attempted to realize without misgivings.

Thus, for example, if a higher risk of dementia is predicted, the affected person might interpret normal moments of forgetfulness as first signs of the outbreak of the illness and decide against, for example, beginning an expensive additional training course.

Secondly, there may be mistakes and over-interpretations which leave the affected person unnecessarily convinced that he will become ill, because the test cannot give any certain information as to the great probability of a disease. As explained in Chapter 2, the interaction of various factors in the genesis of illness is very complex and predictions of probability must be taken with great caution. There are a variety of possibilities of misunderstanding and misinterpretations here, including with regard to recommendations as to the best way to deal with risks. Today there are already business models in which preventive strategies are developed on the basis of genetic tests, for example in the form of nutrition programmes or sports recommendations. Without the proof of actual benefit and without expert counselling which is capable of dealing appropriately with the complexity and the many uncertainties in translating genetic data into individual health risks, it may be impossible for the individual to inform and orient himself appropriately.

Thirdly, there may be burdens on the family members who may also be affected by genetically determined disease risks. Blood relations may also carry the risk, depending on the constellation. Family members who are not blood relations and friends are at least involved in the life decisions which the person undergoing the test makes as a result of the findings.

But there are also arguments against the assumption that the postulated interim status between health and illness leads to problems or is to be seen as a particular mark of the new genetic diagnosis at all. According to this view, the new genetic diagnosis possibilities by no means represent the beginning of a change which under the label “latently sick person” leads to a radical change in the understanding of illness and health and

in the personal and social treatment of these phenomena. Instead, a view beyond genetic diagnosis shows that people have for a long time had to deal with a divergence between diagnosis and subjective feelings of illness and on the basis of this discrepancy have had to deal with a changed self-perception. High blood pressure, the detection of a cancer marker which is not genetic, an ultrasound finding of cystic kidney disease or a positive HIV test, for example, may, if the person affected currently feels well, be very clear indicators that the person affected will be serious ill in the foreseeable future and will also feel ill.

Against this background, a possible feeling of uncertainty as a result of sometimes very unreliable predictive health information is placed by many in a greater context. In this opinion, coping with such information forms part of the personal and cultural opportunities and risks of dealing with the possible discrepancy between diagnosis and subjective feeling of health and the beginning of a necessary treatment or recommended changes of behaviour. It is one of the self-evident truths of being human in a modern society to integrate the management of technological changes into one's relationship with oneself and one's own way of life.

Irrespective of which of these approaches to interpretation is favoured, one ethical conclusion may be derived relatively clearly from this discussion: the use of postnatal genetic diagnosis procedures calls for information on the residual uncertainty of the predictions derived from them. The aim connected with these procedures is not making people's life prospects more insecure, but helping them to cope with uncertainties and risks with the greatest possible degree of inner clarity.

4.2.2 Self-determination and responsibility

The possible effects of predictive genetic diagnosis on the understanding of disease and health set out above are closely

linked with varying concepts and expectations on the autonomy, self-determination and responsibility of users of genetic tests. Autonomy, self-determination and responsibility are central concepts in ethics in general and medical ethics specifically. In view of their great importance, particularly for the ethics of modern times, it is not surprising that these concepts are used with a variety of meanings. The words “autonomy” and “self-determination” are here sometimes used as synonyms, which is unconvincing when one considers their differentiated meaning and usage. Below, these concepts will therefore be distinguished in a way which will now be briefly sketched out.

The concept of autonomy refers to the fundamental ability of humans to engage in sensible reasoning, exchange reasons for actions with other individuals and make responsible decisions on their own initiative. This ability marks humans as moral beings. From this, the right to self-determination and to the development of one’s personality is ethically and legally derived, as is the individual’s responsibility for his acts, for convictions which guide him in this and for the foreseeable consequences of his acts.

Against the background of this autonomy which human beings in principle enjoy, self-determination is the possibility of realizing one’s own plans of actions and decisions on action. The realization of this possibility depends on concrete conditions. They relate to the place and time of individual life and to its stage of development. Physical and mental health are just as important for this as are diseases or disabilities. Self-determination is a fundamental anthropological idea whose realization depends on empirical circumstances. Self-determination is at the same time a legal entitlement which is variously structured in various legal systems.

Consequently self-determination, when its normative content is fully recognized, is empirically dependent on and related to social, cultural and individual conditions in which the individual lives. Thus the cognitive and emotional ability of a person to have self-determination may be present and may at the

moment of decision not be restricted by emotional or physical impairments, but the circumstances do not allow it to be exercised or at least only with a great effort. In the extreme case, this may be a matter of coercion. More subtle threats to possibilities of self-determination may arise through pressure from a group or from socially widespread ideas of normality, for example if the individual believes that he cannot defend himself against it or if he does not even reflect on them critically.

If self-determination is understood in the above sense, as the concrete development of a human personality, then legally and ethically it comprises the protection of and the respect for pursuing one's own decisions and life plans.

The concept of responsibility is also complex and calls for a number of meanings, forms and functions to be distinguished. There is a widely observed distinction between a causal responsibility, which seeks to attribute actions carried out in the past; a responsibility for roles, which is displayed in the competence associated with a particular function; and a consequential responsibility, which is directed towards the future consequences of present actions. All three definitions are substantially important for dealing with genetic diagnosis. A causal responsibility relates to all persons who were involved in past processes and are accountable for them. The responsibility for a role primarily relates to those who in connection with their respective profession are competent for legislating on the scientific development and practical application of genetic diagnosis. Consequential responsibility involves all persons who participate, through the democratic process, in finding provisions and approaches through which life-promoting opportunities of genetic diagnosis are used and the associated dangers as far as possible averted.

Responsibility contains a retrospective and a prospective element. Looking back, the question arises as to causes in the past with whose consequences the individual and society must come to terms today and tomorrow. Looking forward, the concern is to reflect in good time on the future consequences

of present action and to choose from the available possibilities of action those which are most compatible with human autonomy and self-determination.

In connection with predictive genetic diagnosis, retrospective responsibility appears most clearly in the fact that the recommendation of a genetic diagnosis measure and the interpretation of its results may have life-shaping significance, for the person directly affected, for his family members and for a circle of further family members to whom a comparable diagnosis might apply. Reflecting on this retrospective responsibility creates an obligation to deal with these possibilities as carefully as possible and to put the necessary emphasis on information, interpretation and counselling. Prospective responsibility appears at the moment when a latitude of judgment exists within which considerations must be weighed against each other and no final certainty exists. In these cases, the discussion between the person affected and doctors, on the basis of which the necessary decisions are made, has paramount importance.

Genetic self-determination

The central ethical concept (which is legal, although not only legal) in the context of genetic diagnosis is self-determination as the core element of human personality. It comprises not only the power to decide oneself to whom genetic data are to be disclosed, for what purposes they are to be processed and used, and to whom they are communicated (informational self-determination), but also the *right to know* one's own genetic status. Genetic self-determination attains particular importance in its manifestation as the **right not to know**; this guarantees protection against genetic information that is forced upon people.

The right to know and the right not to know are supported by the argument that knowledge of one's own genetic makeup may influence personal development and one's ideas of a good life.¹⁹¹ It might restrict the freedom of personal development if

191 Cf. Woopen 2000.

we were forced to anticipate essential elements of our future as a result of their genetic disclosure. On the other hand, it might restrict the shaping of our life if we were forbidden access to genetic information about ourselves (see below, section “Lifestyle and psychology”).

The possibility of having recourse to an extended genetic basis of knowledge – although those affected are not generally able to interpret this and it in part has only an unclear or uncertain evidential value – and the necessity of interpreting the significance for one’s own lifestyle of statements on probability can nevertheless make it more difficult to make a responsible and accountable decision. The extended possibilities of (apparent) knowledge also result in a larger area of potential responsibility; what earlier had to be accepted as fate may now fall into the area of conscious structuring if the factual basis is comprehensible and can be related to one’s own lifestyle. In this connection, inherited genetic characteristics present the particular challenge that decisions on genetic knowledge may affect not only the person deciding, but also that person’s relatives if these have the same genetic predispositions. Against this background there are fears that genetic possibilities of diagnosis which impose greater burdens of responsibility on the individual for himself and for others might make it increasingly difficult to sustain the desire not to know in view of molecular health risks against the pressure of medical possibilities of diagnosis and the expectations of family members and of society. By reason of the highly complex questions in connection with the procedures of genetic diagnosis, the highest standards apply to the information and counselling of the person who is considering undergoing a genetic test. Such information and counselling is a necessary condition for a self-determined decision of the person affected.

Under the aspect of self-determination, finally, it must also be taken into account that in a liberal society everyone is free to do things, even for reasons which others find it hard to understand – even harming himself – as long as others are not

adversely affected. In order to reduce as much as possible unintentional self-harm, for example by reason of lack of information or lack of product quality, the quality and the communication of information have particular ethical significance.

A large number of questions arise in the current ethical discourse. How far do the right to know and the right not to know extend? Does the right not to know apply without exceptions, or is there a duty in certain circumstances to inform family members? Even if one conceded to the right not to know a high rank as an individual defensive right, it may possibly reach its limits where serious injuries to the health of others are to be feared. Then, exceptionally, a moral "duty to know" may even arise, that is to say, a duty to have oneself tested and to make it possible for information to be passed on to third parties.

The right to know and not to know can only be appropriately exercised in the area of genetic diagnosis if the person who wishes to be tested is adequately informed. In the Genetic Diagnosis Act this ethically relevant ability of self-determination is to be guaranteed by the fact that the person undergoing the test is informed before the sample is taken and the test made, consents in writing, and when the findings are given is counselled by a doctor or (in the case of a predictive genetic test) by a medical specialist. Genetic diagnosis is increasingly broader in design and quantities of genetic information result from this, including information whose interpretation and effects are as yet unknown or questionable, and in view of this it will scarcely remain possible for the person undergoing the test to be informed on all individual conceivable findings and the possible consequences in advance before making use of every form of genetic diagnosis.

The Genetic Diagnosis Act has already considered this question. It provides that for genetic diagnosis for medical purposes, the medical person must inform the person undergoing the test before the genetic test of the intended means of examination and the findings which can be obtained by this, and before consent must ensure that there is a decision by the

person undergoing the test on the scope of the genetic test and whether and how far the test results are to be communicated or destroyed. When this is done, however, there is still no clarity as to the scope and differentiation of the information and counselling if a method of analysis is chosen with which many genetic characteristics or even the whole genome can be analysed and the person undergoing the test does not before consent firmly decide to be informed only of very specific possible test results and rejects other knowledge.

Against this background the question arises as to whether the same high standards must apply for all genetic tests as are currently laid down for conducting genetic diagnosis for medical purposes. In addition it must be clarified how far the mandatory involvement of a doctor, as the Genetic Diagnosis Act prescribes for all genetic tests of medical purposes, is to be retained for all genetic tests and if this must also be extended to what are known as lifestyle tests. It must also be asked what is to apply where the person undergoing the test wishes to have a complete genome analysis and there is no medical indication.

It would be ethically conceivable to design the information for a genetic test with which a large number of genetic characteristics are diagnosed in such a way that the potential of these characteristics to cause health disorders was presented only with regard to types of health disorders, without going into detail in each case. Such a categorization could be made, for example, on the basis of a set of criteria which takes into account the distinguishing characteristics set out above (cf. section 4.1) with regard to the type of information, the probability that a phenotype will occur, the time of manifestation, the degree of severity and the possibility of influencing the disorder.

Finally – above all in view of the flood of information to be expected from very different medical fields – the question as to how far information and counselling could be allocated to a specially trained profession (“genetic counsellor”) such as is already established in other countries. The aim of genetic information and counselling must be to give the user high-quality

advice, on the basis of comprehensive information representing the latest status of knowledge as neutrally as possible and non-directively and to enable him to make his own critical evaluation. It may be that this cannot always be automatically expected of general practitioners or medical specialists. There is another problem in the case of persons who have a strong personal interest, particularly a financial interest, in the conduct of a particular genetic diagnosis, such as in particular employees of genetic diagnosis enterprises or counsellor who are financially dependent on such enterprises. If the present form of medical counselling is held to be solely applicable, then the clearly increasing number of persons who are seeking genetic tests are left alone with tests offered on the internet which are often dubious. Here, it would be possible to create public offers of information on the possibilities of genetic diagnosis, including their limited validity, and on the current state of science.

Culturally sensitive information and counselling

In addition to the fundamental difficulty of appropriately communicating complex information for varying target groups, there is an intercultural dimension which presents an additional challenge in Germany. If one takes into account the fact that approximately 20% of the people in Germany have a migrant background, then doctor-patient relations are often burdened with linguistic and cultural barriers which may also adversely affect the quality of genetic counselling. Communication with the help of “chance interpreters” from the affected person’s circle of friends often suffers from poor translation competence and cannot in general guarantee a desirable exchange. In this way, not only may there be mistranslations, but information may also be omitted, and the doctor is unable to establish this and/or monitor it. There may also be a relationship of authority between the interpreter and the patient or client, and this will increase the possibility that the conversation will be censored, which makes the necessary authentic communication impossible. This difficulties arising from language

barriers not only prevent genetic counselling from succeeding, but in addition they are subject to legal problems. For they mean that the requirements for a self-determined decision are not guaranteed.

The cultural barriers to non-directive and open-ended genetic counselling should be taken into account in the same way. Marriage between relatives, which carries a higher risk of the genesis of autosomal recessive diseases, is an accepted practice in some cultures. As a result, the parents from these cultures are often clients of genetic counselling. A discussion of this practice calls for addressing the topic and designing the conversation in a manner that is sensitive to cultural differences. The cultural barriers often make doctors in genetic counselling practices feel overtaxed.

Lifestyle and psychology

The arguments *in favour of* comprehensive genetic knowledge include advantages to be expected for one's personal lifestyle, for family life and for career decisions. With regard to lifestyle, there are expectations that with the help of genetic information it will be possible to make decisions which can prevent or mitigate a later illness or improve quality of life on another level through optimum reactions to one's personal genetic potential.

But empirical studies show that the claim that people will be able to influence the development of their own health that was expected has not been confirmed, at least up to now, by the actual behaviour of most person undergoing the test.¹⁹² According to an evaluation of the reactions of the participants in several studies to the information that their test results were negative, it appears that the opposite is more likely.¹⁹³ Although the persons with positive test results were conscious

192 Cf. still the comprehensive reference, Schröder 2004 and the recently published review by Mand et al. 2012: the topic of this is the ethical problems of genetic tests on minors for late-manifesting disease, but the ethical challenges identified apply to predictive genetic diagnosis as a whole.

193 Cf. Marteau 2010.

of their risk, they clearly relied more on the effectiveness of treatment with medicinal products than on changing their lifestyle.¹⁹⁴ They placed their hopes in the belief that the fact that they belonged to a risk group would have no consequences for them personally; after all, not every smoker develops lung cancer. Although predictive medical genetic tests do not as a general rule encourage a fatalistic attitude to a potentially arising illness, only to a small extent do they result in awakening people's personal responsibility in the form of a foresighted management of health.

However, genetic knowledge may also have an emotional value beyond measurable successes in prevention. Even in the case of genetic characteristics for which the possibilities of influence or prevention are slight, a predictive genetic test can contribute to reducing the personally felt threat of a health risk, even in the case of serious illnesses. The motivation can consist in ending the uncertainty which at present is felt to be tormenting or depressing.¹⁹⁵ Admittedly, one primarily hopes that the finding will be negative and thus relieve the strain, in order to overcome depression or fear and to develop a new self-perception beyond the uncertainty currently experienced as to whether one is living with a serious health risk. But even a positive result which is hard to live with may help to better adapt one's own life plans with regard to this knowledge. Genetic tests which achieve such clarity are also seen as opportunities for the persons affected and their families to critically and more intensively consider one's own fate or health probabilities, and for example to take this into account in family planning. In addition, several studies indicate that the use of genetic tests in existence at the present time has fewer negative consequences than is generally suspected.¹⁹⁶ The increasing personalization, extended possibilities of responsibility in the area of more

194 Cf. Kollek/Lemke 2008; Marteau 2010.

195 Cf. Kollek/Lemke 2008, 99; Marteau 2010.

196 Cf. Heyen 2011.

medical health offers and also the easier availability of genetic tests are sometimes also understood as a gain in freedom.¹⁹⁷

4.2.3 Justice and solidarity

The ethical analysis of the new developments of genetic diagnosis must also refer to the broader social context in which they occur. In this connection, the principles of justice and solidarity must be taken into account. Justice here means the equal and justified consideration of what is appropriate in each case; it creates a duty in the social, political and legal context if a claim is to be characterized as universal and particularly strong. Claims out of solidarity, on the other hand, articulate calls for help which arise from the fact that the persons who are mutually obliged to solidarity share characteristics or concerns in a particular respect. This felt or – as in the statutory health insurance scheme – legally established “shared destiny” gives rise to a requirement for the stronger person to give help.

In connection with genetic diagnosis the elementary question as to justice presents itself as a question whether the new developments of genetic diagnosis will result in the discrimination and stigmatization of people with particular genetic characteristics. The question of access to genetic tests is also a question of justice. Solidarity may be regarded as threatened, for example, if the individual is excessively required to demonstrate personal responsibility for the use of individual tests for genetic characteristics. Conversely, it may also be seen as a contribution to solidarity to have a test carried out in the knowledge of a family predisposition, in order to avoid costs for the social security system if the findings are negative. These costs might otherwise be incurred through the use of a large number of early diagnosis tests if the person affected refuses genetic diagnosis, invoking his right not to know.

¹⁹⁷ On this summary, cf. Mand et al. 2012, 3.

Concern about stigmatization and discrimination

There may be fears that a person undergoing the test will be stigmatized and discriminated against on the basis of genetic findings, in particular if one is of the opinion that genetic information is highly deterministic. In this connection, stigmatization refers to a social practice in which a person is held to have a flaw if he has a particular characteristic. Discrimination refers to the unjustified unequal treatment following from this, which restricts the person's chances of development.

As the scientific section of this Opinion has shown, however, genetic tests produce a broad range of diagnostic statements. Correspondingly it must be expected that there will be varying degrees of encroachment on the self-perception of the person undergoing the test, their lifeworld and society. Consequently ethics must treat both misgivings and expectations in a differentiated way. Where genetic tests for monogenic diseases, as in the case of Huntington's disease, provide virtually deterministic results and it is essentially only the time when the disease will manifest that remains uncertain, the above misgivings as to the danger of discrimination and stigmatization must be taken very seriously.

But it would be inappropriate to extend such fears of stigmatization and discrimination to all other areas of genetic tests and in this way to fuel anxiety in the population and to base the need for regulatory measures on this. This applies in particular to tests which can detect only slight risks, in which as a result of the interaction of genome, behaviour, nutrition and exposure the strength of the disease in each case remains unclear, to say nothing of the date when it may occur.

Admittedly, at present the provisions of the Genetic Diagnosis Act prevent discrimination on the basis of genetic characteristics in working life and in insurance, but a reference to legal provisions is not enough to conquer the risks of discrimination in practice in social life. It must therefore be carefully observed whether this "new knowledge" does not subconsciously give rise to negative value judgments of persons.

Access to genetic tests

The access to health benefits may give rise to problems of justice. In Germany, at all events, it would widely be seen as a violation of an elementary right to justice if an individual did not receive medical treatments which are part of necessary health care. What was set out in the section on social law also corresponds to a social and ethical approach: genetic tests which are part of a necessary treatment must be borne by society, for reasons of the theory of justice. This applies at all events when the possibility of taking part in social life is understood as the yardstick of justice.

The situation is more complicated if justice is understood as the compensation of social inequality and not solely as enabling social inclusion. The question then arises whether the use of particular genetic tests exacerbates health inequalities, which not only, but often (and regularly, from a statistical point of view) also correlate with social inequalities. This tendency applies at all events in the degree to which persons who are in a better financial position can have recourse to new genetic tests which are medically valuable but which are not regarded as necessary or expedient by the statutory health insurance scheme and thus are classified as non-reimbursable. It is nothing fundamentally new that the better-off can privately buy themselves more extensive medical care, but in the context of the asserted trend it might increase.

The trend to increasing attribution of responsibility to the individual as a challenge for solidarity?

Solidarity and personal responsibility are in a complex and tense relationship to each other in general and particularly in health care. On the one hand it is expected that individuals should arrange their affairs with as much personal responsibility as possible. On the other hand, everyone in the course of his life needs various forms of solidarity. Help on suffering damage and injury, but also support by the likeminded in the attempt to strengthen shared concerns, and finally assistance and companionship in order to develop the ability to

take personal responsibility at all. On both sides of this tense relationship elements may be overstretched and break: exaggerated assertions of personal responsibility circumvent a culture of solidarity. Excessive solidarity may result in inertia or even in a refusal to accept personal responsibility for particular challenges in one's own life; this might encourage people to shift their own burdens onto the shoulders of others. It should therefore be asked whether the new developments in the field of genetic diagnosis place a burden on the tense relationship between solidarity and personal responsibility.

The growing interest in genetic tests is sometimes seen as the expression of increasing personalization of health-related activities.¹⁹⁸ It is said that this is above all expressed in a stronger development of markets for health services and in connection with this possibly in a greater allocation of responsibility to the individual.

However, this tendency does not relate to what is called personalized medicine, which is often mentioned. For personalized medicine means a differentiation of the collective of patients for the purpose of more precisely targeted treatment, which is to replace a general standard form of treatment which is offered equally to all patients. This term is somewhat problematic in terms of its definition: it is founded on a biological understanding of the person, in that it bases this promise of more precise diagnosis and treatment on genetic and non-genetic biomarkers. Only in a few cases, as in the recent development of cancer treatments, has there been success in using individualized treatment strategies on the basis of genetic tests. There is a more widespread phenomenon known as a stratification of patients: they are allocated to risk groups as a basis for medical interventions.¹⁹⁹

198 Cf. *ibid.*

199 Cf. annual meeting of the German Ethics Council "Personalisierte Medizin – der Patient als Nutznießer oder Opfer?" on 24 May 2012 in Berlin. Online: <http://www.ethikrat.org/veranstaltungen/jahrestagungen/personalisierte-medicin> [2013-03-04].

A personalization which is aimed at commercialization and at allocating responsibility to the individual covers different trends from personalized medicine. They include – and this is increasingly apparent internationally – obtaining medical information over the internet, personal medical data records which can be shared on the internet, the use of internet pharmacies, telemedicine, e-health information and individual health services including direct-to-consumer tests (cf. section 2.5.7).²⁰⁰

In principle, in accordance with the principle of subsidiarity, it is to be welcomed when the person affected in a given case is the first person trusted to solve the problems which he can solve, but it is also expected the he does this. However, the question is whether this is really universally possible and appropriate in the field of health care. Public health studies have for many years shown that there are different degrees of sensibly coping with disease risks, both individually and above all by social class. But in the case of serious illnesses, individual precautions are often very limited, quite irrespective of the class or milieu to which the individual belongs.

It must therefore be considered that such a trend to the privatization of health services in general and of genetic tests in particular might change people's understanding of their role in the health care system. They then no longer experience themselves as patients or as persons seeking advice or as persons who are integrated in a community of solidarity, but increasingly as consumers. This self-perception and the possibility of the consumer freedom resulting from it are quite legitimate. Their position can then be supported by consumer protection measures. As consumers, those seeking services may ostensibly choose confidently among competing sellers of genetic tests. But at the same time they do not have the protection and the legal certainty of the patient and the person seeking advice in a medically regulated environment which complies with

200 Cf. Nuffield Council on Bioethics 2010.

standards. But above all, the attitude towards solidarity might change as a result of the claimed trend.

This may happen in two ways. On the one hand by the individual seeing himself as less attached to the shared risk pool of those with health insurance. He now only sees them as a burden on his individual health care. On the other hand, it might also happen that an individual loses the understanding for the need to show solidarity even to those who are in a worse state than himself. If such developments occur, this would be welcomed by those who have always advocated more personal responsibility in the health system. Conversely, those who advocate the classical solidarity model would regard with concern possible trends towards more personal responsibility as the result of the increasing availability of genetic tests.

However, the knowledge of the complexity of the genesis of diseases, if properly communicated, could certainly also contribute to a strengthening of solidarity: in view of a complex genesis, the transitions between health and disease are fluid, and therefore no one should have a false sense of security; instead, he should know the value of a health insurance system organized on a solidarity basis. This applies all the more in that genetic tests for multifactorial diseases obtain particularly few valid risk details, and on the basis of these it cannot be excluded that a person who has been tested for a multifactorial disease and has been given a negative result will nevertheless develop the disease. Such knowledge of the constitutional vulnerability of a person creates a strong basis for responsibility in solidarity, the scope of which must nevertheless be socially negotiated and regularly balanced.

The restraint shown in imposing on the individual a legal obligation to submit himself to particular medical measures follows from the principle of the free development of one's personality. This does not affect the question whether there might not be good moral reasons to have oneself tested for particular predispositions and to direct one's life according to the results, in order to prevent diseases and not to unnecessarily burden the

collective body of the insured. This should be taken into consideration by the individual if the following criteria are satisfied:

- >> the test has a high degree of validity and reliability
- >> there is great individual benefit in the sense of the possibility of avoiding or treating a serious illness
- >> there is a high degree of social benefit in the sense of avoiding high costs which would be incurred as a result of delayed diagnosis or inadequate treatment as a result of false diagnoses etc.
- >> there is little probability of the persons involved being stigmatized

Where the above criteria become weaker, the degree of moral obligation to have oneself tested for a particular disease or disposition sinks. In every case these considerations show that solidarity is always a question of giving and taking, that is to say, from the perspective of modern theories of justice it is a question of fairness. This should also be considered in dealing with genetic tests.

4.2.4 Consequences for individual problem areas

Genome-wide diagnosis and dealing with increasing quantities of data

The progress in the analysis of individual DNA deviations with manageable effort (and justifiable expense) will considerably increase the area of application of genetic tests. In order to answer a specific medical question, genetic analysis of a more or less restricted genetic localization (by locally restricted PCR analysis or targeted hybridizing DNA chips) could in future be extended more often to large sections or to the whole genome. The new genetic test strategies, based on high-throughput methods, range from the diagnostic panel to exome sequencing to whole genome sequencing (cf. section 2.3).

Ultimately, in addition to identifying the causes of new monogenic disorders, more precise prognoses on the course of existing diseases are expected, as are extensive predictive forecasts of possible monogenic or multifactorial disease dispositions. In the case of multifactorial diseases, this requires other factors to be included. In addition, information which may be relevant to a person's general state of health or to lifestyle questions may also be found. A broad genetic diagnosis by way of sequencing the whole exome or genome could in future also help to explain unclear disease symptoms, to diagnose an unclear health disorder and to attribute it to a particular cause.

However, a large part of the gene variants identified in whole-genome analysis will in future remain of unclear biological or health relevance, which entails further challenges for the treatment of such data. If genetic defects are identified, this is often not accompanied by the possibility of effective treatment or prevention of the health disorder caused by them; however, the diagnosis may nevertheless be a relief to those affected (cf. section 4.2.1).

The knowledge of the exact structure of one's own genome is a highly personal item of information, and in principle no one can be forbidden to obtain and interpret it. But this may only apply to persons capable of consent. For no one may encroach upon the right to know and not to know of a person who is not yet capable of consent or anticipate that person's later decision unless this is directly necessary in the best interests and for the personal benefit of the person affected. Statutory provisions on genetic diagnosis must provide for the protection of the right to know and not to know and must serve the goal of avoiding discrimination on the basis of genetic characteristics.

A person's genome may contain many indications of physical and mental characteristics and dispositions the knowledge of which is useful and sometimes very important for the individual. The information obtained from a genome-wide analysis may, however, be of dramatic significance if it results in the discovery of serious genetic defects, untreatable diseases or a

susceptibility to psychological disorders. This may impose an enormous burden on the individual and become an occasion for others to discriminate against him. Provisions of protection against unfavourable treatment are necessary here. Above all, an adequate explanation must be given before the diagnosis as the requirement for informed consent and there must be protection of personal data against third-party access. It is necessary to find provisions which guarantee an explanation adjusted to the situation on the nature, scope and possible consequences of the diagnosis; at the personal wish of the person involved this must be in the detail corresponding to the state of knowledge of genetic research and composed in such a way that the patient or “customer” without special training can understand it.

The question of the scope of the explanation before consent arises above all with regard to the treatment of superfluous genetic information and additional findings. The terms “superfluous genetic information” and “additional findings” are always linked to the question which occasions the genetic analysis. The Genetic Diagnosis Act distinguishes between the term “genetic analysis”, that is, the establishment of genetic characteristics by way of cytogenetic, molecular-genetic or gene product analysis (Section 3 no. 2) and “genetic test”, which means the genetic analysis directed to the purpose of the test (Section 3 no. 1). The question as to how far superfluous genetic information and additional findings will accrue is connected with the purpose or the goal of the genetic test. If its goal is “only” genome sequencing in itself, without a particular question or a particular medical indication, then strictly speaking there are neither superfluous genetic information nor additional findings, because the person wishes to learn everything that can be read from his genome. In view of the resulting flood of data, it is impossible to give information on the nature and significance of every individual obtainable result. Here, other means must be found to give sufficient information on the possible positive and negative consequences

of whole genome sequencing without being able to specify them in every detail. The person affected must know before the genome sequencing what he is letting himself in for, and must be able to assess whether he can also tolerate the results. It must also be clarified how far they are still part of the medical sphere of competence and must therefore be mandatorily conducted by a doctor.

On the level of bioinformatics, the possibility of using filters for this purpose is being considered. In this way, even though the whole genome is sequenced, it would be possible even on the technical level to introduce a restriction of the results to the findings intended by the genetic test or to exclude information the knowledge of which the person undergoing the test has rejected.

In the case where the genome sequence has been established, there must be legislation as to how far it is to be preserved for later medical treatment or investigations and where this preservation might take place. It must also be laid down subject to what requirements the information can be used for research purposes, if needed. It is expected that in future genome sequencing will be increasingly economical, rapid and simple to conduct. As a result, the question might resolve itself as to whether the duty to destroy the data which is laid down in Section 12 (2) of the Genetic Diagnosis Act should be prolonged. For it must be taken into account that the method and technology of genetic analyses are constantly developing and becoming more economical. There is a possibility that later, in the case of medical necessity, a new genetic analysis according to the latest state of science and technology can be carried out on the patient at a reasonable cost. Another argument against a long-term storage of large quantities of data is the fundamental data privacy law principle of data economy (cf. section 3.2.6).

On the choice of the test method for a particular genetic diagnosis – that is to say, either targeted search for genetic mutations by panels or chips or broad whole genome sequencing occasioning a large quantity of unneeded genomic data – the

principle of data economy must be taken into account. The collection of unneeded data should be avoided. The method that is more economical with data may at all events not be excluded at the outset only for reason of saving costs or easier management. From this there follow practical limits on the use of whole genome sequencing.

The requirements of a genetic test for medical purposes which are laid down by the Genetic Diagnosis Act are in principle also applicable to whole genome sequencing in the context of a test for medical purposes. But in the course of the new technical developments and the resulting medical questions they must be made more precise. It is also important here that the medical indication may change or become more extensive in the course of the new possibilities of genetic diagnosis.

Direct-to-consumer tests

Direct-to-consumer tests (DTC tests) offer users, usually through the internet, access to tests and to the results of genetic tests without the involvement of a doctor and without the professional medical explanation and counselling required by statute. DTC tests are in principle offered to the whole population. The tests on offer cover a large number of genetic characteristics, including determining the predisposition for multifactorially conditioned diseases where the probability that these will occur is as open as their specific manifestation if they do occur. Even genetic tests to diagnose serious diseases are offered, without regard as to whether treatment would be possible if the disease occurred. In addition, they often include what are known as lifestyle tests (cf. section 2.2.5), which go beyond genetic diagnosis in medical practice. The whole current spectrum of possibilities of genetic diagnosis can therefore be offered by use of DTC tests and to some extent is actually offered, although many sellers are beginning to be more careful and use more doctors in various functions in the diagnosis procedures, and to this extent deviate from the previous DTC model (cf. section 2.5.7).

In the case of DTC tests, the necessary individual information and counselling on the nature, validity and possible effects of the test results is not usually provided for. The customers here run a particularly great risk of false expectations and false conclusions of test results. This applies especially to exaggerated or unfounded fears or false all-clear messages from the test results. From the point of view of medical ethics, however, informed consent on the scope and implications of the decision for a particular genetic diagnosis and expert individual counselling after the test results are available are the fundamental requirements for the exercise of self-determination in the medical context.

However, it is disputed how far genetic tests must always be accompanied by individual information and counselling and how far this must all be subject to the mandatory presence of a doctor, perhaps a specialist doctor. It is asked whether other procedures and forms of information and counselling might be ethically permissible; but this question arises not only in the case of DTC tests, but also in the use of the new generation of genetic diagnosis in general. For DTC tests which are carried out directly between the seller and the “user”, without personal contact between an expert counsellor and the person undergoing the test, it should be borne in mind that no explanation of any kind whatsoever nor informed consent before the genetic test or expert counselling after communication of the results is guaranteed. This is not ethically acceptable (cf. section 4.2.2).

In addition, DTC tests entail practical problems:

- » It is not guaranteed that the person seeking the genetic test is capable of consent and has given consent of his own free will;
- » It is not guaranteed that the genetic sample sent in actually comes from the person who has sent in the sample as his own, and not from another person whose right of personality would be encroached upon by the genetic test;

- » In particular when DTV test sellers outside Germany are used, it cannot be guaranteed that the data privacy required under German law will be observed in the communication and storage of the genetic data.

It must therefore be asked and clarified: how can the state protect the individual from unconsidered decisions, personal risks of genetic diagnosis and avoidable encroachments upon fundamental rights in accepting the offers of genetic diagnosis without itself intervening too strongly in the freedom and self-determination of the individual – and this against the background of internationally operating sellers of DTC tests which do not comply with domestic law?

Genetic tests of persons incapable of consent

Since self-determination is a central legal and ethical yardstick for the evaluation of genetic tests and information, it is necessary for special considerations to be made with regard to the persons who cannot (yet) consent to genetic diagnosis.²⁰¹ The central emphasis is on the question as to whether and how far representatives can validly give consent to a genetic test in place of the person undergoing the test. Here, it is necessary to distinguish between two groups of persons incapable of consent:

- » those who are solely by reason of their age or their stage of development not yet in the position to make an informed decision on the conduct of a genetic test and the communication (or non-communication) of genetic information;
- » those who – irrespective of their age – are permanently unable or no longer able to make such a decision.

Against this background, the following considerations suggest themselves:

201 On the concept of incapacity to consent, Section 14 (1) sentence 1 of the Genetic Diagnosis Act cf. section 3.2.1.

(1) If the knowledge of genetic tests gives access to treatment options (in the wide sense) – whether preventive, curative or palliative –, then for both groups it the parents or other representatives, observing the best interests of the child or of the welfare of the person under supervision who are called upon to make a decision (Section 14 (1) of the Genetic Diagnosis Act).²⁰² The opinion of the person undergoing the test must be appropriately taken into account in the decision as to his best interests.

(2) With regard to genetic tests without direct possibilities of medical intervention, the question arises as to whether the parents or other representatives should also be granted this kind of authority to decide; this applies in particular to minors. If it can be foreseen that the disease or disability will manifest while the person undergoing the test is still incapable of consent, then information on genetic disposition may open up options which are in the interests of the person incapable of consent. These options may relate to the psychosocial support of the family, and in certain circumstances even the influencing of epigenetic factors, and in addition they may (only) in the case of minors relate to education and upbringing.

(3) If, on the other hand, it is a question of late-manifesting diseases, there must be a clear distinction between the two above groups. In the case of minors, the genetic diagnosis test may be deferred until a time when the person affected can decide for himself. The second group may be able to recognize a right not to know only to a restricted extent or not at all. In certain cases the group is in danger of being stigmatized by persons close to it by reason of such knowledge. It seems more important, however, that such information may make it possible for the persons supervising and caring to deal with the person involved in a better and more targeted way. For this reason, an early genetic diagnosis with regard to the

²⁰² See also guideline for genetic studies in persons incapable of consent (*Gendiagnostik-Kommission 2011b*).

interests of the persons in the second group may be ethically justified.

(4) A targeted genetic test of a person who is incapable of consent may under current law even be undertaken if in view of a planned pregnancy of a genetically related person it cannot otherwise be determined whether a particular genetically conditioned disease or health disorder may be suffered by the planned child (Section 14 (2) of the Genetic Diagnosis Act). In contrast, however, associations for the disabled have objected to this, as they regard it as an altruistic purpose and they warn against instrumentalizing people with disabilities.²⁰³

Preconception tests

Heterozygote tests determine whether persons are carriers of particular recessive hereditary diseases if they themselves are not affected by the manifestation of the disease; they may influence decisions on reproduction if one of the two partners has genetic material which results in an increased risk of genetic disease in the offspring (cf. section 2.5.1). If a person is such a carrier, then if a child is conceived with a partner who is a carrier of the same genetic defect, there is a high degree of probability that the child of the partners will suffer the disease.

By reason of the increasing knowledge of the genetic foundations of rare hereditary diseases and the sinking costs of genome-wide analyses, in the course of the current developments in genetic diagnosis it will be increasingly possible to offer heterozygote tests for many hereditary diseases simultaneously and cost-effectively, in principle to everyone who wishes to have this diagnosis even without a known family risk for family planning. Such broadly designed carrier tests are also sold direct to interested customers by DTC test companies.

The ethical challenges which arise in this connection affect above all the self-determination of the future parents and questions of social responsibility and solidarity. They may

²⁰³ Cf. *Bundesverband evangelische Behindertenhilfe* 2011.

have a radical effect on the nature and scope of prenatal and preimplantation genetic diagnosis.

In the recommendations on mass screening in population groups with particular increased genetic risks currently implemented in other countries, the central ethical challenge has been shown to be weighing the freedom of decision of the individual for or against such tests on the one hand and the social interest in the avoidance of suffering in population groups affected, the reduction of the frequency of carriers of genetic dispositions and the reduction of the costs of the treatment of illnesses by avoiding the conception of affected individuals on the other hand.

By reason of the rarity of most recessive hereditary diseases outside such risk groups, the value to be expected of a broad use of preconception tests carries relatively little weight. This applies even if many very rare genetic predispositions can be simultaneously and cost-effectively diagnosed, since the probability that both partners have the same genetic predisposition for a particular disease remains extremely small. An exception is the genetic predisposition for cystic fibrosis, which is not quite so rare.²⁰⁴ In the USA, for example, preconception genetic tests for cystic fibrosis are routinely offered to couples who wish to have a child.

An increasingly broad and cost-effective range of preconception genetic tests on offer may be the condition for reproductive self-determination if interested persons wish to use such tests in order to dispel the fear of particular genetic diseases or, where disease-related genetic predispositions are detected, in order to be able to critically consider their options for action if they wish to have a child.

On the other hand, the availability of such tests increases the burden of responsibility for those wishing to have a child. It is conceivable that the fact that preconception genetic tests are easily available creates implicit pressure to make use of them.

²⁰⁴ Approximately every 25th German citizen is a carrier.

An additional problem is that preconception tests, which examine many genetic characteristics at the same time, in a similar way to other genome-wide tests for diagnosis or prediction of genetic characteristics, considerably increase the complexity of the test, with corresponding demands for explanation, consent and counselling. Recessive or X-linked genetic predispositions admittedly do not lead to characteristics in the test subject, but “only” in a hypothetical proportion of future children. But the previous experiences with tests for carriers of genetic dispositions, which were used for only a few genes and only on people with a higher risk, showed that negative emotional reactions to test results are in fact frequent. In addition it cannot be excluded that carriers of heterozygous predispositions wrongly interpret these results to mean that they themselves would also be affected by the disease.²⁰⁵

For preconception tests there are therefore similar ethical questions and challenges to those for other extensive genetic tests. Such preconception tests are predictive genetic tests within the meaning of the Genetic Diagnosis Act (Section 3 no. 8b).²⁰⁶ Quality-assured information, explanation and counselling before and after a preconception genetic test is therefore a requirement for every use. However, these tests are not permitted in the form of screening (Section 16 of the Genetic Diagnosis Act).

4.3 Prenatal diagnosis

Prenatal diagnosis of genetic characteristics of the unborn child has always been the subject of intensive ethic controversies.

205 Cf. Borry et al. 2011; EuroGentest, online: http://www.eurogentest.org/patient/leaflet/german/carrier_testing.xhtml [2013-03-04].

206 Under Section 3 no. 8b of the Genetic Diagnosis Act “predictive genetic testing is a form of genetic testing with the aim of clarifying whether a person is a carrier of a genetic predisposition for diseases of health disorders among offspring”.

These relate in particular to the moral status of the unborn child, its right to life, rights and responsibility of the pregnant woman, the justifiability of a termination of pregnancy, consequences for the experience of a pregnancy and the social consequences of the practice of prenatal diagnosis. These controversies will not in themselves be the subject of this Opinion. Instead, the following observations concentrate on two recent developments. Firstly, the possibility of the isolation of fetal DNA from the mother's blood offers a non-invasive and thus, in comparison to invasive diagnosis, low-threshold access to test material, with the result that the course of prenatal diagnosis will probably change in the use of the various possibilities of screening and diagnosis. Secondly, the new sequencing technologies (cf. section 2.3) extend the spectrum of genetic diagnosis, culminating in the sequencing of the whole genome.

From an ethical point of view, these two new developments give rise above all to questions in connection with the self-determination of the pregnant woman, parental responsibility, the possible consequences for the protection of the life of the unborn child, the self-determination of the future born person and possible social consequences of the introduction of new procedures for prenatal genetic diagnosis.

4.3.1 Self-determination and freedom of reproduction of the pregnant woman

Self-determination in questions of reproduction is usually discussed under the heading of reproductive self-determination, reproductive autonomy or freedom of reproduction. It is largely undisputed in ethics and law that people have a right to decide whether and when they wish to reproduce, with which partner they wish to do this and how many children they wish to have. The right to reproductive self-determination, like the general right to self-determination, is a defensive right, which means that encroachments by the state require a particular

justification. If a pregnant woman makes decisions about her pregnancy, these must be seen *inter alia* in the context of her right to reproductive self-determination. The particular nature of this situation, however, consists in the fact that decisions often also relate to the unborn child, and therefore the woman ultimately makes decisions not only about herself but also about the other life which she carries within her.

Explanation and counselling to encourage self-determined decisions

Prenatal diagnosis measures are interventions in the body of the woman, and she must consent to them. For consent to be sufficiently qualified, she must have understood what intervention is involved, the meaning of this intervention and what implications it may have. Even in the form of prenatal diagnosis (PND) which is usual today, this is a challenge, and this is particularly the case in first-trimester screening, in which no diagnosis is made, but there is merely a calculation from several findings to determine whether and to what extent the pregnant woman, in comparison to the group of all pregnant women of her age, has a higher risk that the unborn child will have a health disorder. The primary concern is chromosome abnormalities such as trisomies, but also organ deformations.

If a higher risk is established, the woman is recommended to undergo a further diagnosis, normally amniocentesis. If this then shows that the unborn child has a health disorder, the question of a medically indicated termination of pregnancy may arise.²⁰⁷ This possible consequence is still far too often not

²⁰⁷ The concept of medically indicated termination of pregnancy here refers to the indication for a termination of pregnancy by reason of the fear of a danger for the life or health of the mother; Section 218a (2) of the German Criminal Code provides that the "termination of pregnancy performed by a physician with the consent of the pregnant woman shall not be unlawful if, considering the present and future living conditions of the pregnant woman, the termination of the pregnancy is medically necessary to avert a danger to the life or the danger of grave injury to the physical or mental health of the pregnant woman and if the danger cannot reasonably be averted in another way from her point of view". [Translator's note: Adopted

discussed in detail with the woman before the screening is carried out, since as a rule the test results in the desired inconspicuous findings and the doctor wishes to avoid disturbing the pregnant woman in a way which is regarded as unnecessary.²⁰⁸ But if the finding indicates a higher risk, the woman may find herself confronted by the necessity to make a large number of further decisions which she might have wished to avoid if she had been aware of the consequences before the screening.

In the case of tests sold commercially, which the pregnant woman must finance privately, there is the additional danger that no sufficient explanation is given. For in that situation there is an incentive to sell which could result, for example, in the information of the companies selling the test or the explanation by the doctor placing advantages in the foreground and disadvantages in the background.

In principle, the effect of a differentiated prenatal diagnosis is ambivalent. It may relieve the pregnant woman of fears, but on the other hand there is the danger that the very availability of the test and the associated burden of deciding make the couple affected and in particular the pregnant woman insecure and may even overstrain them. More and more frequent tests during pregnancy, increasing possibilities of seeing abnormalities in the unborn child and the matter-of-course way in which the varying measures of prenatal diagnosis are offered and made use of put pressure on some women and may create the deceptive impression that they will only satisfy their responsibility for their children if they make use of all possibilities.

Non-invasive prenatal genetic tests like PraenaTest, which was placed on the German market in August 2012, aggravate the ambivalence described. In particular the low-threshold nature of this test might result in it being used without sufficient self-determined assessment of the consequences. After

from the translation provided by Michael Bohlander, online: http://www.gesetze-im-internet.de/englisch_stgb/index.html (2013-10-02).]
208 Cf. *Bundeszentrale für gesundheitliche Aufklärung* 2006; Biehl/Woopen 2010.

all, it is restricted to trisomy 21 – and possibly also to the rare trisomies 18 and 13; this may reinforce the impression that a positive finding will result in a termination of pregnancy. The test is at present classified as a second screening procedure²⁰⁹ and under a current agreement between the manufacturer and prenatal diagnosis practitioners using it, is only to be used if the first-trimester screen has shown a higher risk. If the PrenaTest produces a trisomy 21, 18 or 13 result for the unborn child, this diagnosis should be confirmed by an amniocentesis.

The conduct of such tests is technically possible from the tenth week of pregnancy on, and in the USA, for example, it is already offered from this time.²¹⁰ But all other health disorders for which the unborn child has a higher risk according to an abnormal first-trimester screening are not excluded by a non-invasive prenatal genetic diagnosis solely for trisomy 21, 18 and 13, and therefore only practice will show whether and how far it can really replace amniocentesis, which is often proclaimed as its great advantage. The complexity of the decision which the pregnant woman must make is at all events increased, and thus so are the requirements of explanation and counselling by the doctor who must explain to the pregnant woman the various options and the possibilities which result from them. In particular it should be ensured in this counselling that the pregnant woman is given information on the conditions and possibilities of life of people with trisomy 21, who generally do not suffer as a result of their special condition and who today have a wide variety of possibilities to live in society and lead a satisfying life.

The situation becomes more complex if a larger amount of information on the unborn child can be obtained – culminating in complete fetal genome sequencing from the mother's blood. Even if such a comprehensive collection of data from

209 Cf. Benn/Cuckle/Pergament 2012.

210 For example the offer of Natera. Cf. online: http://www.panoramatest.com/patients_faqs [2013-03-08].

the unborn child is not permissible under the current Genetic Diagnosis Act, in view of potential future social attitudes, the ethical aspects will be discussed here: it should be considered that the doctor could certainly not give explanations for all conceivable findings, but at best a general explanation might be possible; this would distinguish the various types of possible health disorders only in very general terms, and the pregnant woman would have to decide on this inadequate basis what information she would like to receive. At the same time it would have to be guaranteed that the explanation and counselling on the purpose, nature, scope and validity of genetic diagnosis took place in a manner which would genuinely enable the pregnant woman to make an informed decision for or against wanting to know the individual results to be obtained by a genetic test.

The scope of reproductive self-determination and responsibility

Before the question of appropriate support of the pregnant woman in making a self-determined and responsible decision there stands the more fundamental question as to what value various types of genetic information may have for this and what information the pregnant woman has a right to access at all when invoking her own self-determination. After all, this is a question of information about another human being and only indirectly of the consequences for her own life.

One opinion is as follows: the freedom of reproduction comprises the right of the parents to obtain all desired information and thus all genetic information about the unborn child; this right does at all events include the information which is necessary for a self-determined decision with regard to creating a family. Some information about the genetic makeup of the fetus is suitable to enable therapeutic or preventive measures to be taken; they also serve to evaluate the burden of duties with which the pregnant woman and the family affected have to cope. On the other hand, this right also extends to information on the genetic constitution of the fetus which does not result

in any therapeutic or preventive measures, but also opens the possibility to decide whether to continue or terminate the pregnancy. Where an abnormal genetic diagnosis finding gives occasion for the question as to whether the woman wishes to continue the pregnancy, she cannot automatically herself decide on a lawful termination of pregnancy; for the doctor must certify that there is a medical indication under Section 218a (2) of the Criminal Code. However, it is not defensible to withhold the relevant information from the woman and in this way to deprive her at the outset from the possibility of giving the doctor the basis of decision for the medical information he is to certify. In addition, Section 218a (1) of the Criminal Code makes it possible to terminate a pregnancy without criminal liability provided no more than twelve weeks have passed since conception and the pregnant woman has counselling before the termination. For this decision too, knowledge of the genetic makeup of the unborn child could be important. With regard to the individual rights of the pregnant woman, every restriction of her right to know must have a justification. This justification may follow from the fact that the unborn child must be recognized as a human being with its own ethically founded rights, a right to life and to the corresponding duties of those who are responsible for its protection.

It is pointed out in this connection that the knowledge of a particular genetic characteristic of the unborn child by no means has the inevitable consequence that the parents decide not to continue the pregnancy. The development of modern reproductive medicine and the use of prenatal diagnosis by no means result in children being made the objects of parental preferences. Anyone who indiscriminately suggests this is discriminating against all those parents who use their genetic knowledge responsibly. And nor may it be imputed to those who in such a case decide in favour of a termination of pregnancy that they any other motive than what Section 218a (2) of the Criminal Code expressly concedes them as the reason for a lawful termination: the establishment of the limits of

their individual capabilities and possibilities of coping in their personal sphere of life with the burdens caused by a severely disabled child without running the risk of serious dangers to the life or health of the pregnant mother in the process. Such a decision on the limits of one's own ability to endure stress implies no derogatory judgement or even a social message on people who manage their lives with such a disability.

It must also be taken into account, the argument continues, that a genetic test of the embryo or fetus in the overwhelming majority of cases produces no abnormal findings. Against this background, the test usually contributes to relieving the pregnant woman of existential worries. The test thus benefits her psychological and possibly her physical health and – also for the benefit of the embryo or the fetus – encourages a pregnancy with fewer psychological complications. The pregnant woman, against this background, may not be refused the test without adequate justification. The woman may all the more not be refused a testing method which is without risk for herself and the unborn child. No. 2.2 of the Directive on prenatal diagnosis of diseases and disease predispositions of the *Bundesärztekammer* (German Medical Association) rightly provides that the pregnant woman, before prenatal diagnosis is carried out, must also be informed of alternatives to not making use of invasive prenatal diagnosis; in supplement, no. 10 provides that the potential endangerment of the child by invasive interventions in the course of prenatal diagnosis requires that the possibilities of a low-risk diagnosis must be exhausted.²¹¹

Finally, advocates of this view affirm a right of the parents to know even of late-manifesting diseases of their child. In particular if other family members are already affected by a serious late-manifesting disease it may be an unjustifiable imposition for the pregnant woman to have to adjust to seeing her child grow up while she is constantly concerned that the

211 Directive on prenatal diagnosis of diseases and disease predispositions (*Bundesärztekammer* 2003).

disease may break out. The decision of the pregnant woman as to whether she will choose not to continue the pregnancy is highly personal in nature and incapable of any categorization. Apart from this, the prohibition of Section 15 (2) of the Genetic Diagnosis Act to test the embryo or the fetus for disease which will probably not manifest until after the child reaches the age of eighteen is unconvincing if for no other reason that because late-manifesting diseases (also) usually show a broad range of times of manifestation.²¹²

Another view holds that the freedom of reproduction has an intrinsic limit. This follows from the fact that the unborn child must be recognized as a human being with its own ethically founded rights, a right to life and the corresponding duties of those who are responsible for its protection. This also applies to the genetic testing of the unborn child. Responsible parenthood therefore consists precisely in not attaching any conditions to the acceptance of a child. This has effects on the scope which one grants at the outset to a right to reproductive self-determination. Collecting genetic data usually depends on the consent of the persons affected. To this extent, the duty of justification lies not with those who call for a limit to the access of the genetic data of the unborn child, but with those who wish to collect genetic data on the unborn child.

In the case of adults, the permissibility of a genetic test is tied only to their own consent. In the case of a child, it is only permissible if it is necessary to the best interests of the child's health and the disease found is not, for example, a disease which does not manifest until the child is an adult and cannot be preventively treated. To justify a collection of genetic characteristics of the unborn child, it can undoubtedly be asserted that preventive or therapeutic measures for the benefit of the fetus may be taken as a result. This reason justifies a right to access to such data on genetically conditioned health disorders which can in fact be preventively or therapeutically influenced.

212 Cf. *Deutsche Akademie der Naturforscher Leopoldina et al.* 2010.

Another factor which may be regarded as the justification for a diagnosis is that the genetic information on the unborn child may be relevant for the health of the pregnant woman, that is, if it can be foreseen that completing the pregnancy would sufficiently endanger the physical or mental health of the woman to be an indication for a lawful termination of pregnancy under Section 218a (2) of the Criminal Code. As a general rule, when such an indication is established, it is a question of the stress caused by the responsibility for the child after the birth. Such an endangerment must be examined by the doctor making the indication where applicable, taking account of the present and future circumstances of the woman.

But there is an earlier question to be answered: what information about her unborn child may a pregnant woman know? We can apply the same yardstick here: the smaller the threatened health disorder or genetic deviation of the unborn child, the more improbable is a health endangerment of the mother, even though in the individual case, taking account of the specific psychosocial situation of the pregnant woman, this may vary widely. It is all the more important to consider the specific individual case. The individual decision of a pregnant woman to terminate a pregnancy after a PND finding of this kind must at all events be respected, subject to the conditions of Section 218a (2) of the Criminal Code. According to the view described here, at all events, these grounds for a justified genetic diagnosis of the unborn child in no case include the right to a whole genome sequencing, nor to a diagnosis which, depending on the outcome, makes it possible for a pregnant woman to have a termination of pregnancy which is unlawful, albeit unpunished.

In addition, it is sometimes pointed out that the relationship between parents and child could be changed fundamentally and detrimentally by a comprehensive possibility of disposing over the child in the case of genetic diagnosis on a broad scale. The reproductive autonomy of the parents gives no right to an intervention in the life of the unborn child; instead, it

finds its limits in the dignity of the child and the fact that its life is not at anyone's disposal. The use of genetic diagnosis in pregnancy makes it possible for the parents to attach the realization of their desire for children to conditions they choose themselves and which the child must satisfy. In this way, an ethically dubious attitude of the parents towards their future children may develop. They would no longer be regarded as coequal subjects who are to be respected for their own sake, that is to say, in their individual essence. The development of modern reproductive medicine and the broad use of prenatal diagnosis instead lead to children being regarded more and more as objects of parental desires and preferences. The willingness to assume parental responsibility is made dependent on the existence or non-existence of particular characteristics on the part of the child. Even if the child is in principle wanted, its definitive acceptance is attached to the condition that it satisfies the parents' own ideas of health and suitability, of physical and mental freedom from impairment. From the viewpoint of the advocates of this position, this leads to an unacceptable discrimination against the embryo, which is rejected by reason of such undesired characteristics.

Reproductive self-determination, according to all viewpoints described here, means not only being able to make use of particular diagnostic possibilities after detailed explanation and counselling, but also being able to do without such tests. The moral ideal of parenthood is marked by a willingness to accept the future child as it is. The genetic tests which in Germany go beyond the relatively detailed routine maternity care have long been criticized in that a woman can scarcely any longer experience pregnancy in its natural course and as a gift, but is forced to conduct a kind of quality control of the child, with the consequence that if she gives birth to a disabled or sick child, which is regarded as avoidable, she is reproached or at least encounters lack of understanding. This attitude can be questioned by a further differentiation of prenatal diagnosis, which as a non-invasive method also carries no risk of

intervention. The impression may be reinforced that it is the primary task of parental responsibility to make use of prenatal diagnosis, and the pressure experienced by women to have these tests carried out is increased. Such an implicit compulsion may restrict parental autonomy and calls for particular sensitive explanation and counselling.

A further problem follows from the fact that in new methods of genetic diagnosis information on the unborn child may be collected to which the test was not directed but which can nevertheless be of significance for health. In this case, a variety of approaches are in principle conceivable. They range from comprehensive information of the pregnant woman on all findings, however unclear, to withholding all unsought information which has additionally accrued. If one follows the principle that the collection and knowledge of genetic characteristics of the unborn child needs to be justified, then a restriction of the doctor's duty to communicate results to the pregnant woman can be well justified if this is only information which is not of immediate relevance to health for the pregnant woman, the unborn child or the future born child during the whole of its childhood. The pregnant woman would have to be informed *before* the diagnosis of this restriction of the information which at most would be given her *after* the diagnosis, in order that she knows in good time of the limits of the diagnosis or of the following disclosure of the test results.

Against this background, the question arises as to whether and to what extent prenatal diagnosis should be restricted at an early stage, with regard to the choice of the technical method and the information on the findings, as the legislature already provides in the Genetic Diagnosis Act for the communication of the child's sex. The particular ethical requirements of explanation and counselling of the pregnant woman after an abnormal finding, which also relate to protecting the life of the unborn child, apply in any case under the statutory provisions of the Conflicted Pregnancy Act and the Genetic Diagnosis Act even in early prenatal genetic diagnosis; but there is no

guarantee of the protection that is to be given by the requirement of a medical indication for termination of pregnancy, for the pregnant woman may decide to terminate the pregnancy after mandatory counselling under Section 218a (1) of the Criminal Code before the end of the first twelve weeks of pregnancy and thus circumvent this protection.

4.3.2 Self-determination of the future child

In the case of born persons, access to the genetic information of another person without that person's consent is regarded in principle as unjustified, indeed, as a violation of that person's right to free development of his personality and his right to informational self-determination. Does the unborn child also have such a right to protection against access to its genetic data?

As already explained, it follows from the protection of the child's and of the mother's health that the woman has a right not to be denied access to the genetic data of the unborn child which are important in this connection. But a right with regard to genetic tests of the embryo or fetus extending further than this would in the opinion of some make it impossible for the later born person to exercise his right not to know. The adult is deprived of the right to decide for himself whether he wishes to have his genetic predispositions for particular characteristics determined or not determined. Thus, many people who know of their family risk of Huntington's disease decide, after careful reflection, not to have a diagnosis carried out. People who learn that they have an increased risk of developing dementia report of great uncertainty and helplessness. The unborn child may not be deprived, by a form of genetic diagnosis which is not oriented towards its best interests, of the possibility of asserting its right not to know even at a later time and of deciding as an adult what information it would like to have collected about itself and what not. Another argument in favour of this

is that in certain circumstances the child may be obliged to disclose genetic data which it knows in taking out particular kinds of insurance, which substantially affects its right of self-determination.²¹³

Advocates of another opinion point out that the right of the later born person to know and not to know comes into existence only in the future, at the earliest on birth, and can be exercised in practice only later. In contrast, a restriction of prenatal diagnosis has a direct and present effect on the right of self-determination and the right to reproductive freedom of the pregnant woman. This direct effect has a heavy weight – or at all events makes it necessary to weigh the rights involved, and this weighing does not automatically favour the later right of the child not to know.

Some also see it as a solution that the later born person need not be informed of the test results; for in this way the person's right not to know is also satisfied.

But others point out that the protection of access to highly personal data is not exclusively a question of guaranteeing the possibility of not knowing, but also of the person involved himself later being able to decide who and when may (collect and) know what genetic data of his. If complete informational access to the fetal genome were permitted, this would mean that it followed from the unborn status that one was exposed to the complete access of another person, in this case the pregnant woman, without interests like the protection of highly personal data being regarded as worthy of protection. The person involved can only exercise his right in this connection personally at a much later date – at a time when other persons possibly already know everything about his genetic makeup. In addition, knowledge of the genetic makeup of the child, even

213 This applies to life insurance, occupational disability insurance, disability pension insurance and long-term care annuity insurance if a payment of more than EUR 300,000 or an annuity of more than EUR 30,000 is agreed (Section 18 (1) sentence 2 of the Genetic Diagnosis Act).

if the child is not told of it, has effects on the way the parents interact with the child.

In this view, the right to a guarantee of the possibility of a future right to informational self-determination and the right not to know extends in particular to information on diseases which manifest only in adulthood, and to genetic predispositions for diseases which do not cause the outbreak of a disease in the carrier himself, but may result in a disease in his offspring if his partner passes on the same predisposition. The affected person should also be able to decide himself whether he wishes to be examined for genes indicating disposition which result in a higher probability that a disease will break out, for genetically conditioned untreatable diseases and for genes which are relevant to non-health characteristics. In the case of children this is already valid law with regard to genetic information for diseases and health disorders. In the opinion of many, it should also apply to prenatal genetic diagnosis in general, unless the possibility of danger to the mother's health needs to be taken into account.

4.3.3 Social implications

As a result of the new technologies of genetic and non-invasive prenatal diagnosis, it is expected that genetic tests will have extended possibilities in the unborn child which make it easier to access genetic information and produce a broad spectrum of genetic information, which also has social consequences in view of the development of stigmatization and discrimination (cf. section 4.2.3).

Thus, for example, a test solely for trisomy 21 is of particularly stigmatizing effect, according to critics, as a result of its immediate and frequent association with terminations of pregnancy. In this way, it is claimed, prejudices are reinforced; this makes it more difficult to implement the obligation to guarantee all persons with physical or mental impairments the

right to social inclusion which the Federal Republic of Germany recognized in approving the United Nations Convention on the Rights of Persons with Disabilities. Against the background that according to estimates approximately 90% of all pregnancies in which a trisomy 21 is detected are terminated²¹⁴, such a test ultimately has the aim of making this decision possible or of reassuring the pregnant woman. The fact that it is freely available on the market may be seen as a sign that this practice is normal and socially approved. Whereas the search for signs of trisomy 21 has previously been part of a more comprehensive search for fetal abnormalities, in such a test it is the only aim and therefore unmistakably offers the chance to avoid children with Down syndrome. For parents of children with Down syndrome, this means an additional burden, and it reinforces the impression that they have done something wrong measured against social ideas of normality. In addition, it is pointed out that a trisomy 21 can manifest in a wide range of phenotypes. Only in accompanying ultrasound examinations can it be determined whether the child has additional malformations of the cardiovascular system or the gastrointestinal tract, and only on this basis can a somewhat more differentiated impression of the health situation of the child be obtained. This more differentiated and individual view is shifted still more into the background by the introduction of the PraenaTest; at all events this is the case if its use is not integrated into a strict prenatal diagnosis system of care.

An extension beyond this of the possibility of genetic diagnosis with increasingly large amounts of information of varying relevance and validity on the unborn child may in addition encourage an attitude that the important aspect of offspring is their genetic characteristics. In addition, the impression might be reinforced that genetic information can quite generally give

²¹⁴ For figures from Europe cf. Boyd et al. 2008. A current survey on terminations of pregnancy after receiving prenatal diagnosis of trisomy 21 in North America, however, suggests that the numbers of terminations are possibly falling (cf. Natoli et al. 2012).

essential information about a person and his health development, but this is in fact only rarely the case. It is not appropriate if parents regard their children's characteristics and possibilities of development as genetically determined, as it were, and it would not be beneficial for the development of the children if upbringing were oriented above all towards genetic makeup. Thus, for example, it is fatal if there were the genetic prediction – albeit a vague one – that a child had a low IQ and parents then scarcely or no longer stimulated the child intellectually in the misguided belief that this had no point in any case.

Finally, a comprehensive right of the woman to every possible genetic test of the unborn child might result in the attitude that children are a form of property and at the disposal of the parents, and not human beings at no one's disposal and with their own rights. Children are people in a particularly vulnerable phase of their development who have a right, in view of their individuality and their own future, to be regarded and treated in such a way that it serves their best interests and their development into persons capable of self-determination. At first, they are completely dependent on the care of others and they grow into greater independence and exercise of their self-determination. From the point of view of developmental psychology in cooperation with the social circumstances and the upbringing in childhood, the essential course could be set as to what possibilities of development are open to the child at all. The child may be decisively shaped in the positive or in the negative sense. At no time may the child be treated like property; after all, its individuality, the fact that it is fundamentally not at the disposal of others and later self-determination must be respected.

In the last instance, it is not a question of the purposes of the parents which they associate with the child but of the person, who is still a child, as a purpose in itself, and of maintaining and encouraging the possibilities for the child itself to be able increasingly to pursue its own goals, and not the putative best goals determined by the parents on a genetic basis.

The child should be perceived and encouraged in its integrated development without genetically founded justifications or excuses outside the area relevant to health being adduced. This fundamental level of relationship may certainly also have more extensive effects on the perception of people and the social complex of relationships as a whole.²¹⁵

In contrast, others point out that genetic information about the child which is obtained through a particular test has no fundamentally different meaning from genetic information which for example is obtained by merely looking at the child or by use of imaging procedures. And the possibility of obtaining *particular* genetic information about the child by no means encourages a tendency to reduce children in general to their genetic makeup or even to regard them as “property” or “at the disposal” of their parents. Those who claim different are themselves suffering from a mistaken genetic reductionism. The knowledge of particular genetically conditioned deficits may, in addition, be used precisely to counter it by appropriate support and upbringing – in the same way as in the case of deficits which are not genetically conditioned or at all events knowledge of which was not obtained through a particular test. Especially when the cause of a particular deficit is known it may be possible in certain circumstances for appropriate possibilities of reaction to be asserted. It may also be that a child is spared reproach in connection with a particular form of behaviour if it is known that the conduct does not result from a fault of the child. In this way, it is possible to avoid serious traumatization by unjustified reproach. Precisely because children are people in a particularly vulnerable phase of their development, they have a right, in view of their individuality and their own future, to be regarded and treated in such a way that it serves their best interests and their development into persons capable of self-determination.

215 Cf. Beier/Wiesemann 2010.

The question as to whether the parents of a child with trisomy 21 reproach themselves also has nothing to do with the question as to whether a test can identify only trisomy 21 or other genetic abnormalities too. The fact that a trisomy 21 may manifest in many different phenotypes and that it can only be determined in accompanying ultrasound examinations whether the child has additional deformations of the cardiovascular system or the gastrointestinal tract must indeed be taken into account by appropriate information and counselling for the pregnant woman. The necessary differentiated and individual consideration is by no means shifted to the background by the introduction of the PraenaTest.

It is an important social duty to enable the disabled and their family members to live in society without stigmatization and discrimination. But stigmatization and discrimination do not come into being as the result of a particular prenatal test, but in the interaction between people.

5 SUMMARY AND RECOMMENDATIONS

The new developments in genetic diagnosis are characterized by three trends. Firstly, thanks to new high-throughput technologies, the volume of data of many genetic analyses is growing, extending to examining the whole genome. Secondly, progress in the bioinformatics evaluation of genetic data makes it possible to obtain more findings which are potentially relevant for health, disease and lifestyle. Thirdly, as costs sink, analysis is more rapid and information and options become increasingly widely available in the internet, many obstacles to accessing genetic tests are less obstructive. In prenatal diagnosis, the threshold to use is becoming lower as a result of new, non-invasive diagnosis analysing maternal blood, which in contrast to previous invasive methods carries no risk of miscarriage.

In the clinical context, there are indications from early experience that new methods of genetic diagnosis will be successful in certain areas of medicine. In the field of basic and clinical research, genetic diagnosis is today already producing important findings on the causes and course of genetically conditioned illnesses and on the planning of treatment for them, in particular for monogenic disease and disorders, tumours and pharmacogenetics. The technology ranges from panels which are used to make targeted searches for particular characteristics, to test chips which can simultaneously test for hundreds of characteristics for monogenic hereditary diseases, to the sequencing of all genes (exome sequencing) or even of the complete genome. It is to be expected that genome-wide analyses will become more and more important in medical practice too, specifically for the diagnosis of patients with serious impairments whose cause is unknown.

Over and above this, there are efforts to use genetic diagnosis on healthy people preconceptionally and predictively. Tests that might be used in this way are tests for genetic

predisposition for an increasing number of monogenic diseases, which may not affect the persons undergoing the test themselves, but possibly their offspring, and a still small number of tests for late-manifesting monogenic diseases which often only manifest in late adulthood, and then usually only with a certain degree of probability.

A further area of predictive genetic diagnosis is aimed at detecting genetic factors which are intended to determine more precisely the personal risk of widespread diseases such as diabetes or cardiovascular diseases, or at creating particular genetic profiles, the knowledge of which is to be used in lifestyle decisions, for example metabolic information in the choice of nutrition or sports programmes. But the diseases or characteristics whose genetic influence is relevant here are usually multifactorially conditioned, that is to say, influenced in a complex way by many genes, non-genetic factors and the interaction between them. Consequently, genetic analyses of multifactorially conditioned characteristics as yet provide very limited information. They offer findings which are difficult to interpret or unclear, and contributions which are usually hard for medical practice to exploit.

The above developments entail ethical challenges: for our understanding of disease and health, for the exercise of self-determination and responsibility, and for social developments which relate above all to justice and solidarity. The questions are not all new, and sometimes they are variants of challenges already discussed, although these are more pressing as a result of the combination of growing complexity and sinking barriers to access.

In the field of genetic diagnosis, quality-assured standards are the condition for the aim which is particularly important from the ethical point of view of enabling and encouraging self-determined decisions on using genetic tests and the responsible treatment of their findings. For this purpose, suitable social and legal framework conditions must be created.

The German Ethics Council regards the following aspects of the new development in genetic diagnosis as particular challenges:

1. Genome-wide analyses: For the clinical use of particularly extensive genetic tests culminating in exome and whole genome sequencing, ways must be found for the data and findings accruing to be appropriately and safely preserved in each case and for dealing with the superfluous genetic information and additional findings which may be expected to accrue in great numbers in this context. This applies all the more if extensive genome analyses in future become a standard method as a result of further technological progress and cost reduction.
2. Direct-to-consumer tests: Offers of genetic tests which are primarily directed at giving predictive information – for example on disease risks or genetic predispositions – for healthy people are often offered to the customer without observing the provisions of the Genetic Diagnosis Act, either direct over the internet or through non-medical cooperation partners such as pharmacies, fitness studios or nutritionists.
3. Non-invasive prenatal tests. The possibility of conducting prenatal genetic tests at low cost and non-invasively, that is, without a risk of miscarriage, in the first trimester might make such tests interesting for many pregnant women in future. Especially in the case of pregnancies without a particular risk for the characteristics tested for, however, there is increased probability that a test will give false positive results, that is, will show an impairment which is not in fact present. In addition, there is the fact that genetic tests often give limited information on the probability and strength of many impairments. In view of these uncertainties and the potentially far-reaching consequences which genetic test results are capable of having for the decision for or against a pregnancy, the information and counselling on prenatal genetic

tests create special challenges. This applies both to the decision as to whether to have recourse to tests and also to the way in which the test results are dealt with subsequently.

Many aspects of genetic tests on human beings are already governed in Germany by the Genetic Diagnosis Act, which entered into force in 2010. At present, for the protection of patients, genetic diagnosis has generally been carried out within an individual doctor-patient relationship and targeted to clarify and treat particular health disorders. Genetic diagnosis for medical purposes may only be undertaken by doctors, and predictive genetic diagnosis for medical purposes may only be undertaken by particular medical specialists. Account could be taken of the protection of the patient's concerns and self-determination by specific information and counselling on the results of genetic diagnosis to be attained by the diagnosis.

But in view of the developments outlined above and examined in more detail in this Opinion, the German Ethics Council sees a need for more legal and social action. In particular the broadening of the extent of the results to be attained through genetic diagnosis calls for an adjustment of the concept of protection. In the area of generation of and dealing with genetic knowledge, patients or consumers will probably increasingly find themselves in a situation in which they themselves have to bear, or are allocated, the responsibility for the use of the new technical possibilities and for dealing with the knowledge thus generated. This transfer of responsibility, however, is only acceptable if the self-determination of the persons affected is preserved in the process. They can only decide in a self-determined way if they have been informed on the facts in question neutrally, reliably and in a way that they can understand. They are also dependent on the genetic data collected from them being interpreted in accordance with the current state of science, but this is something which they themselves are scarcely able to review. As a result, the protection of patients must be supplemented by the aspect of consumer protection.

The German Ethics Council recommends:

A *On genetic diagnosis in general*

- A1. It is necessary to counteract a one-sided genetic and biological understanding of illness. This should be done by providing the public with information, by persons engaged in basic, advanced and postgraduate training and through balanced promotion of research including multidisciplinary research.
- A2. A publicly run platform should be established in the internet, financed in the long term and quality assured, giving information on available genetic tests, their significance and validity; this site should be regularly updated. Such a platform offers an easily accessible foundation for information in order to prepare a decision as to whether to make use of genetic diagnosis. Expert information for the health professions should be linked to this.
- A3. Every doctor should know the importance of genetic factors in the prevention, diagnosis and treatment of diseases and developmental disorders. The basic and postgraduate training regulations for doctors must create the conditions for doctors to have the up-to-date knowledge necessary in a given case to undertake genetic diagnosis and deal with its results in general and specialist medical care and to be able to assess when they need to refer their patients to specialists. The guidelines of the Genetic Diagnosis Commission on the requirements for qualifications for genetic counselling should be incorporated nationwide in the medical postgraduate training regulations. In advanced training too, more emphasis should be given to elements of this kind in order to give prompt information on current developments.
- A4. Since both linguistic and cultural barriers have an adverse effect on the quality of genetic patient information and counselling and thus also on attaining their goals, these special aspects should be taken into account in the

organization of counselling and in the advanced and postgraduate training of the counsellors.

- A5. Experience in other countries with the occupational description of the genetic counsellor should be evaluated in order to establish whether such an occupation should also be introduced in Germany and what areas of responsibility genetic counsellors could assume.
- A6. In the Genetic Diagnosis Act it should be made clear that the information and counselling governed by Sections 9 and 10 and the information of results must be carried out in a personal discussion between doctor and patient. Handing out written materials is insufficient.
- A7. Under Section 8 (1) of the Genetic Diagnosis Act, the patient, in the course of his decision on the scope of genetic diagnosis for medical purposes, must also make a decision as to what parts of the genetic information which can be obtained by the intended genetic testing means or with the intended method should be given to him or to be destroyed. But when the new generation of genetic diagnosis is used, considerably more genetic data may accrue than are needed for a specific medical occasion of genetic testing. It is then often impossible to give detailed information in advance on all conceivable results. The Genetic Diagnosis Act should make it clear that information on and consent to the nature and the scope of the test need not deal with every individual genetic characteristic which is significant for a disease or a predisposition which might possibly be detected; they should be able to concentrate on types of possible findings, for example particular groups of diseases, the severity, the treatability, the probability or the time when diseases manifest.
- A8. In Section 14 (3) of the Genetic Diagnosis Act (genetic tests for medical purposes for persons incapable of consenting), it should be made clear that for the protection of the right to informational self-determination and the

right not to know in the case of minors, it should be permitted to collect only the genetic data which are necessary for the test purposes named in Section 14 (1) and (2). The restriction of data collection to avoid superfluous genetic information must begin on the technological level through the choice of appropriate methods of analysis. Collecting superfluous data which is barred until a potential later use when the affected person is capable of consent should not be permitted, since the protection of sensitive highly personal data for a long period of time is problematical, requires a high degree of organization and altogether the collection and storage of unneeded data is inconsistent with the principle of data economy.

- A9. It should be made clear by statute that findings of a genetic test for medical purposes which accrue outside the scope of specific consent are not entered in the patient's records but are deleted.

Section 12 (2) of the Genetic Diagnosis Act should remain the provision governing the preservation and deletion of the analysis data.

- A10. It should be possible for the genetic sequencing data to be given to the patient.
- A11. The Genetic Diagnosis Act should be amended to provide that newborn screening may also be undertaken by midwives and nurses and that it is necessary to involve a doctor only where the findings are abnormal. In this way it is to be ensured that newborn screening is carried out as comprehensively as possible on a clear statutory basis.
- A12. The permissibility of genetic tests for non-medical purposes for minors is not governed by the Genetic Diagnosis Act, but by the Civil Code and the provisions on the best interests of the child contained there. A majority of the Ethics Council members recommend restrictive provisions that genetic analyses and genetic tests of minor should only be permissible if this is necessary on the grounds of the best interests of the person in question.

- A13. The German Ethics Council rejects the introduction of an independent right of the doctor to inform relatives of the patient who might also be affected by the genetic disease diagnosed of their risk or to recommend them to obtain genetic counselling. In particular conflict situations, the criminal offence of necessity (Section 34 of the Criminal Code) provides an adequate possibility for the doctor to intervene to protect elementary third-party interests.
- A14. Before a genetic test which has no medical purpose but nevertheless may produce results which are medically relevant, as is the case, for example, in whole genome sequencing or in a nutrigenomic analysis, under current law it is not mandatory for a doctor to give information and counselling.
- The majority of the German Ethics Council recommend that the Genetic Diagnosis Act should also govern the conduct of such tests. They should be subject to the requirements of the Genetic Diagnosis Act and medicinal products law on quality assurance require prior information and counselling, which may be carried out by a doctor or, if appropriate, by a genetic counsellor (cf. recommendation A5).
- A15. In addition to the provisions of criminal and regulatory penalties in the Genetic Diagnosis Act, it should be laid down that a person who as perpetrator or accessory occasions the genetic test of another person without the necessary consent or gives false information on the identity of the person from whom the test material originates must be punished.
- A16. The German Ethics Council welcomes the fact that the EU Commission has presented a proposal for a Regulation on *in vitro* diagnostic devices. This is to provide that in particular genetic tests of the born person, genetic tests of fetuses to test for genetically conditioned disorders and genetic tests for companion diagnostics including the medical software used for this purpose are controlled

as products by a particular quality management system, improved evidence and technical documentation. It is to be welcomed that the conformity assessment procedure, which is the requirement for commercial sale of the above *in vitro* diagnostic devices, is in future to be carried out by an independent institution to be appointed by the national authorities.

- A17. For quality assurance, all laboratories which carry out genetic analyses should be subject to accreditation under Section 5 (1) of the Genetic Diagnosis Act.
- A18. It must be ensured that the costs of genetic diagnosis which are necessary to use a medicinal product on the basis of its license are reimbursed by the health insurance funds. Thus, for example, it could be made mandatory under Section 87 of Book V of the Social Code that immediately after a medicinal product is licensed in the outpatient area, the evaluation committee creates a fee scale item for the accompanying test for the statutory health insurance scheme. This also applies to the situation where the Federal Joint Committee licenses a new procedure for health insurance doctor care and a new fee scale item is to be created for this.
- A19. Uniform provisions should be created on the use for research purposes of data collected in a genetic analysis; these must be compatible with the relevant UNESCO declarations. With regard to the biobanks which are in the centre of genetic research, in 2010 the German Ethics Council submitted a proposal for the framework conditions to be laid down by statute.
- A20. Research and health policy should take suitable measures in order to counteract structural changes in clinical care which restrict the access of academic medicine to the genetic data which are important for clinical research and medical application.
- A21. Decisions on public funding of the development of new products or procedures should be subject to a review as

to whether the products or procedures raise fundamental ethical questions with regard to persons and society. If this is the case, the development should proceed with appropriate accompanying research or possibly, after an independent review, not be publicly funded.

A22. DTC tests are in general not permitted in Germany; protection against potential personal risks by using these tests should be ensured by public funding of measures of independent consumer education and consumer protection provisions.

A23. The Federal Government should take the initiative in prompting EU-wide joint provisions for the protection of patients and consumers against DTC tests. Where the sellers of DTC tests do not have their seat in the European Union, efforts should be made to ensure that particular combinations of tests, in particular tests which can diagnose predispositions to serious hereditary diseases, cannot be offered by way of DTC marketing or can only be supplied by the sellers through doctors.

B Prenatal diagnosis

The possibilities of genetic prenatal diagnosis are being increasingly further developed, as is shown by the introduction of non-invasive genetic tests. This places ever higher requirements on the selection and conduct of the appropriate test methods, the interpretation of the findings and the explanation and counselling given to the pregnant woman. The ethical assessment of non-invasive prenatal diagnosis tests (such as the PraenaTest) can be made consistently only by expanding the perspective to genetic prenatal diagnosis as a whole. Against this background, the German Ethics Council recommends:

B1. In view of the multiplicity of diagnostic methods and their validity and the need to make decisions which may arise, the explanation and counselling preceding genetic prenatal diagnosis should take account of the particular

emotional situation of the pregnant woman. In this connection, reference should be made to two responsible options; the possibility of not undergoing the diagnosis and the possibility of restricting the extent of information to be given.

- B2. Society and the state should respect the readiness of parents to give care, security and love to a child which will possibly suffer physical or mental impairments. This includes in particular making it easier for parents of children with disabilities to access possibilities of support and respite in order to counter the understandable feeling of many affected parents that in particular in the first years they are left alone with the particular demands on them. A change of attitude towards people with disabilities should be more firmly integrated in society and easily accessible possibilities of counselling and respite also support the social and inclusive model of disability on which the UN Convention on the Rights of Persons with Disabilities is based.
- B3. The majority of the members are of the opinion that non-invasive prenatal genetic diagnosis, and also chorionic villus sampling and amniocentesis, should only be carried out if there is an increased risk of a genetically conditioned disease or deformation.
- B4. Prenatal genetic diagnosis should only be carried out in institutions for prenatal diagnosis where if necessary a follow-up differentiating ultrasound examination can be made and cooperation with an independent psychosocial counselling organization is available.
- B5. Genetic prenatal diagnosis may only be carried out if it is guaranteed that on an abnormal finding a follow-up differentiating ultrasound examination can be given in order to obtain more detailed information on the specific nature of the impairment anticipated.
- B6. The majority of the members recommend ensuring by an appropriate choice of the methods of analysis that no

information which goes beyond genetically conditioned diseases or deformations is determined.

- B7. The use of both non-invasive and invasive prenatal genetic tests should be the subject of further observation. By way of socio-empirical and ethical accompanying research, more detailed knowledge of the extent and problems of these methods of making findings should be obtained, in order if necessary to introduce regulation.
- B8. The possibility of ever earlier genetic diagnosis results in a situation where information on the genetic makeup of the unborn child may be available even in the first twelve weeks of pregnancy post conception. This may result in the pregnant woman who establishes that the physical or mental health of her child is impaired wishing to have a termination of pregnancy under Section 218a (1) of the Criminal Code. In this case, the stricter conditions of a medical indication under Section 218a (2) of the Criminal Code do not apply.

The majority of the members of the Ethics Council, in view of the fundamental problems raised here with regard to the recognition and inclusion of persons with disabilities and the fundamental importance for the parent-child relationship, are of the view that a protective concept going further than the mandatory counselling under Section 218a (1) of the Criminal Code is necessary. In this connection, some members of the Ethics Council recommend that there should be no further regulation, since counselling is already necessary under Section 2a (1) of the Conflicted Pregnancy Act.

- B9. For the cases in which genetic prenatal diagnosis provides information on a genetic predisposition for a disease (heterozygosity for an autosomal recessive disease) which will have no effect on the health of the born child, it should be made clear that this finding may not be communicated to the pregnant woman.

DISSENTING POSITION STATEMENT 1

In May 2008, the Federal Republic of Germany consented under international law to the United Nations Convention on the Rights of Persons with Disabilities and in doing so recognized the right of persons with physical or mental impairment to inclusion in society. In this Convention, the right to be part of social life is conceived as a universal human right which is enjoyed by every person by reason of his humanity without restriction on account of particular characteristics such as age, stage of development or sex. The public funding of a genetic testing procedure which as a kind of electronic profile searching serves the purpose of detecting the carrier of a particular genetic anomaly, in which the motivation in the vast majority of cases (depending on the study, between 90 and 95%) is a prior decision to terminate the pregnancy, is in contradiction to the duty assumed to protect the rights of persons with physical and mental disabilities. In addition, genetic testing procedures which conclude from a genetic anomaly that the child is expected to have a disability are based on a one-sided, deficit-oriented understanding of disability which contradicts the resource-related point of view which is predominant today in education and social policy. The signatories of this dissenting position statement are therefore of the opinion that in addition to the recommendations made in the Opinion on prenatal diagnosis, procedures such as the PraenaTest or corresponding follow-up diagnosis should not be supported by public funds; equally, they should not be included in the catalogue of services of statutory and private health insurance funds.

A number of arguments are cited against this demand; in our opinion, these are found to be unsound on closer examination. Whether the right to social inclusion and the prohibition of discrimination of Article 3 of the Basic Law, contrary to their wording, relate only to persons already born is disputed in legal scholarship. From an ethical point of view, such

a restriction of a universalist understanding of human dignity and human rights cannot be justified. Those who wish to invoke an incremental degree of protection of unborn persons are on uncertain ground. For in order to justify a termination of pregnancy, the boundary between an incremental and an unlimited right to protection would have to be postponed to a later date (possibly until the birth). In the context of the public debate on embryonic stem cell research and preimplantation genetic diagnosis, the advocates of an incremental conception of protection still assumed that the developing embryo was subject to unrestricted protection at the latest after implantation in the womb. If the beginning of complete protection were to be shifted to a still later date, the nature of incremental protection, which is related to findings, would become clear. In these conditions, the boundary between restricted and complete protection would be drawn not from an impartial standpoint, but with regard to the changing situations of the interests of those already born.

The reference to a serious endangerment of the health of the pregnant woman is also incapable of justifying the selective regard of the embryo which results in a termination of pregnancy, since it may certainly not be assumed that an intolerable health endangerment for the pregnant woman is the normal case in every foreseeable impairment of the child. It is therefore not apparent how the rejection of unborn persons who will possibly suffer physical or mental impairments could be compatible with the right of every person to social inclusion and with the constitutional prohibition of every kind of discrimination on the basis of particular characteristics. Medical research and public health policy may not reinforce the social pressure of expectation that disabled children should no longer be born. On the contrary, they must counter it by giving a signal that every child, whether with or without physical or mental disability, is welcome. A social atmosphere of acceptance and encouragement may make it easier for parents to give love and care to a child which enriches their lives in another

way from the children who lead their lives without physical or mental disablement.

Thomas Heinemann, Anton Losinger, Peter Radtke, Eberhard Schockenhoff

DISSENTING POSITION STATEMENT 2

We are of the opinion that some recommendations on prenatal diagnosis in the main position of the Ethics Council are directed too much to making it more difficult for the pregnant woman to access important information which she regards as essential for her responsible decision. At the same time, these recommendations, if the legislature followed them, would reinforce the right to a termination of pregnancy, which is broadly accepted in society.

The ethical analysis should be guided by the real everyday lives of people. This indicates a special feature of pregnancy and parenthood. The main aspects of the ethical debate relate on the one hand to the reproductive self-determination of the pregnant woman¹ and on the other hand to the right to protection of the life of the embryo or fetus and the right of self-determination of the future child. This touches on three important and relevant moral principles. However, these three principles must be supplemented in connection with conflicted pregnancy by a further perspective in order to do justice to these special features. For in real everyday life, the actions of women in the context of prenatal diagnosis are oriented not primarily towards their right to decide on the concerns of their *own lives*, but towards their responsibility associated with this *for the future child and the family*. As a general rule, women usually exercise their right of self-determination in order to do justice to this particular responsibility for the life of one or more other persons. This comprehensive, totally personal responsibility is unique in the experience of human interaction. It relates not only to a particular duty, but to the existence of another person per se, and it applies lifelong without time limitation. Since the right to reproductive autonomy in this sense

1 This and the following observations apply equally to the couple who wish to have children.

is directed towards responsible reproduction, it is insufficient to describe it merely as a defensive right. This is a special moral feature which must be taken into account in the ethical debate.

Decisions for or against prenatal diagnosis belong in this special moral context. Women who make use of prenatal diagnosis as a general rule wish to satisfy their general responsibility for the future welfare of the child. In certain circumstances this may mean from the viewpoint of the pregnant woman that in the last instance she decides against carrying the unborn child to full term. Currently, such decisions are respected by a broad section of our society and also by the legal system – in full knowledge of the associated serious moral dilemma, not least for the woman herself. The PraenaTest as a current development in the area of prenatal diagnosis must be assessed against this background.

However, it is necessary to distinguish from this the availability of tests which go beyond the detection of disease characteristics and which in the future may gain importance during pregnancy, too. Such tests have the potential to considerably increase the degree of parental responsibility and uncertainty. The flood of information, the value of which is sometimes dubious, may result in a serious overstraining of parents. Another factor which must be taken seriously is the concern that informing the parents of characteristics of the unborn child which are not relevant to disease might result in a kind of competition on performance and responsibility among parents which would increase social inequality and change the parent-child relationship to a relationship with quite specific expectations and corresponding potential for disappointment, against which parents and future children must in certain circumstances be protected.

At present it is only possible to speculate how potential parents will use the future possibilities suggested and what advantages or disadvantages would result from these for the children affected or for society. Reflections in this regard are speculative and thus scarcely suited to justify particular prohibitions.

Nevertheless, the public and politicians should be prepared for possible problems, which may for example be associated with the knowledge from whole genome sequencing and test procedures based on this. The socio-empirical and ethical accompanying research called for in recommendation B7, including all affected groups in an open and equal social discourse, is therefore important for an evaluation of such future scenarios and their desired and undesired moral consequences. In this connection, the couple who have just become parents or who plan to become parents should be taken into particular account.

Collection data of the embryo or the fetus on direct risks of hereditary diseases or disease-related mutations will in the near future be possible in the overwhelming majority of cases only with the use of invasive diagnosis (amniocentesis, chorionic villus sampling). Since these technologies are costly and risky and are used by women who wish to have a child, an expansion of the diagnosis to findings of dubious relevance is somewhat unlikely. In all probability, therefore the development will therefore not result in a trivialization of the reasons for a termination of pregnancy, although this is at least a possibility and the number of persons using it should therefore be kept under critical observation.

It is true that the PraenaTest offers a particularly simple way to obtain genetic information on the unborn child; however, it does not provide diagnostic information that is in principle novel or different. The knowledge about the unborn child recorded by the PraenaTest can be obtained in any case at present; its problems are therefore essentially the same as those of a pregnancy conflict after prenatal diagnosis. A positive factor to be taken into account is the fact that this test has no side effects for the woman and for the unborn child and that it makes a decision on a termination of pregnancy possible at an earlier date, when the fetus is even less developed. On the other hand, it must also be taken into account that such tests may create difficulties in decision-making for women who do not have an individually increased risk, because of the reduced predictive

value and the increasing rate of false positive findings, without providing them with sufficient safe or sufficiently relevant information. The explanation for the pregnant woman must take particularly careful account of this aspect.

An extension of non-invasive diagnosis procedures such as the PraenaTest to a large number of characteristics, in particular rare characteristics, is somewhat unlikely in view of the proneness to error of such test systems or where the predictive value decreases. But the restriction of fundamental rights which is always considered in such a context requires realistic and sufficiently probable misdevelopment.

Against the background of these considerations, we cannot concur in recommendations B3 and B9. In our opinion, recommendation B6 is worded in too undifferentiated a way. We cannot support the majority opinion in recommendation B8, particularly since it does not make it clear in what the broader conception of protection should consist. In supplement, we recommend the repeal of Section 15 (2) of the Genetic Diagnosis Act, which prohibits a test for late-manifesting diseases. For the grounds, we refer to page Seite 143 f.

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ABBREVIATIONS

A	Adenine
ApoE	Apolipoprotein E
BAnz	Bundesanzeiger (Federal Gazette)
BGBI.	Bundesgesetzblatt (Federal Law Gazette)
BGH	Bundesgerichtshof (Federal Court of Justice)
BRCA	Breast cancer
BT-Drs.	Bundestagsdrucksache (Bundestag printed paper)
BVerfGE	Entscheidungen des Bundesverfassungsgerichts (Decisions of the Federal Constitutional Court)
C	Cytosine
cDNA	Complementary DNA
CFTR	Cystic fibrosis transmembrane conductance regulator
CNV	Copy number variants
DIN	Deutsches Institut für Normung (German Institute for Standardization)
DNA	Deoxyribonucleic acid
DTC	Direct-to-consumer
EBM	Einheitlicher Bewertungsmaßstab (statutory health insurance doctors' fee scale)
ENCODE	ENCyclopedia Of DNA Elements
EU	European Union
G	Guanine
GWAS	Genome-wide association study
IVD Directive	Directive on In Vitro Diagnostic Medical Devices
mRNA	Messenger RNA
nc-RNA	Non-coding RNA
NJW	Neue Juristische Wochenschrift
OJ	Official Journal
PCR	Polymerase chain reaction
PGD	Preimplantation genetic diagnosis
PND	Prenatal diagnosis
ref.	Reference
Rh factor	Rhesus factor
RNA	Ribonucleic acid

SNP	Single nucleotide polymorphism
T	Thymine
U	Uracil
UNESCO	United Nations Educational, Scientific and Cultural Organization

GLOSSARY

Additional finding	Finding generated from superfluous genetic information, going beyond the medical purpose of a specific genetic test
Algorithm	An exact description of a procedure which serves to solve a problem or a class of problems and contains clear instructions which are so precise that they can be carried out by computers
Allele	Gene variant; form of a gene located at a specific gene locus; varying alleles contribute to the genetic variability of a population
Alzheimer's dementia	Degenerative brain disease which begins with memory disorders and develops into dementia
Amniocentesis	Extraction of amniotic fluid; invasive test procedure in prenatal diagnosis
Aneuploidy	Numerical chromosome abnormality; deviation from the regular number of chromosomes Partial aneuploidy: aneuploidy in which only part of the chromosome is affected
Assembly	Bioinformatics merging of DNA sequence fragments
Association	A statistically confirmed correlation between genotype and phenotype
Autosomal recessive inheritance	Inheritance of autosomal genes in which the related characteristic only manifests if a mutation is present on both homologous autosomes
Autosome	Autosomes are the chromosomes which are not sex chromosomes, that is, chromosomes 1 to 22; every cell contains two copies of each autosomal chromosome
Base pair	In the DNA double helix, the bases adenine and thymine or cytosine and guanine are paired by way of hydrogen bridge bonds; the bases connected by this interaction are called base pairs
Beta thalassemia	Autosomally recessive inherited blood disease in which hemoglobin synthesis is disturbed
Bioinformatics	Discipline comprising biology and information technology which, with the aid of computers, collects, stores, evaluates and makes available biological data
Biomarkers	Biological substances which serve as indicators for particular biological processes; with the help of biomarkers, <i>inter alia</i> the cellular or chemical activity of a tissue, a disease or a mutation in the genetic makeup can be detected
Biopsy	Removal of tissue samples from the living body for diagnostic purposes

BRCA1/BRCA2	Tumour suppressor genes whose mutation increases the probability of breast cancer, ovarian cancer and other cancers
CFTR gene	Various mutations of this gene may cause the disease pattern of cystic fibrosis
Chorionic villus sampling	Sampling of some chorionic villi (part of the placenta); used as an invasive testing procedure in prenatal diagnosis
Chromosome anomaly	Change in the structure or number of the chromosome set; a distinction may be made between balanced anomalies (the total amount of the genetic makeup is unchanged) and unbalanced anomalies (increase or reduction of the total amount of genetic makeup)
Chromosomes	Carriers of genetic information; chromosomes consist of DNA and associated proteins; the genes are located on them; humans have 23 chromosome pairs
Coincidence	Used in genetics to refer to the chance correlation between a single particular gene variant (allele) and a special phenotypical characteristic
Companion diagnostics	Genetic test to plan and accompany treatment
Control gene	Gene which controls gene activities through its gene products
Copy number variants	Individual differences in the number of repetitions of certain sequence segments at particular sites on the genome
Cystic fibrosis	Autosomal recessive inherited metabolic disease which results in a malfunction of exocrine glands and thus can cause functional disorders in various organs
De novo mutation	Mutation which is not inherited from parents but is present for the first time in the person affected
Deletion	Loss of one or more nucleotide pairs
Diagnostic panel	Analysis procedure in which a potentially very large number of different gene variants are searched for at any desired large number of gene loci, always specified in advance
Diploid	Double, relating to the set of chromosomes
Direct-to-consumer test	Direct-to-consumer tests are offered for sale on the open market by companies – usually over the internet – in principle direct to the whole population. The customers can usually order them, without a doctor as intermediary, direct from the seller and the test results can be downloaded or obtained from the company by the customers themselves
DNA	Deoxyribonucleic acid; bio molecule; carrier of genetic information

DNA chips	System for the simultaneous analysis of several DNA sequences on a carrier surface (chip); the surface of the chip carries a large number of spots, each consisting of minute quantities of known DNA, which enables complementary DNA sequences from the test sample to be bound and thus detected in the sample
DNA sequence	Sequence of the four building blocks (adenine, cytosine, guanine, thymine) in DNA
Dominant inheritance	Inheritance in which characteristics in the child are manifested even if they are found on only one of the two homologous chromosomes
Down syndrome	See trisomy 21
Duchenne muscular dystrophy	X-linked recessive inherited disease, usually fatal, which results in muscle weakness and muscle degeneration
Embryo	The organism which develops from a fertilized acolyte which is capable of development until the formation of organs is complete (end of the eighth week of pregnancy post conception)
Enzyme	Protein molecule which creates and accelerates biochemical reactions in the metabolism (catalytic effect)
Epigenetics	Molecular mechanisms which without changing the DNA sequence influence the activity of genetic information (e.g. methylation of DNA building blocks)
Epigenome	Totality of epigenetic modifications of a particular cell type
Exome	Totality of the coding DNA segments (exons) of an organism
Exome sequencing	Determination of all coding DNA segments (exons) in the genome
Exon	Coding DNA sections in a gene
Expressivity	Degree of expression of a phenotype where the genotype is the same. "Variable expressivity" refers to the situation where all carriers of a genotype display the phenotype, but in varying degrees, so that for example the severity of a disease varies
False negative	The result of a test is referred to as false negative if persons who are carriers of the characteristics tested for are wrongly not recognized as such.
False positive	The result of a test is referred to as false positive if persons who are not carriers of the characteristics tested for are wrongly recognized as such.
Fetus	The human organism developing in the woman's body after the formation of organs is complete (from the ninth week of pregnancy post conception)

First trimester screening	Prenatal determination offered in the first trimester of pregnancy of two biochemical test results from the blood of the woman and the nuchal transparency of the unborn child, measurable by ultrasound; serves to determine a probability of the possible presence of a chromosome abnormality in the unborn child
Gene	DNA segment which contains the code for a functional product, for example for a particular protein
Gene activity	The genes that are actually read and converted into gene products at a particular point of time in a cell
Gene expression	Transcription of genetic information to RNA and thence to proteins
Gene locus	Refers to the precise location of a gene or part of a gene in the genome
Gene product	The RNA and proteins which come into existence through the expression of a gene
Gene regulation	The controlling of the activity of genes, produced both by the cell itself (endogenous) and also by outer influences (exogenous)
Gene variant	See allele
Genetic analysis	Procedure which aims to determine genetic characteristics of an object (cell, tissue, organism)
Genetic data	Information on the genetic makeup of an organism which have been collected by means of genetic analysis
Genetic disposition	Genetic susceptibility to develop a genetically co-determined characteristic, for example a disease
Genetic finding	The result of a test which gives information on a particular genetic characteristic of the person undergoing the test
Genetic test	Analysis of genes or gene products for a particular purpose (Section 3 no. 1 of the Genetic Diagnosis Act)
Genetics	A branch of biology; deals with the basis of inheritance, that is, with the passing on of genetic makeup either to the next generation of individual cells or to a new organism
Genome	Totality of the genetic information of a cell
Genome-wide chip analysis	In this, DNA chips are used to test a potentially very large number of gene variants
Genotype	Depending on context, refers either to the totality of genes in a whole organism or individual gene segments in the genome
Germ cells	Collective term for oocyte and sperm cell (also known as gamete)
Germ line mutation	Accidental alteration of genetic information in the formation of a germ cell, which can be transferred to the next generation through the germ line

Haploid	Single, relating to the set of chromosomes
Haplotype	Abbreviation of “haploid genotype”; refers to a series of alleles at a particular location of a chromosome which are inherited together (by coupling); they may be identified and characterized by particular SNP patterns on one chromosome.
Heritability	Measure of the extent to which characteristics can be inherited
Heterozygote test	See predisposition test
Heterozygous	Where different variants of a gene are present on the two homologous chromosomes
Homologous	Corresponding to each other; here: chromosomes with a largely identical gene structure, one of which is inherited from the mother and the other from the father
Homozygous	Where the two copies of a gene are present in identical form on the two homologous chromosomes
Huntington’s disease	Dominant inherited neurological disorder which leads to severe movement disorders and also to mental degeneration; it usually manifests in middle age; it is incurable and fatal
Hybridization	Used here to refer to a molecular genetic technique in which a single DNA or RNA strand has the complementary single DNA or RNA strand attached to it; this bonding can be shown by particular markings
In vitro	Outside the living organism (“within glass”)
Incidence	Number of new cases of a condition in a defined population group within a particular period of time
Insertion	Gene mutation in which one or more nucleotide pairs are inserted into the genome
Intron	Non-coding DNA segments in a gene
In-vitro fertilization	Method of artificial insemination
Locus heterogeneity	Is present if an identical (or similar) phenotype may be caused or partly caused by mutations in various gene loci
Marfan syndrome	Autosomal dominant inherited defective structure of the body’s connective tissue, with mild to severe symptoms of the stability of body organs, varying from case to case
Medical indication	Refers to the reason which gives sufficient medical justification for (indicates) the use of particular diagnostic or therapeutic procedure; a medical indication for a termination of pregnancy is given if a danger for the life or health of the mother is feared
Metabolic syndrome	Multifactorially conditioned disease in which the four metabolic disorders high cholesterol, high blood pressure, high blood glucose and overweight occur at the same time

Methylation	Attaching a methyl group to the DNA, which may influence its readability
Microarray	See DNA chips
Molecular-genetic analysis	Test procedure which detects details of the nucleotide sequence of DNA or RNA or the amino acid sequence of a protein
Monogenic	Development of a characteristic where this results from the influence of a single gene
Monosomy	Chromosome abnormality in which only one of the two homologous chromosomes is present in the genome
mRNA	Messenger RNA; primary transcription product of DNA, which serves as an interim stage for protein synthesis
Multifactorially conditioned diseases	Diseases which are triggered both by inherited factors and also by additional environmental and/or lifestyle factors
Mutation	Chance alteration of genetic information at a gene locus
Newborn screening	Screening of newborns for particular genetic characteristics
Next generation sequencing	High-throughput methods of DNA sequencing
Non-invasive prenatal genetic diagnosis	Prenatal tests which do not invade the body of the mother or the child
Nucleotides	Building blocks of the nucleic acids DNA and RNA
Numerical chromosome abnormality	See aneuploidy
Nutrigenomics	The influence of genetic factors on the utilization of food
Oligogenetically	Characteristic which is caused by a few genes
Oligonucleotide	A DNA or RNA molecule which consists of only a few nucleotides; often used in molecular biological tests to detect a complementary DNA or RNA sequence
Oligonucleotide hybridization	Genetic procedure which makes it possible to detect in a cell or tissue sample a short DNA fragment whose sequence is known
Oncogenes	Carcinogenic genes
Pathogenic	Causing diseases
Penetrance	Refers to the percentage of carriers of a particular genotype who actually have the phenotype associated with the genotype; reduced penetrance: refers to the intensity of the manifestation of particular genetically caused characteristics between different individuals; some of the individuals of the same genotype do not display the expected form of characteristic

Personalized medicine	Concept to differentiate patient collectives for the purpose of differentiated treatment, which is to replace a general standard form of treatment offered in the same form for all patients; the diagnosis and treatment are based on genetic and non-genetic biomarkers
Pharmacogenetics	Medical and genetic analysis aimed to determine gene variants in genes which are responsible for the effect or the decomposition of medicinal products
Phenotype	The totality of physical characteristics of a person, formed by epigenetic processes on the genetic foundation; characterized by anatomical, physiological, biochemical and psychological elements; individual characteristics (such as eye colour) may also be defined as phenotypes
Point mutation	Genetic mutation in which a nucleotide and its partner in the complementary DNA strand are replaced by another nucleotide pair
Polygenic	Determination of the phenotype by several genes
Polymerase chain reaction	Method by which individual DNA fragments are amplified and can thus be analysed
Polymorphism	The presence of two or more alleles at one gene locus in a population
Polysomy	Chromosome abnormality in which more than two copies of a particular chromosome are present in the genome
PraenaTest	Test sold by the company LifeCodexx in which fragments of fetal DNA from the mother's blood are examined
Preconception	Before conception
Predictive genetic diagnosis	Genetic test with the aim of clarifying a disease or health disorder, or a genetic predisposition for diseases or health disorders of offspring which will only occur in the future
Predisposition test	Test in which the genetic status of healthy people is analysed in order to determine whether the person is the carrier of a recessive hereditary disease
Preimplantation genetic diagnosis	Procedure for the genetic testing of artificially produced embryos before they are implanted in the uterus
Prenatal diagnosis	Medical examination of the unborn child during pregnancy, <i>inter alia</i> to recognize disorders of or damage to the unborn child
Prevalence	Frequency of a disease in a particular population group at a particular time; relative proportion of carriers in the random sample
Prognostic diagnosis	Giving a prognosis on the course of a disease to be expected in future
Recessive	Inheritance in which characteristics only manifest if they are present on both homologous chromosomes

Retinitis pigmentosa	Disease of the retina which may be caused by mutations at various gene loci; results in night blindness, cataracts and other visual impairments
RNA	Ribonucleic acid; in human cells, transfers genetic information into proteins
Screening	(1) Term for a test which as a mass test is systematically offered to the whole population or to particular groups of persons in the whole population, without need for a reason to assume that the person in each case has the characteristics the presence of which are to be detected by the test (2) Comprehensive test of an individual person to identify potentially relevant characteristics in the case of unspecific symptoms or an unspecific risk
Sensitivity	Measure of the technical quality of a test; a genetic test is 100% sensitive if it captures every carrier
Sequencing	Determining the sequence of the four building blocks (adenine, cytosine, guanine, thymine) in DNA
Single-nucleotide polymorphism	Genetic variations with changes to individual nucleotides of DNA which may be used as markers for particular diseases
Somatic mutation	Mutation which affects a somatic cell
Specificity	Measure of the technical quality of a test; a genetic test is 100% specific if it reports only carriers, and no non-carriers
Superfluous genetic information	Information produced by a genetic analysis which is not needed for the specific issue of the test or is unexpected or undesired.
Syndrome	In medicine, refers to a group of connected disease symptoms which are characteristic of a disease pattern and whose genesis is unknown
Systems biology	A new field of research which attempts with the help of bioinformatics to link large data quantities from various biological levels and thus to analyse genetic information in context in order to describe the biological organism in its entirety
Transcription	Conversion of the four-letter DNA text into a four-letter RNA text in order to create a protein molecule; it is followed by translation
Transcriptome	Totality of RNA molecules, that is, of all genes of a cell or a tissue converted by DNA into RNA at a particular point of time
Translation	Process of conversion of the four-letter RNA text into a twenty-letter alphabet of protein building blocks (amino acids) to create a protein molecule; in gene expression, it follows transcription

Translocation	Transfer of a chromosome segment onto another (non-homologous) chromosome
Trimenon	First trimester of pregnancy; medically defined as the period of the first twelve weeks from the first day of the last menstrual period
Triple test	Prenatal testing method which attempts, on the basis of the hormone level in the mother's blood, to draw conclusions on diseases and disabilities of the child
Trisomy	<p>Presence of a particular chromosome in triple instead of double form</p> <p>Trisomy 13: Numerical chromosome abnormality in which three copies of the thirteenth chromosome are present, resulting in a serious developmental disorder and a short life expectancy</p> <p>Trisomy 18: Numerical chromosome abnormality in which three copies of the eighteenth chromosome are present, resulting in a serious developmental disorder with many special physical features and death in the first years after birth</p> <p>Trisomy 21 (also: Down syndrome): Numerical chromosome aberration in which three copies of chromosome 21 are present</p>
Tumour suppressor genes	Genes which suppress cancer; their gene products can prevent the development of tumours by suppressing the uncontrolled division of genomically damaged cells; mutations in these genes result in an increased probability of tumour formation
Type 2 diabetes	Multifactorially conditioned metabolic disease
Whole genome sequencing	Test with the aim of identifying the "textual sequence" of the whole genome, that is, the haploid nucleotide sequence in all 46 chromosomes
X-linked inheritance	Inheritance in which the characteristic is on the X chromosome, that is, sex-linked inheritance

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