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Statement

Predictive Genetic Diagnostics as an Instrument of Disease Prevention

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Predictive Genetic Diagnostics as an Instrument of Disease Prevention

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Preface

The early recognition of treatable illnesses is playing an ever-increasing role in modern medicine. Predictive genetic diagnostics, combined with rapidly developing analysis methods and the sequencing of entire genomes in this respect, represents new territory.

*The central task of the German National Academy of Sciences (*Nationale Akademie der Wissenschaften*) is to deal with such themes and questions, with which the society is entering new territory, and point out science-based recommendations in order to answer them.*

With this statement, Leopoldina - Nationale Akademie der Wissenschaften, acatech – Deutsche Akademie der Technikwissenschaften *and the* Berlin-Brandenburgische Akademie der Wissenschaften *(for the* Union der deutschen Akademien der Wissenschaften*) is tackling a subject, which is extraordinarily relevant and controversially discussed in society.*

The statement explores the wider field of predictive genetic diagnostics from various sides. In light of the current state of knowledge, opportunities and limits will be considered with as much care as the medical, ethical, economical and legal dimensions of predictive genetic diagnostics.

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Summary and Recommendations

Preamble

Predictive genetic diagnostics are part of an individualised medicine. In connection with extraordinarily efficient analytical methods through to the sequencing of entire genomes, predictive genetic diagnostics represent new territory for society. They are subject to the largely accepted and, in many cases, stipulated ethical principles of medicine: predictive genetic diagnostics should help people remain healthy, to regain their health or, at least, to alleviate the consequences of illness. The person being examined must agree voluntarily to each diagnostic investigation after being provided with information and consultation.

The three academies responsible for this statement consider it necessary to inform society, politics, funders of research, the medical profession and health insurers about the chances, limits and risks of predictive genetic diagnostics. During the preparation phase of this statement, the Deutsche Bundestag adopted the Gene Diagnostics Act (*Gendiagnostikgesetz* - GenDG). Due to the fact that some regulations of this law concern predictive genetic diagnostics, these regulations will also be commented upon.

Self-determination

1. The medical significance of predictive genetic diagnostics for individual people emerges especially when an illness is predicted with a high probability through a genetic examination and can be successfully prevented or treated through prevention or early treatment. In addition, predictive genetic diagnostics can be advantageous for the life planning of a person.

see chapters 3, 8, 9

Predictive genetic diagnostics must only be carried out at the request of and in the interests of individual people.

2. ***The Academy Group expressively rejects eugenic ideas, such as the aim of wanting to eliminate certain genes from individual genomes or wanting to systematically "improve" the human gene pool.***

see chapters 2, 3, 5, 8, 9

Responsible Handling of Information from Genetic Analyses

3. In the future, systematic analyses (array technology, high-throughput sequencing) will be available in genetic diagnostics. In doing this, more information will sometimes be generated than is necessary for the intended examination. If such an "excess of genetic information" is conceivable and generated with the informed consent of the person being examined, a decision must be made jointly with this person in advance as to whether this information should be a) immediately used in a specific manner, b) destroyed or c) saved for the time being in an unused state.

see chapters 5, 9

The problem of dealing with an excess of genetic information should be discussed appropriately with the person concerned and should bring about their "enlightened decision".

4. Longer-term storage of genetic information can be wise because the information can gain in importance for the health of the examined person in the future. Storage has both technical and legal aspects. Genetic information is subject to the power of disposition of the examined person. In order to be able to use new insights in genome research for the benefit of the examined person, the examined person should have the opportunity to undergo a secondary analysis of the saved sequence information at a later point in time.

see chapters 5, 9

The* Gendiagnostikgesetz *should take into account the aspects of long-term storage and subsequent analysis of the excess of genetic information. The medical files should only contain the genetic information and its interpretation, which relates to the indication for examination (primary genetic information). An excess of genetic information should not appear in the medical file or any doctor's letters.

5. In Section 14, the *Gendiagnostikgesetz* regulates the handling of genetic examinations and any data arising therefrom in the case of an incompetent person. A systematic genetic examination can be in the health interests of an incompetent person, for example to precisely diagnose a genetic illness. After the diagnostic aim has been achieved, the excess of genetic information should not be permitted to be interpreted in the case of a child or a temporarily incompetent adult because this would take the option of ignorance away from the examined person. However, the excess of genetic information should be saved in a restricted form to ensure that this group of people is not disadvantaged relative to an adult competent person. As soon as competency is bestowed, in the case of an examined child once he has reached his 18th birthday, the affected person should be able to decide of his own free will and after a genetic consultation whether the information a) is immediately used in a specific manner (primary information), b) destroyed or c) continued to be stored for the time being. If a person is deemed incompetent on a permanent basis due to a severe and non-reversible impairment to his intellectual abilities, the legal representative should decide according to No. 3.

see chapters 8, 9

The* Gendiagnostikgesetz *should accommodate for the considerations of genetic diagnostics in terms of longer-term storage of an excess of genetic information for an incompetent person and regulate the subsequent use. This recommendation presupposes that security against misuse is technically possible.

6. Samples from abroad are quite often sent to German laboratories for genetic examination. This is not regulated in the Gendiagnostikgesetz. If the law is applied strictly, de facto, the Gendiagnostikgesetz would transfer to foreign patients. The patient must be informed about the procedure in accordance with the detailed specification of Section 9. Alternatively, it would also be conceivable that a higher level of explanation, which is legally required abroad, would have to be "downgraded" to German law. Neither option is reasonable or practical.

see chapter 9

The genetic analysis of a sample acquired abroad by a German laboratory should be acceptable if the doctor that has sent the sample confirms that the person concerned has been provided with information about the being, scope and significance of the genetic examination in accordance with the legal regulations in the sample's country of origin and the person concerned has subsequently granted his consent. If the German laboratory has doubts about the assignment of the sample to the person concerned or a substantiated suspicion that there has been insufficient information provided or even misuse, then the laboratory must refuse to examine the sample sent.

Newborn Screening

7. In many countries, including Germany, newborns are systematically screened for genetically-caused and treatable metabolic disorders. The children concerned would become severely ill without the diagnostics but develop normally if treated correctly.

see chapters 1, 3, 9

The newborn screening is a successful example of the use of early recognition of illnesses using predictive diagnostics. Surveys for other genetic illnesses should be aligned with the newborn screening.

8. The *Gendiagnostikgesetz* considers the newborn screening as a genetic survey. Accordingly, since the Gendiagnostikgesetz came into force, the parents must be provided with a genetic consultation before blood is taken. Baby nurses and midwives, who previously took the blood, are no longer allowed to do this on their own responsibility. There are already indications that this is leading to the newborn screening not being carried out for some newborn babies. This can lead to life-long disability, which could have been avoided with early diagnosis and appropriate treatment.

see chapter 9

The* Gendiagnostikgesetz *should regulate the newborn screening separately and in accordance with the special circumstances. The person, who takes the blood sample as part of the newborn screening, e.g. the baby nurse or midwife, should be allowed to explain the aim of the examination to the parents. The examination should then be dependent on whether the parents provide written confirmation of their consent. If a normal result is provided, the parents would not need to be contacted again. If the findings, on the other hand, were abnormal, the parents should then be provided with extensive information and genetic consultation from the responsible doctor.

Monogenic Diseases

9. A series of genetically-caused and essentially treatable diseases, which have a high probability of occurring during the course of a life, can be predicatively diagnosed. These include, for example, hereditary forms of bowel cancer, breast cancer, ovarian cancer and thyroid cancer, the dominant hereditary hypercholesterolemia or the recessive hereditary haemochromatosis. In Germany, patients with these diseases have only been recorded in an unsystematic and incomplete manner to date. If the genetic diagnosis is not provided, the patients cannot be cared for appropriately.

see chapter 3

Organisational measures should be taken within the health system to more efficiently identify predicatively diagnosable illnesses, which are treatable, before the illness manifests, so that the patients concerned have the option of availing themselves of appropriate medical care. The Academy Group recommends appropriate research programmes should be set up in Germany.

10. The diagnostics, treatment and long-term care of patients with genetically-caused and essentially treatable illnesses and their families requires special knowledge and cross-sectoral care. To date, this structuring has not been sufficiently provided in the Federal and sectoral health system in Germany.

see chapters 3, 5

For the illnesses listed as examples in No. 9 and other illnesses, where particular expertise is required to care for the persons affected, more specialists in human genetics should be trained further, the genetic competence of specialists in the relevant clinical sectors should be improved and an adequate number of interdisciplinary and cross-regional centres of competence should be set up.

11. In the future, the technical development of genetic analytical procedures will make it possible to identify the risk of healthy people for treatable genetically caused and related illnesses through screenings along the same lines as the newborn screening test. The first experiences of this are available from abroad.

see chapters 3, 5

The Academy Group suggests research projects to identify the prerequisites and criteria that must be fulfilled in Germany in order to expand the range of genetic screenings on offer.

12. Before pregnancy, healthy people or couples can be interested in finding out whether they are genetic carriers of any recessive hereditary disease, even if there is no index case for such an illness in their family already. This is to assess the health risk of their own child. Such a heterozygote examination represents a new situation for our society with far-reaching ethical and social implications.

see chapter 5

For the time being, systematic heterozygote examinations with regard to the health risks for the children of the examined people should only be carried out as part of research projects. They should be embedded in secondary medical, ethical and social research in order to gain experience about the personal and social effects.

13. Before predictive genetic diagnostics can be integrated into the health system, evidence for their efficiency and cost effectiveness must be provided. This includes patient benefits, which arise from the diagnostics and connected prevention and care as well as the related costs.

see chapters 4, 5, 7

In parallel to the fundamental genetic research, evidence, which verifies the effectiveness of predictive genetic diagnostics and takes into account the profitability should be compiled.

14. Without exception, the *Gendiagnostikgesetz* considers confidentiality for patients to be of a higher significance than the medical fiduciary duty towards relatives that have a high risk of developing a treatable, monogenic illness under certain circumstances. The doctor has no opportunity to verify whether the person affected by a genetic illness has passed on the information and medical recommendation of a consultation to his relatives. In individual cases, the doctor should weigh up which of the two legally protected interests should be categorised more highly: the duty of confidentiality or the medical fiduciary duty.

see chapters 8, 9

In very concrete cases and in cases of clear medical benefits, the doctor should consider appropriately indicating the risk of an at-risk person among the relatives of a patient with a treatable, hereditary illness and advising him to undergo a genetic consultation. The Academy Group recommends modifying Section 11, Paragraph 3 of the GenDG in this sense.

15. In Section 15, Paragraph 2, the *Gendiagnostikgesetz* prohibits the antenatal diagnosis of the embryo or foetus for an illness, which "will only appear after the 18th birthday of the child in accordance with the generally recognised state of medical science and technology". The formation of the law is incomprehensible. It is unwise to connect the appearance of an illness with "the general state of medical science and technology". Often, symptoms of a subsequent illness, which are discrete and not yet clinically relevant, can be determined before the 18th birthday. The formulation of Section 15, Paragraph 2 suggests that the legislator no longer wants to prohibit an antenatal genetic examination of a late manifesting illness as soon as more sophisticated analytical methods have succeeded in objectifying the appearance of the illness from very early on. From genetic consultation, the experience is that it is very rare for an antenatal genetic examination of a pregnant woman to be desired to test for the increased risk of a late manifesting illness.

see chapters 3, 9

Section 15, Paragraph 2 of the GenDG should be deleted due to the fuzzy definition of the age of onset.

16. In Section 12, Paragraph 1, Number 1, the *Gendiagnostikgesetz* stipulates that, in principle, the responsible medical person must destroy the results of genetic examinations and analyses ten years after the examination. However, before the expiration of the 10-year deadline, the significance of a certain genetic finding for an affected person at a later point in time cannot always be assessed. Genetic findings are often also relevant for family members. If the previously ill person (index case) died, they would be irretrievably lost. For the rest, it is a recurrent experience in human genetics that previously examined people and their family members inquire about their collected genetic findings long after 10 years because new viewpoints have arisen.

see chapter 9

It should be permitted to store the results of the genetic diagnosis without any concrete time limit, as was previously the case, in the interests of the person seeking consultation and their family members.

Multifactorial Illnesses

17. The majority of frequently occurring illnesses, such as diabetes mellitus, hypertension and arteriosclerosis, develop through a complex interplay of genetic factors and external influences. The development of these multifactorial illnesses can only be partially explained by genetic factors. Even if a series of gene variations, which contribute to the risk of illness, are already known, it must be ascertained that the scientific prerequisites for valid predictive genetic diagnostics are not currently fulfilled and the resulting clinical and health economical consequences are not yet sufficiently clarified.

see chapters 2, 3, 5

The complete sequencing of the genome of well-defined patient groups with genetically complex illnesses in comparison with healthy people opens up the opportunity of identifying all differences relevant to illness in the DNA sequence. This research strategy can help to cover the genetic contributions to multifactorial illnesses. The difficulty in the interpretation of such, extraordinarily extensive data records is in distinguishing differences relevant to illness from irrelevant differences. The Academy Group recommends intensively setting up appropriate, systematic research programmes.

18. It is a long path from the discovery of an association between genes and an illness and the improvement of health ("translation"). Before a wide use of certain predictive genetic diagnostics is suggested, effective prevention or treatment for the illness in question must exist and a reliable diagnostic procedure must be developed. The patient must be properly advised before the test and the presentation of the results and the result must be confirmed. Sufficient specialist capacities must be available for the entire procedure.

see chapter 5

The Academy Group recommends promoting translational research as well as basic research. In addition, medical guidelines for predictive genetic diagnostics should be developed.

Direct-to-Consumer-Tests (DTC)

19. Genetic tests, as they are currently offered directly over the internet – so-called DTC-Tests (Direct-to-Consumer tests) –, largely have an uncertain scientific basis and do not tend to fulfil the requirements of adequate genetic consultation. The examining laboratory is also unable to check whether the DNA samples sent actually come from the person, who has issued the investigation assignment.

see chapter 5

DTC tests (Direct-to-Consumer tests) should not be permitted because they do not fulfil the requirements of medical and ethically acceptable predictive genetic diagnostics.

20. In the case of DTC tests, the same risks exist as for prescription medications, which are prohibited outside the expert groups with good reason.

see chapter 5

As for prescription medications, a ban on advertising should be anchored in the law for predictive gene tests.

Information of the General Public and Further Medical Training

21. The opportunities of genetic analysis will gain in significance for an increasing number of people in the future, particularly in terms of the prevention of illness.

see chapters 2, 3, 5

The population should be informed properly and continually about the possibilities and limits of genetic medicine, including predictive genetic diagnostics. The new findings of inheritance research should be presented in schools, in particular.

22. In their past education and further training, doctors on a whole have not been made familiar enough with the significance of genetics in medicine. However, the treating doctor must be able to recognise family illness risks in his patients.

see chapters 3, 5

The Academy Group recommends providing doctors with further training in genetic medicine using special measures. They must be in the position to recognise high-risk people for treatable hereditary illnesses and refer them to specialists for consultation, diagnostics and care.

1 Introduction

Modern medicine is striving to detect diseases as early as possible and to treat them in their initial stages or to completely prevent their onset. The healing success generally depends on the correct diagnosis as well as the availability of an effective therapy. The general rule is: the earlier the better. General education regarding a healthy lifestyle, accident prevention and vaccinations are used from the outset to prevent disease and are considered to be the primary form of prevention. The early detection of treatable diseases and susceptibility to disease, which facilitates a secondary prevention, is of great and increasing importance in modern medicine.

General prevention programmes

Disease prevention concerns every human being. In the future, predictive genetic diagnostics can also affect every human.

Distributed amongst all stages of life, secondary prevention is virtually programmed into our health system, and in many other countries. This includes:

1. Prenatal examinations in pregnancy,
2. Screening for treatable diseases in newborns,
3. Clinical-chemical early detection examinations from middle age upwards and
4. Early detection examinations for the most common forms of cancer.

In Germany, the financing of this procedure is controlled by the guidelines of the Joint Federal Committee (*Gemeinsamer Bundesausschuss*[1]) in the scope of the statutory health insurance. They are based on a risk-adapted early detection of diseases and relate to the following aspects:

1. The persons to be examined are at an age-dependent increased risk of the diseases concerned.
2. If detected early enough, there are good possibilities to prevent the disease or to treat it effectively.

Prenatal care. Prenatal examinations in pregnancy, which serve the health of the mother and child (based on the "maternity guidelines"), have become paradigmatic for preventive medicine. Here a distinction is made between screening examinations using ultrasound and further examinations. Should, for example, "abnormal fetal features" be found by screening, further examinations can be introduced by a specialist in order to take therapeutic measures if necessary. The result of "abnormal features" in the scope of prenatal care can also, however, be a termination of pregnancy.

Newborn screening. Newborns are examined for 12 hereditary metabolic diseases in the form of a screening with chemical analysis methods. To do this, a small quantity of blood is taken from the child's heel with the consent of the parent with the right to custody. Every single one of the diseases investigated is rare. On average, one in every thousand newborns has an illness, which would lead to a serious developmental disorder if left untreated. With the appropriate therapy, specific to the indi-

1 Joint Federal Committee (*Gemeinsamer Bundesausschuss*) http://www.g-ba.de/informationen/richtlinien/.

vidual disease, whether it be dietetic or medicinal (e.g. in the case of the absence of the thyroid hormone), the children develop normally. Moreover, screening is carried out for congenital hearing disorders. The early treatment of deafness, for which there are effective methods available today, is vitally important for the language acquisition and mental development of the child. Further examinations are planned throughout the course of childhood and adolescence, which are all recorded in an examination logbook for children.

Clinical/chemical early detection examinations. From the age of 36, all legally insured persons can undergo a medical examination as well as an analysis of laboratory parameters with regard to cardio-vascular diseases, kidney function as well as diabetes mellitus ("Health Check"). This allows normal persons to be clinically monitored in good time and be treated if necessary.

Examinations for the early detection of cancer. The prognosis of some, but unfortunately not yet all, cancers is better the earlier they are detected and treated. They occur more frequently in certain age groups. Screening examinations[2] are therefore recommended in certain age groups and intervals for the common organ carcinomas. Guidelines[3] of professional associations joined together in the Association of the Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, AWMF*) exist for their implementation and for the measures to be taken after an abnormal finding.

Individual preventive care in the family context

Genetic factors have more or less a strong influence on the development of most diseases. Until now, these factors have only been partly known. For a large number of diseases, which are inherited according to Mendel's rules (so-called monogenic diseases), genetic methods are used for their diagnosis. Genetic methods also represent a medically established procedure for prediction. This applies, for example, to hereditary breast/ovarian cancer and the various forms of hereditary cancer of the colon. For genetic carriers, predictive genetic diagnostics could be considered in the form of a so-called cascade screening (see chapter 6): beginning with the index patient, each carrier of the gene in a family can be the starting point for further examinations as regards to their first-degree relatives. The Gene Diagnostics Act (*Gendiagnostikgesetz*) stipulates that the advantages and disadvantages of such diagnostics should be discussed with the person looking for advice in the scope of genetic counselling, in order to allow them and their family to make an appropriate decision.

After the birth of a child with a genetic disease or after an abnormality elsewhere in the family, genetic counselling can provide the family members with the medical information necessary to make their own decision on further family planning. This can also include the examination for a genetic predisposition of a recessive disease which has occurred in the relatives of a person seeking advice.

The Gene Diagnostics Act of 31st July 2009

The increasing possibilities of genetic diagnostics promise additional new knowledge which fascinates many people but also unsettles others. After debates in the German Fed-

2 German Cancer Society (*Deutsche Krebsgesellschaft*): Cancer early detection guideline of the Federal Joint Committee of Doctors and Health Insurers (*Gemeinsamer Bundesausschuss der Ärzte und Krankenkassen*) http://www.g-ba.de/downloads/62-492-410/RL_KFU_2009-10-15.pdf. Overview in: http://www.krebsgesellschaft.de/re_krebsfrueherkennungsuntersuchungen_mann,59012.html and http://www.krebsgesellschaft.de/re_krebsfrueherkennungsuntersuchungen_frau,59013.html.

3 AWMF http://leitlinien.net/.

eral Parliament, which lasted over three parliamentary terms, the area of genetic diagnostics was regulated by law on 31st July 2009[4]. The Gene Diagnostics Act (*Gendiagnostikgesetz*) came into force on 1st February 2010. It is also important for predictive genetic diagnostics (see chapter 9). The statement presented here therefore also elaborates on the relevant legal provisions. Amendment proposals are presented for some of these.

The future of genetic examinations – hopes and fears

Genetic analysis methods have developed rapidly in recent years. Modern genetic methods have been used increasingly consistently for some years for the scientific study of common traits and diseases in society (so-called common diseases) which do not follow a monogenic inheritance model. In the near future, it is highly likely that reliable sequencing of the entire genome of a single person at comparatively low costs will be possible ("1,000 dollar genome"). There is hope that the genetic foundations of the genetically complex diseases will gradually also be better understood, which will potentially result in new treatment possibilities.

However, the extent to which concrete links between genetic variants and diseases i.e. predispositions to diseases can be detected and thus relationships between genotype and phenotype can be established, still remains unclear. If a relationship is great enough, susceptibility to disease can be predicted and treated in due time, provided therapies are available. Genetics could open up new opportunities for secondary prevention. The efficiency of methods must, however, be validated based on experience and the costs must also be taken into consideration.

Yet the problem is very complex. By decoding i.e. sequencing a large part of the individual genome, information on the predisposition to such characteristics and diseases which the person examined had not requested is also discovered. The justification for Section 9 of the Gene Diagnostics Act appropriately uses the term "excess information" for this. This could include information on the predispositions to untreatable diseases, and abnormal features, which cannot be interpreted could arise. This could all lead to significant stress for the individual.

There is widespread fear, particularly in the self-help groups for patients with genetic diseases, that the future possibilities of genetic methods are opening the door to a "genetisation" of society. Genetic examinations of saliva samples bypassing the medical system are already being offered on the internet ("Direct to Consumer Genetic-Testing"). This raises problems of appropriate indication for examination, quality control and the interpretation of findings obtained.

Genetic tests are associated with value questions. It is difficult for the public and in many cases also politics to form a reasonable opinion, given the rapid progress of the development. This is added to by the fact that scientists, doctors and the media interpret results and methods in public differently, create false hopes or fuel fears. It is, however, important that society and those politically responsible are adequately informed. The following document should, as a critical statement, make a contribution to the entire problem area of predictive genetic diagnostics.

4 Law on genetic testing of humans (Gene Diagnostics Act – GenDG) 2009.

2 Genetic and Epigenetic Foundations of Health and Illness

The aim of this chapter is to present the intellectual scientific framework which, according to today's current state of knowledge, can act as a basis for decisions concerning predictive genetic diagnostics.[5] While almost every adult has some idea of the scientific field of genetics, the field of epigenetics has barely even made its way into biology lessons in schools. However, both genetic and epigenetic concepts and findings are essential for a proper understanding of predictive genetic diagnostics, its possible success and its limits in maintaining a healthy human body.

Introduction

The aim of predictive genetic diagnostics and personalised medicine based on this is to help people to remain healthy, to regain their health or to at least alleviate the consequences of the illness. It is subject to the widely accepted and diversely codified ethical principles of medicine. The unique history of human genetics in Germany at the time of national socialism has shown what a violation of these principles can lead to. Today's outright rejection of any eugenic aims is among others expressed in the position paper of the German Society of Human Genetics *(Deutsche Gesellschaft für Humangenetik)*.[6]

The vision of eugenists in the early 20th century was not least based on the ignorance of the complexity of genetic mechanisms. According to the Mendelian way of thinking of many geneticists at the time, genes were considered as intrinsically effective units which control certain phenotypic characteristics. The fact that individual genes could have diverse (pleiotropic) effects on the construction and function of an organism (phenotype) was recognised at an early stage but the significance of pleiotropic gene effects and the extent of existing functional redundancy in genetic networks was long under-estimated. The latest discoveries of epigenetic influences has again deepened the knowledge of the complexity of the relations between genotype and phenotype in an unforeseen way.[7]

"Genetics will have a real influence on all our lives – and an even stronger influence on the lives of our children. It will revolutionise the diagnosis, prevention and treatment of most, if not all, human diseases", said US President Bill Clinton in July 2000 during the provisional closure of the international Human Genome Project[8], the largest biological/medical research project in the world. In actual fact, genetic diagnostics is gaining increasing importance. While the first ever definition of the nucleotide sequence of the human genotype with its 3.2 billion elements cost approx. 3 billion US dollars, the new sequencing systems will allow analysis times and the costs to be drastically reduced to the extent that it should be possible to sequence the genome of an individual for 1,000 US dollars or even less within

5 Müller-Röber B et al. (2009).

6 German Society of Human Genetics (*Deutsche Gesellschaft für Humangenetik e. V.*) (2007) Position paper from the German Society of Human Genetics http://www.medgenetik.de/sonderdruck/2007_gfh_positionspapier.pdf.

7 Cremer T (2010).

8 Human Genome Project http://www.genome.gov/10001356.

a few years. If one also considers that genetic material plays a part in almost every disease, diagnostics at the DNA level will be an important element of personalised medicine in the future. However, the development of diseases (pathogenesis) cannot be reduced to the changing of genes alone. Equally as important are the increasing possibilities of molecular diagnostics at the protein and metabolic molecule level as well as the recording of environmental factors, which are relevant for the cause and progress of a certain, multifactorial disease.

Genetic information

As a carrier of the genetic information, which can be passed on through generations, desoxyribonucleic acid (or DNA) is found in the chromosomes of the nucleus, with the exception of the mitochondrial DNA. Humans have 23 pairs of chromosomes in the nuclei of all normal body cells, one of which are sex chromosomes. The male sex has the sex chromosomes X and Y, the female has two X chromosomes. The remaining chromosomes are pooled under the term autosomes. Each chromosome has a thread-like DNA, which is constructed from two chains wound around each other like a double helix. The entire DNA a human receives from both parents contains approx. 3.2 billion components. Each component consists of a sugar molecule, a phosphate molecule and one of the four DNA bases adenine, guanine, cytosine and thymine. Each adenine molecule in one of the chains is chemically paired with one of the opposite thymine molecules in the other chain, and each guanine molecule is paired with a cytosine molecule. With the exception of genetic material on the male sex chromosomes, all genetic information coded in the DNA in every human exists in duplicate. However, the DNA is not bare; it forms an extremely complex structure with lots of proteins, the so-called chromatin. Recent investigations have made clear that it is not the DNA alone which is the carrier of hereditary information but the chromatin as a whole.

The genome of a human cell contains approx. 25,000 genes, the DNA base sequence of which is required for the formation of specific proteins. These genes can be compared to a huge orchestra which exists in every cell. This "genetic orchestra" seems to play its cell-type-specific music without a conductor. In addition, there are many DNA fragments which do not encode for proteins and which have regulatory functions. Molecules, which are produced by neighbouring cells or even far away cell groups of the body, and not to forget environmental influences also play an important regulatory role. This results in a gene expression pattern of the trillions of cells in the human body tailored to the needs of the individual tissues and the entire body. Using the idea of the orchestra, this is the tuned "genetic music" of these cells.

The variation of a gene is only a component in this complex system, whereby the metabolic state can differ greatly from person to person as a reaction to genetic changes. The example of research into the human genome clearly shows how, on the one hand, an insight into the complexity of the relations between genes and normal or pathogenic physical characteristics is achieved through reductionist methods but, on the other hand, how closely the formation of concept and theory is interconnected with this. After it was discovered at the start of the 20th century that there are also human characteristics, i.e. diseases which are inherited according to Mendelian laws, this information was very quickly generalised to the inheritance of all possible characteristics. Thus, a gene was equated with a phene. Even if the empirical findings were not consistent with a simple mode of inheritance, people tried to save the validity of a monogenic mode of inheritance with auxiliary hypotheses. In actual fact, the significance of an individual gene can be most easily deduced when it is spontaneously modi-

fied by a mutation and leads to a modified phenotype. In this respect, the effect of the variant gene can be analysed against the background of all other genes.

In the mid 19th century, Gregor Mendel carried out groundbreaking cross-breeding experiments with pea plants, which proved that the yellow or green colour of a pea was clearly genetically determined. A gene existing in duplicate for this colour (as is also the case for all human genes) appears in two modifications (alleles). In order to produce a yellow pea, one allele for this colour is enough, even if the second allele produces the colour green. Mendel called this mode of inheritance dominant. In order to create a green pea, both alleles have to produce the green colour. The genotype for both gene copies considered here is homozygous if both copies are identical and heterozygous if both copies are different. Environmental influences, for example, fertilisation and watering, do not play any role. There are also a large number of human Mendelian diseases, the inheritance of which has proven to be just as genetically determined as the colour of peas. This causal relationship between the genotype and the phenotype, that is the impact on certain visible or measurable characteristics which can be presented on individual examples, leads people to believe that they know more than they actually know. The previous discussions on the effects of the genome project on diagnostics (keyword: "the transparent man") show that these beliefs still exist.

The significance of monogenic characteristics

Since the laws of inheritance first phrased by Gregor Mendel[9] were rediscovered at the beginning of the 20th century, monogenic characteristics have played an important role in genome research in general and in particular in human genetics. The simple, i.e. dominant or recessive mode of inheritance of a trait verifiably demonstrates a specific genetic cause. If the relevant genetic variant is located on one of the 22 human autosomes, then the mode of inheritance is described as autosomal. A trait is called autosomal dominant if an allele or a mutation in one of the two homologous genes, which are localised at the same location of a pair of existing, homologous autosomes, is enough to cause a phenotypical manifestation (Mendel's example of the yellow peas). It is autosomal recessive if both homologous genes have to be changed (mutated) in order to cause a phenotypical manifestation (Mendel's example of the green peas). As already mentioned, the genetic status (homozygous or heterozygous) at a certain gene locus is called the genotype. A dominant modified gene is, on average, passed on by carriers to half of their children, regardless of the sex. It can be traced over generations in families concerned using the clearly different phenotype of the carrier. A recessive trait normally appears in siblings in a family who are homozygous as regards the homologous genes required for the development of characteristics. Heterozygous parents who are carriers of one normal and one changed gene are, however, usually phenotypically normal but can be identified on closer examination. The term Mendelian hereditary disease for monogenic illnesses, in which the underlying genes are inherited according to Mendelian laws, is firmly established. Despite the linguistic abbreviation it must not be forgotten that it is not the phenotypical characteristics but genes, which are inherited and that the genotype does not necessarily determine the affected phenotype in many monogenic diseases. It has long been known from family observations that not every variant genotype also has to phenotypically develop according to the Mendelian inheritance model. This particularly applies to the dominant mode of inheritance.

9 Mendel GJ (1866).

This is called reduced penetrance. The expressivity, which is considered as the phenotypical intensity and severity of a monogenic disease, can also differ greatly amongst those concerned, even if the same mutation is responsible. This can be due to the fact that various alleles of other genes and/or environmental factors influence the effect of the mutated major gene, which is decisive for the development of the disease in different ways.

It is essential that we caution against the careless use of non-scientific expressions such as "healthy" or "ill", "good" or "bad" genes. Alleles which appear at a certain location can have advantageous or disadvantageous phenotypical effects, depending on the environmental influences. For example, the ability to consume milk and the lactose contained in it as a child and adult (lactose tolerance) represents an evolutionary advantage when settling in regions with little sunshine (due to the increased intake of calcium and better formation of bones). Babies can digest the lactose in breast milk all over the world. After weaning, however, children in some parts of the world develop a lactose intolerance. The cause of this is the inactivation of a gene which codes for an enzyme required for the breakdown of lactose. If these persons continue to drink milk, they suffer severe colics as now the bacteria in the colon ferments the lactose. This means carriers of the normal gene have a health-related disadvantage in these environmental conditions. However, the effect a certain allele has on human health can also depend on the availability of the second allele in the same gene locus and other alleles on other gene loci. The risk-benefit evaluation of an allele is therefore not to be carried out in isolation, but in the context of the unique combination of all genetic variants of an individual and their particular environment. The multitude of human genotypes is of great value as it allows humans to adapt to different environmental conditions.

In the history of human genetics, the simple mode of inheritance played an important role during the first half of the 20th century, a time the importance of DNA as a chemical-physical foundation in inheritance was not yet known. The change in physical (phenotypical) characteristics provided the first insight into the "black box" of inheritance.[10] Thousands of monogenic diseases were differentiated based on their particular phenotype and mode of inheritance and have been collected in an encyclopaedia by human geneticist Victor McKusick since 1966. Most of these diseases are a result of mutations in genes which code for certain proteins. Examples are cystic fibrosis (mucoviscidosis) and spinal muscular atrophy (both automal recessive), Huntington's disease and Marfan's syndrome (both autosomal dominant), haemophilia A as well as Duchenne muscular dystrophy (both X-chromosomal recessive). The change in the nucleotide sequence of such a gene caused by mutation produces a change in the amino acid sequence of the protein coded by this gene. However, there are also other mutation mechanisms which can lead to genes being altered in some tissues or development stages into RNA molecules which themselves are practically relevant, i.e. which are not decoded into proteins (e.g. the group of the microRNA). Moreover, a multitude of proteins with various functions can be produced from one gene through different forms of processing at an RNA level (alternative splicing). Disorders in this system can also be involved in the development of diseases.

In the scope of the Human Genome Project, the DNA base sequence of the human genome was almost completely decoded. So far more than 2,000 genes have been identified, the mutation of which leads to approx. 3,500 monogenic diseases, most of which are rare (frequency is less than 1:2,000). In these cases, the prerequisites for a diagnostic of the

10 McKusick VA (1966-1998).

mutations which cause the diseases are given. In total 3 to 4% of newborns are affected by a monogenic disease.[11] The majority of these diseases become apparent during childhood. The remaining ones only become apparent later on in life, sometimes several decades after birth.

Multifactorial (genetically complex) diseases

Diseases, which are common in society (such as diabetes mellitus, cardio-vascular diseases, allergies, psychological diseases) differ from the monogenic diseases in that, although they show a certain familial frequency, they have no clear inheritance mode. The disease expressivity such as the age of onset and the severity vary greatly. They are based on the interaction of hereditary and environmental factors. Most of these diseases are said to develop through various genetic mechanisms.

Archibald Garrod's[12] concept of "biochemical (today we would say "genetic") individuality" understands disease not only as the opposite of health but as a disorder of the homeostatic, i.e. the self-regulating network which is the result of a long evolutionary process. This network represents a strongly buffered system which can compensate detrimental effects. Changes to individual genes only affect individual components of the system. Accordingly, the individual reaction to such changes is variable.[13]

Monogenic sub-types are, however, known in many multifactorial diseases. The exact genetic facts are usually not identifiable in the individual cases of ill persons; suspicion can only arise for the doctor based on the family constellation. Examples are the dominant forms of breast and colon cancer, the dominant form of Alzheimer's disease and the dominant form of hypercholesterolemia. In these cases the monogenic forms represent a small part of the predominantly multifactorial diseases; these are genetically complex.

The genetic individuality of a human is, for example, a possible explanation for the differing levels of susceptibility to infectious agents or civilisation diseases and for the individually different reactions to the intake of certain medicines. With the knowledge of a genetic predisposition, a manifestation of a disease can often be alleviated, delayed or prevented completely by suitable preventive measures. We can assume that every human has different degrees of genetic predispositions for several multifactorial diseases in their genetic make-up.

In recent years, the number of identified genetic variants, which produce a predisposition for various multifactorial diseases, has significantly increased. It will, however, take considerable time for their genetic set of conditions and their clinical relevance to be clarified. The genetic complexity of the multifactorial diseases is much more demanding in terms of genetic analysis than it is for monogenic diseases.

If you consider the outstanding technical progress in DNA sequencing, then it is conceivable that sequencing complete genomes of populations with genetically complex diseases and comparing this with suitable test groups will open up the opportunity to identify all disease-related differences in the DNA sequence. This research strategy can help to uncover the genetic contributors to multifactorial diseases. The difficulty when interpreting such extremely large data records is in distinguishing between disease-relevant differences and irrelevant differences.

Using the new sequencing technology, the genomes of a few healthy people have been completely sequenced, whereby it appears that each person carries a large number of

11 EURORDIS (2005) Rare diseases: understanding this public health priority http://www.eurordis.org/IMG/pdf/princeps_document-EN.pdf.

12 Garrod AE (1908).

13 Cremer T (2010).

disease-related mutations ("deleterious mutations"), usually in the heterozygous form.[14] The location of the variants, i.e. mutations in the genome, their functional effects and their frequency in the population make the overall picture increasingly complicated.[15] At present, the genomes of 1,000 healthy people from various ethnic groups in the world are being fully sequenced under the management of the English Sanger Wellcome Centre ("1,000 Genome Project"), in order to record the genome variability amongst healthy people.

One of the biggest tasks will be to distinguish between the pathogenically important sequence changes and the many functionally unimportant variants. The availability of large cohorts of clinically well-characterised patients (and test persons) is extremely important as regards the disease research.

The role of the genome, the epigenome and the environment in the individual development of humans, the maintenance of their health and the development of diseases[16, 17]

The development of any human, their health and the formation of diseases are a phenotypical expression of interactions between all their genes (genome), the packaging and organisation of the genetic material in the chromatin of the nucleus (epigenome) and environmental influences. The moment a human begins to develop is generally considered to be the end of the fertilisation of the oocyte and the unification of both parental genomes. As all body cells ultimately develop from the fertilised oocyte (zygote) through repeated cell divisions (mitosis), they also all receive (with a few exceptions) the same genome, i.e. the entire DNA has the same base sequence in every cell. This implies that, in principle, a molecular-genetic diagnosis can be carried out on any body cell and at any moment in the development, including long before birth (prenatal diagnosis) or throughout life, decades before the onset of a disease (predictive diagnosis).

The British biologist Conrad Hal Waddington introduced genetics in embryology in the middle of the last century and established the field of epigenetics.[18] The term "epigenetics" which he coined, is a fusion of the words "epigenesis" and "genetics". Waddington defined epigenetics as the study of the interaction between genes, their products and external factors which create the phenotype. He saw the developing organism as a self-organised system which is characterised by robustness (Waddington spoke of canalisation) and plasticity. Robustness and plasticity mean that the development course of a cell or organism does not change in the case of small disorders but does change during sensitive development stages as a result of certain influences.

Although the field of epigenetics is now 70 years old, it has only experienced a breakthrough in the last 20 to 30 years. This has primarily been made possible through progress in molecular biology and genetics. Today we know that cells of various tissues and development stages differ in the quantitative and qualitative expression of numerous genes. While certain genes are active in a certain cell at a certain time, other genes are inactive. The activity of genes is determined by the methylation of cytosine in the DNA and enzymatic modification (acetylation, methylation, phosphorylation) of histone proteins, around which the DNA is wound. These patterns can remain stable over several cell divisions (canalisation) but can also generally be modified (plasticity).

14 Chun S, Fay JC (2009).

15 Cooper DN et al. (2010).

16 Berlin-Brandenburg Academy of Sciences and Humanities (*Berlin-Brandenburgische Akademie der Wissenschaften*) (2009).

17 Sperling K (1999).

18 Waddington CH (1966).

The changeability of these patterns is convincingly shown in the reprogramming of the genome of a differentiated cell through nucleus transfer into an enucleated oocyte (the cloned sheep Dolly) or through transfection with pluripotent factors (induced pluripotent stem cells, iPS). Totipotent or pluripotent cells can be produced through reprogramming.

Chromatin marking through methyltransferases and other enzymes is an example of the interaction between genes and gene products postulated by Waddington but only presents one of four epigenetic systems. Other systems are regulatory RNAs, auto-regulatory feedback loops and self-maintaining structures. A common feature of all factors is that they can exist in various, metastable conditions.

How significant is epigenetics for human development and its disorders? There are numerous epidemiological studies which prove the importance of prenatal and postnatal events for later life. Barker was the first to discover that low weight at birth is correlated with an increased risk of cardiovascular disorders in old-age.[19] This and other similar observations are summarised under the phrase "fetal origin of adult disease". The hypothesis implies that unfavourable influences during the prenatal development and early childhood can lead to permanent changes in the gene expression, the number of cells in a tissue, the receptor density on a cell, the physiology and the metabolism of a human, so that there is an increased risk of age-related diseases. Amongst the unfavourable influences are a lack and excess of nutrients as well as stress hormones during pregnancy. In early childhood these influences are a wrong diet as well as neglect by the parents. These relationships are not new; what is new, however, is that molecular epigenetics is now capable of understanding the genetic and cellular mechanisms of this imprinting. Whether such characteristics in humans can be inherited from one generation to the next is often disputed.

The importance of genetic and epigenetic influences for the development of disease has been convincingly demonstrated using the monogenic disease, Angelman syndrome. This serious development disorder is based on an epigenetic and/or genetically determined functional disorder of germ cells. The responsible gene is only active in the relevant tissues if it is passed on to the child from the mother, while the gene inherited from the father remains inactive. The epigenetic process which leads to this difference is called imprinting. Another clinically relevant example is the inactivation of tumour suppressor genes through epigenetic mechanisms in somatic cells. The malfunction of such genes plays an important role in the development of tumours, for example, if a tumour suppressor gene can no longer be transcribed as a result of a faulty chromatin marking. Nowadays the first steps are being made to reactivate such genes through a pharmacologically induced change in the chromatin marking.

The findings of epigenetics are still too new to be able to evaluate their importance for predictive diagnostics. The relationships which were merely indicated here, should make clear that simple Mendelian inheritance concepts are no longer sufficient and why this is the case. In this context, for example, the predictive value of DNA variants can be largely restricted or even zero as a result of the plasticity of the development.

Chromosomal aberrations

In human cells capable of cell division, the number and structure of the individual chromosomes can be investigated during mitosis under a microscope with a 1,000-fold magnification. Nowadays, it is possible to make all chromosomes and even individual genes directly visible in the nucleus even during the

19 Barker DJ, Osmond C (1986).

interphase, the cell stage between two mitoses. These examination methods have discovered a multitude of innate chromosomal aberrations which relate to the number or their structure. Such chromosomal aberrations are generally connected to serious health effects, especially innate malformations and mental disability, as a large number of genes are often either lost or duplicated. Down Syndrome is particularly well-known, whereby the chromosome 21 appears in all nuclei of a person concerned in three copies instead of two (trisomy 21).

Such faults, which, in principle, can affect each of the 23 chromosomes, often appear in the formation of germ cells, especially in the formation of the oocyte. The majority of these faults lead to the embryo dying early and are the most common cause of miscarriages.

When chromosomal fragments are exchanged between various chromosomes, this is called a translocation. If no genetic material is lost or gained during this process, then the chromosomal aberration is balanced and its carrier is generally healthy. However, a loss or gain of genetic material results in an unbalanced condition. The carrier of a balanced translocation, however, has an increased risk of their children having an unbalanced translocation. Examining other family members often also uncovers other carriers of the balanced translocation due to the inheritance of the chromosome aberration.

If the siblings of a patient who shows an unbalanced chromosomal aberration are examined, then a statement is made about whether their children have an increased risk for an unbalanced chromosomal status. This is a form of predictive genetic diagnostics. In the sketched constellation it is part of genetic counselling, as a chromosomal imbalance is generally associated with a serious negative impact on the health of a person.

Today chromosome analysis is no longer limited to cells which are capable of cell division but can be carried out on any cells. To do this, the DNA is extracted and hybridised on DNA chips which can have more than 500,000 different sequences of the human genome. Microdeletions or microduplications, which can include less than 1,000 DNA base pairs and can exist in various copy numbers, so-called "gene copy number variants" (CNVs), can therefore be detected in a single test. In comparison to the diploid genome of a human with approx. 6 billion base pairs, this involves less than the millionth part of the entire genome. A few years ago CNVs were still unknown. On average, two humans have approx. 80 genes which differ in their number of copies.[20] The possible consequences of this range from neutral polymorphism to pathogenic or even protective effects.[21]

Mitochondriopathies

The mitochondria, the "power plants" of the cell, have their own ring-shaped genome, which codes for 37 genes and which are almost exclusively passed on to the offspring from the oocyte of the mother. The number of mitochrondria per cell can be well over one thousand, especially for cells with a high energy demand. When detecting mutations in the mitochrondial genome the problem often arises that, in addition to mitochondria with mutations, the person concerned shows functionally sound mitochondria (heteroplasmy), the relative number of which can vary between various tissues. All prognostic statements are correspondingly difficult. A defect of these genes has a detrimental effect on the energy balance of the cells, whereby several organs are regularly affected.[22] Somatic mutations of the mitochondrial genome play an important role in the ageing process.

20 Alkan C et al. (2009).
21 Beckmann JS et al. (2008).
22 Finsterer J (2004).

3 Medical Context of Genetic Diagnostics

Clarifying the genetic foundation of monogenic diseases opens up the opportunity for the molecular safeguarding of the clinical suspicion of a monogenic disease, specification of the prognosis, predictive diagnostics of monogenic diseases with a late onset, prenatal diagnostics and genetic screenings.

Causal gene mutations can be identified in around 3,500 monogenic diseases. The number of monogenic diseases which are still unknown is definitely several times higher.[23] Thanks to modern methods for genome sequencing, this situation will, given the appropriate support, change fundamentally. However, given the large number of possible mutations (so-called allelic heterogeneity) and against the background of functionally irrelevant variants, it can still be difficult to identify the mutation responsible for a monogenic characteristic in individual cases.

The diagnosis of a clinical picture is primarily based on the clinical symptoms. This was traditionally also the case for monogenic diseases. Attributing clinical pictures to mutations in the DNA has triggered a fundamentally new direction also in clinical medicine. Thanks to the clear molecular genetic classification of many clinical pictures, more precise diagnostics, easier to plan therapies, and safer prognosis have been made possible. 30 years ago, the life expectancy of a patient with cystic fibrosis was 10 years, today it is estimated at 30 to 50 years in centres which specialise in this disease, whereby it is predicted that the course of certain genotypes will be less serious.

23 Ropers HH (2007).

The molecular safeguarding of the clinical suspicion of a monogenic disease

Clinical diagnoses are often uncertain. This is primarily true for the initial stage of the disease, i.e. the time at which secondary preventive measures must be started. Clinical diagnostics is therefore traditionally supplemented by medical laboratory and imaging techniques (X-ray, ultrasound and the like). Genetic tests complement these examinations. As they are not concerned with symptoms but with cause, genetic tests produce an unmatched depth of knowledge. In a monogenic disease, the same clinical symptoms can materialise as a result of mutations in various genes. The reverse is also possible: various diseases are the result of various mutations in the same gene.

There are an increasing number of examples in which the results of genetic tests lead to important therapeutic, i.e. preventive decisions. In the case of Long QT Syndrome, a very heterogeneous genetic disease group with often fatal heart rhythm disorders, the treatment is increasingly based on the respective underlying genotype.[24] In the case of hereditary connective tissue diseases, which involve a high risk of life-threatening dissection (splitting) of the aorta (Marfan syndrome and related syndromes), the timing of a prophylactic aorta replacement is determined by the gene[25] which shows a mutation responsible for disease in the patient. A third example are

24 Lu JT, Kass RS (2010).

25 von Kodolitsch Y et al. (2010).

the various forms of cystic kidneys (autosomal recessive hereditary cystic kidneys, ARPKD; autosomal dominant hereditary cystic kidneys, ADPKD). Children with ARPKD can be born with severely changed kidneys and, under conventional therapies, may have limited viability at best. On the other hand, early bilateral nephrectomy and consequent kidney transplantation can give such children a chance to live, provided a donor organ is available. In the case of ADPKD, the symptoms usually begin in adults and dialysis therapy or transplantation can give many patients an almost normal life expectancy. A prenatal diagnostic can be considered but is not undisputed if a termination of pregnancy is considered.

In this context, pharmacogenetics should also be mentioned as a special dimension in genetic diagnostics. The effect of a medicine can be influenced by genetic factors both in terms of the (desired) effect of a medicine as well as (undesired of course) side effects. The number of known, clinically important pharmacogenetic phenomena has been limited up until now. The possibilities for molecular genetic analysis should make discovering new, also clinically relevant pharmacogenetic mechanisms much easier.

Some of the classic examples of pharmacogenetics-related disorders are porphyria, a complex clinical picture with abdominal colic and sometimes psychiatric symptoms which can be triggered by alcohol and a number of medicines, and malignant hyperthermia, a life-threatening disorder in the body temperature regulations as a reaction to anesthetics.

A pharmacogenetic phenomenon which is relevant for 10% of people in Central Europe concerns the medicine Tamoxifen. It is administered to women who have had an operation as a result of breast cancer. If the tumour tissue which was postoperatively examined proves to be estrogen receptor positive, then it is wise to administer Tamoxifen for several years. The substance counteracts the development of a breast cancer relapse. Tamoxifen is itself, however, not effective; it must be transformed into an active form through a body's own enzyme. Due to genetic reasons, the necessary activation of the medicine fails to materialise in approx. 10% of Europeans.[26] These women should receive different treatment. An appropriate genetic examination of these patients before beginning the therapy is therefore recommended.

The developments of genetics and genomics have, in their application, introduced the concept of "personalised medicine" to medical problems. The best possible therapy for each individual should be found using elaborated differential diagnosis and the personal selection and/or dosage of therapeutic substances which are comparatively the most effective and have the least possible side effects for the person to be treated. It is to be assumed that, in the near future, numerous other gene variants which individually control the reaction of the medicine will be identified. Also possible are polymorphisms of anonymous DNA markers (SNP profiles) which allow predictions to be made about genetically influenced reactions to medicines, without any knowledge of the underlying genes.

Specifying the prognosis

The findings of genetic tests are, to a certain extent, suitable for specifying the prognosis in individual cases, particularly if there is a definite correlation between a certain genotype and a certain phenotype. Here are a few examples of this:

1. Numerous mutations in the CFTR gene can lead to a clinical picture of an autosomal recessive mucoviscidosis (cystic fibrosis). Some mutations, however, appear with partial symptoms (e.g. infertility as the sole

26 Schroth W et al. (2009).

expression of the disease) or they are signs of an extremely positive course of the disease.

2. Mutations in genes which code for enzymes with enzymatic residual activity show a milder disease course than mutations, which lead to a complete loss of enzymatic activity.
3. The greater the expansion of the trinucleotide CAG in the Huntington gene, the earlier the person concerned will suffer from the symptoms of Huntington's disease.
4. In the case of the autosomal dominant hereditary familial adenomatous polyposis, the age of onset of the disease depends on the position of the mutation in the gene.
5. Autosomal recessive hereditary spinal muscular atrophy develops as a result of homozygosity for a disease-related mutation in the SMN1 gene. The degree of muscular atrophy can, however, be compensated depending on the number of SMN2 genes a person has.

Predictive diagnostics of monogenic diseases with a late onset

The possibility of detecting predispositions potentially decades before the actual outbreak of the disease represents the real new dimension, which places genetics at the centre of the current discussion. In order to better understand its medical, psychological and social effects, predictive genetic tests must be viewed in context.

Today, the use of a predictive tests is primarily discussed if a person has an increased risk of a monogenic disease as a result of previous family history. Examples of these are familial cancers (breast, colon, thyroid cancer), neurodegenerative diseases, Huntington's disease, spinocerebellar ataxias, spinal muscular atrophy, various metabolic diseases, immune deficiency diseases, haemochromatosis, the dominant form of hypercholesterolemia and a genetic predisposition to thrombosis (thrombophilia).

A predictive genetic diagnostic procedure can be a great help for healthy persons who have a high risk of a late manifesting hereditary disease as a result of a family history. On the one hand, in many cases an exclusion of the risk can be a relieve for the person being examined. On the other hand, evidence of a mutation which causes disease can also be a help, as the disease concerned can be avoided through preventive measures or can be treated more effectively with early therapy. In the case of hereditary colon cancer (Lynch syndrome, hereditary nonpolyposis colorectal cancer, HNPCC) it has recently been shown that, for high risk persons, the existing carcinoma can be successfully diagnosed using systematic colonoscopies at an early stage.[27, 28, 29] Early stages of colon cancer can be cured to a large extent by an operation. There is every indication that this leads to a considerable increase in life expectancy.

In the case of late manifesting diseases, which medicine has very little or no effect on, e.g. neurodegenerative diseases, high risk persons request a predictive genetic diagnostic much less often than those with easily treatable diseases. Experience shows, however, that some people want to have the predictive knowledge to plan their life and be able to come to terms with the bad news.

The predictive diagnostics of a hereditary disease can nevertheless be connected with psychological, social or financial problems for the person examined. The predictive diagnostics of a disease which is generally treatable, for example, breast cancer or colon cancer, can also cause problems. For this reason, it has long been standard practice that a predic-

27 Engel C et al. (2010).
28 Järvinen HJ et al. (2009).
29 Vasen HFA et al. (2010).

tive genetic diagnostic procedure is preceded by genetic counselling.[30] In this genetic counselling, the person seeking advice is informed about the disease, its course, its treatability, the type of inheritance, the possibilities for genetic diagnostics and the possible psychosocial consequences. Predictive genetic diagnostics usually affects whole families. The members of a family must discuss the disease and its inheritance. Firstly, the causal mutation must be identified in the sick family member. After this, the other family members can be examined in a cascade-like programme to discover whether they are carrying the mutation concerned. If the mutation has been excluded for one person, then the risk for the disease in question is not increased. The burden can be removed from the person examined and their descendants. However, if the mutation is detected in a family member, then an age-dependent, usually high risk of disease (see chapter 4) exists and the person examined must be informed of this in an appropriate manner. The genetic counselling is carried out in the context of an interdisciplinary counselling and monitoring concept by the human geneticists in cooperation with the respective organ, i.e. disease experts and, if necessary, psychotherapists too.

The request for predictive genetic diagnostics should be handled with particular care in the case of untreatable diseases. Huntington's disease has become paradigmatic for this. Very soon after attributing the responsible gene locus, i.e. before identifying the gene, recommendations were presented by geneticists, neurologists and self-help groups for handling predictive genetic diagnostics in the case of this disease.[31] In addition to genetic counselling, these include a psychotherapeutic consultation as well as a minimum period of time between the decision for predictive diagnostics and its implementation. The recommendations have also been applied for a long time in the context of other late manifesting neurodegenerative diseases.

After appropriate counselling, the possibility of predictive diagnostics is used with different levels of frequency, depending on whether a disease can be treated or not.

Prenatal diagnostics

Some diseases and developmental disorders could be detected in prenatal examinations even before the genome era, either by using chromosome analysis methods (cytogenetics), biochemical methods, or at a phenotype level with imaging techniques. A serious disadvantage of phenotype examination methods such as ultrasound is the, often very late, point in time at which a malformation can be clearly diagnosed or assessed. For most women, deciding on a termination in the second or even last trimenon of pregnancy is either very difficult or they feel such a late termination is completely unreasonable. Genetic tests, however, can always be carried out as soon as embryonal or fetal DNA can be obtained, i.e. practically from the middle of the first three months of pregnancy. However, the chorionic villus biopsy for the prevention of procedure-related damage to the embryo is only taken after the 11th week of pregnancy. In this respect, all diseases and developmental disorders for which a direct or indirect genetic test is available can, in principle, be diagnosed in prenatal examinations.

These diseases also include those which generally become apparent in the individual at a much later development stage (adulthood, old-age)[32], such as familial cancers and

30 German Society of Human Genetics (*Deutsche Gesellschaft für Humangenetik e. V.*) (2007) Position paper of the *Deutsche Gesellschaft für Humangenetik* http://www.medgenetik.de/sonderdruck/2007_gfh_positionspapier.pdf.

31 Went L (1990).

32 However the regulations in Section 15, Paragraph 2 of the Gene Diagnostics Act must be observed in this regard (see chapter 9).

neurodegenerative diseases. Furthermore, it is technically possible to detect genetic disorders with a low clinical significance and genetic or genetically influenced normal characteristics in prenatal examinations. This potential fuels fear amongst many people that prenatal diagnostics is being broadened in a legally and ethically unjustifiable manner. However, after 35 years experience with this invasive procedure in Germany there is no empirical evidence of an excessive use of prenatal diagnostics induced by genome research. The burden of a termination of pregnancy means that pregnant women only ask for a prenatal diagnostic procedure if there is increased risk of serious health-related disorders for their child.

An invasive prenatal diagnostic procedure (amniocentesis, chorionic villus biopsy, fetal blood sample) is carried out on approx. 10% of pregnant women in Germany and essentially on the basis of four indications:

1. The majority of the examinations are used to exclude a numerical chromosomal aberration due to the older age of the pregnant women.
2. If an ultrasound finding indicates a possible chromosomal aberration, the suspicion is followed up by a prenatal chromosomal examination.
3. A couple already has a child who is affected by a serious genetic disease. During the next pregnancy, the parents want a targeted prenatal examination for the genetic disorder.
4. An autosomal or X chromosomal recessive hereditary disease has occurred in the relatives, e.g. the sibling of a parent. In order to assess the risk of disease for their potential child, the prospective parents want a targeted examination for heterozygosity for the disease concerned. Should a risk constellation be found in the couple, they would either avoid having their own children or seek a prenatal diagnostic procedure.

The examinations in the scope of the indications stated here are carried out after extensive explanation and should be integrated into genetic counselling.

The use of genetic tests allows diseases and developmental disorders to be diagnosed even before the pregnancy has occurred i.e. preconceptual (polar body diagnosis) or in a preimplantation procedure on blastomeres. These procedures can only be used in connection with in vitro fertilisation. Preimplantation genetic diagnosis (PGD) is used in a number of countries, including Germany's neighbouring countries. The legitimacy of the procedure was contested in Germany as a result of the Embryo Protection Act; it is widely believed that PGD was banned under the Embryo Protection Act (*Embryonenschutzgesetz*). Many couples who have a high risk of having a child with a serious hereditary disease and who can afford it, have these examinations carried out outside of Germany at their own cost. On 6th July 2010, the German Federal Court of Justice (*Bundesgerichtshof*) ruled in a leading decision that the use of PGD in the examination of a non-totipotent cell in order to determine a serious genetic disorder does not violate the Embryo Protection Act.[33] The court stressed that this does not pave the way to an unlimited selection of embryos using genetic characteristics, for example, the selection of embryos to lead to the birth of a "perfect daughter" or a "perfect son". The exact limits of the legitimacy of PGD, however, still remain unclear.

Due to their high sensitivity, genetic test procedures are generally also suitable for carrying out examinations on the foetal cells which can be isolated from the mother's circulation in small quantities. The advantage of this procedure, which is still developing today, would be the fact that the use of a risky invasive procedure can be avoided. One of the many

33 *Bundesgerichtshof*, Press office http://juris.bundesgerichtshof.de/cgi-bin/rechtsprechung/document.py?Gericht=bgh&Art=pm&pm_nummer=0137/10

unsolved problems is that fetal cells circulating in the mother's circulatory system may come from a previous pregnancy.

Parents who have had a child with a serious and untreatable genetic disease are familiar with the risk of repetition for their other children. They are forced to make a decision: accept the risk, avoid having any more children, adopt someone else's child or insemination using donor sperm in the case of an autosomal recessive disease. One way of preventing the birth of another child affected by the disease is prenatal diagnostics. A number of parents decide upon this option in their despair.

It must be highlighted here that the use of the term prevention in connection with prenatal diagnostics can be unclear. In terms of public health, all measures which reduce the prevalence of a disease primarily have a preventive effect. However, if a prenatal diagnostic procedure leads to a termination of pregnancy, then it is not a disease which is prevented but the birth of a human being with the disease. Here the term prevention has completely different medical, ethical and psychosocial implications than it does in other medical connections.

Genetic screenings

Screenings for genetic diseases are carried out across the world in the scope of newborn screening programmes. In Germany, newborn screening currently covers 12 prevailing genetic metabolic disorders which lead to serious illnesses if left untreated. Among these are phenylketonuria and the congenital thyroid hypofunction (hypothyreosis). However, the newborn screening practiced in Germany is exclusively used to prevent illness. Children develop normally and have a normal life expectancy if the disease is detected early enough and treated immediately. If the disease were one which developed in childhood, testing would also include haemochromatosis. However, as this iron metabolism disorder (it involves an abnormal storage of iron in several organs, which results in serious functional failures) only appears in adulthood, there is no established framework for a corresponding screening. Pilot projects are now being launched in several countries (including the US, Australia and Germany), in which suitable conditions for such programmes are being researched.

A special form of predictive diagnostics is heterozygote screening. This does not concern the disease risk of the person tested but the disease risk which could firstly develop in their descendants. For some diseases this has already been proven for decades now. This form of predictive genetic tests is practiced in numerous countries around the world in the scope of national prenatal programmes, for example, in the Mediterranean countries to determine the predisposition to beta-thalassemia (a form of hereditary anaemia) or in the Ashkenazim Jewish society to identify carriers for some common metabolic diseases here, the Tay-Sachs disease among others. Carrier screening for cystic fibrosis (CF, mucoviscidosis) was only made possible thanks to genome research. Given a life expectancy of up to 50 years, this is problematic because patients could be stigmatised and discriminated and given the impression that they are not welcome (see chapter 6). Since 2001, every American gynaecologist is obliged to offer all pregnant women or women planning a pregnancy a CF carrier test, based on the recommendation of their professional association.[34] The consequences the doctor could face should they fail to observe this recommendation and the fact that test offers during the pregnancy regularly have high rates of use should lead to cystic fibrosis becoming significantly less common as a disease in the US – similar to beta-thalassemia in Sardinia, where carrier screening is carried out very strictly.

34 Grody WW et al. (2001).

Eugenic motives can be said to be behind some of the screening programmes practiced abroad, if one considers eugenic motives to be all those measures which should influence the reproductive decisions of individuals in order to achieve a healthier population.[35] In Germany, where the there is great sensitivity towards eugenic tendencies, such programmes have always been rejected after the Second World War (see memorandum "Genetic Screening" of the German Medical Association *(Bundesärztekammer)*, 1992)[36].

Despite all regulations, there is the danger that a screening situation with eugenic motives will gradually set in even without an organised programme because standards, which put pressure on parents, could be established through a social, individually motivated practice. The German Gene Diagnostics Act (*Gendiagnostikgesetz*) prohibits a formal, broadly based carrier screening but does not prohibit individually requested examinations of this kind (see chapter 9).

Information sources

A large number of internet sources, which accurately reflect the current state of science thanks to rigid quality assurances, are available to provide information on genetic (co-) determined diseases and their management at a glance. To be named first is OMIM[37] (Online Mendelian Inheritance in Man), a catalogue of diseases which are caused by mutations in individual genes including a brief description of the clinical pictures. Orphanet[38] is the world's largest and most frequently used data platform for rare (primarily genetic) diseases, with information on research projects, treatment centres, diagnostic laboratories and patient organisations. The GeneTests[39] database is a textbook-style database of the US American National Institutes of Health with extensive information on the symptoms, genetics, diagnostics and therapy of monogenic hereditary diseases.

The problem of predictive genetic diagnostics in multifactorial diseases

In recent years, patients and their family members have also been requesting genetic tests for genetically complex (multifactorial) diseases, i.e. disorders where several genetic factors and especially environmental conditions also play an important role (see chapter 2). These include, for example, diabetes mellitus, coronary heart disease, allergies, rheumatic diseases, cancers and psychoses. It is difficult to distinguish between genetically complex diseases and monogenic diseases as even the latter only rarely really follow the traditional deterministic Mendelian laws. The genetic factors which contribute to the onset of complex diseases are regarded as susceptibility genes. So far, hundreds of such genes have been identified.[40, 41] The probability of a disease can be specified for a given genotype in the form of a positive predictive value (see chapter 4). The influence a single genotype has on the development of a disease is generally low, meaning that it is not suitable for a risk assessment of an individual person. It is also not surprising that part of the published genetic association findings could not be confirmed by other investigators. This can, for example, be based on the fact that the

35 Holtzman NA (1989).

36 German Medical Association (*Bundesärztekammer*) (1992) Memorandum on Genetic Screening (1992).

37 OMIM (Online Mendelian Inheritance in Man) http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim&TabCmd=Limits.

38 Orphanet http://www.orpha.net.

39 GeneTest http://www.ncbi.nlm.nih.gov/sites/GeneTests/?db=GeneTests.

40 ESHG Background Document https://www.eshg.org/fileadmin/eshg/documents/20090519DraftBackgroundDocumentGeneticTestingandCommonDisor.df.pdf.

41 Ku CS et al. (2010).

examinations have been carried out on samples of the population which are too small and/or not really comparable. Even when association findings were independently confirmed, the contribution which common gene variants in the population could make to explaining a phenotype, i.e. a disease, almost always proved to be low (missing heritability)[42]. The scientific work on this is still underway (see chapter 5).

Today the influence, which the examination method could have on protective predispositions, is still difficult to assess. Certain gene variants protect their carriers against an outbreak of certain diseases or delay it. A "mutant allele" of the CCR5 gene (which codes for a cell surface protein) provides resistance against AIDS and the APOE2 allele provides a certain degree of protection against Alzheimer's disease. Some gene variants are associated with increased physical fitness or with longevity. Such relationships have struggled to become public knowledge to date. Nevertheless, the influence of an individual genotype on the onset of the characteristic, as is the case in susceptibility genes, is limited.

The characteristics of genetic information in the medical context

In addition to the molecular genetic analysis of genetic material, there are numerous other methods of determining the genetic constitution of a person (see chapter 2). The characteristics of the chromosomes in terms of their number and structure (karyotype) are investigated using cytogenetic and molecular cytogenetic methods. Conclusions on the genetic constitution can also be made by determining the phenotype, i.e. by using clinical examinations of the external appearance as well as imaging and biochemical (proteins, metabolic products) procedures. Considering the family history alone can lead to a precise genetic diagnosis. Here is an example of this: anyone who learns that their child has fallen ill with an autosomal dominant disorder (e.g. Huntington's disease) just as a common ancestor did, knows for certain that they too carry the predisposition for this.

The afore-mentioned example shows that genetic information about the individual can always be important for related persons, too. The genetic links between the members of a family are often also genetic links of the fate of disease. Conflicts can arise if, for example, the use of a predictive genetic test violates the right of others to remain ignorant. Beyond the family context, the common genetic inheritance, of ethnic minorities, for example, carries the risk of collective discrimination.

Genetic information can have consequences even after long periods of time. In the case of late manifesting diseases, the phenotypical onset of a disease can occur decades after the genetic tests were carried out or information on the genotype was obtained. Some characteristics do not become apparent in the tested persons themselves but only in their descendants, depending on the penetrance of a genotype, possibly also on the partner's genotype and changing environmental conditions.

The consequences of genetic tests can vary greatly. In the case of a "negative" (i.e. favourable) result, measures, which would have otherwise been induced, can be stopped. This can provide great relief, especially if these measures would have been stressful or even risky (e.g. frequent examinations under general anaesthesia in the case of a genetic risk of a retinoblastoma, a malignant childhood tumour which develops in the retina of the eye). Should the test result be positive, an indication for further diagnostic measures can be stipulated in order to be able to determine the right time for preventive or therapeutic steps. Reactions which appear paradoxical at

42 Maher B (2008).

first must also be pointed out in this context. Thus a person seeking advice can develop a depression after the reliable exclusion of the genetic risk of a serious disease, perhaps because they have a feeling of guilt towards the affected family members. On the other hand, the proof of a mutation leading to a disease can also be accepted with relief because the person concerned now has a definite answer, and this they can cope with better than with the constant threat of an unknown risk. However, the consequences of a test are not always only medical. The results of genetic tests can have far reaching consequences for the entire life and family planning of the examined person.

Interdisciplinary and transregional competence centres for treatable genetic diseases

Many monogenic diseases affect several organs (so-called syndromic diseases). Examples of these are cystic fibrosis, hereditary diseases of the connective tissue, ectodermal dysplasia and hereditary muscular diseases. Isolated specialist treatment of individual organ manifestations is not recommended. It is much wiser to coordinate patient care, especially for chronic diseases. Only then adequate patient care is guaranteed. Interdisciplinary and transregional competence centres for special groups of diseases should be set up for this purpose.

Treatable monogenic diseases which only become apparent during the course of life are only unsystematically and incompletely recorded in Germany. These include, for example, hereditary forms of colon cancer, breast cancer, ovarian cancer and thyroid cancer, dominant hereditary hypercholesterolemia and recessive hereditary haemochromatosis. If the genetic diagnosis is not made, then the patients cannot receive the appropriate care. Patient care must be interdisciplinary and above all cross-sectoral. The risk persons amongst the relatives of an affected person are not fully detected due to the limited genetic knowledge of many doctors. More human genetic specialists must be trained, the genetic competence of specialists in the relevant clinical fields must be improved and a suitable number of interdisciplinary and trans-regional competence centres must be set up for the example diseases stated as well as others similar.

The development of genetic methods is also pushing screenings for some treatable genetic diseases into the realms of possibility. There is corresponding experience, partly from abroad, in this field, e.g. for hypercholesterolemia in the Netherlands. Technical prerequisites and criteria should be developed with the help of research projects in order to offer screenings for such illnesses in Germany.

Need for further medical training

The growing amount of information on the role of genetic variability in the development of an illness is also gaining increasing importance in practical medicine. The doctors in Germany are largely unfamiliar with the significance of genetics in medicine. It is only in the last few years that human genetics has been given more attention in students‘ curriculae. Every doctor should be able to recognise familial risks of disease amongst their patients in their own specialist area, especially in the case of high risk persons for treatable hereditary diseases. The doctor should know when they have to transfer a patient to a specialist for genetic counselling and diagnostics as well as for care. Each doctor should also have an idea of what predictive genetic diagnostics means and when it can be considered. Using this aim as a basis, special further training measures should be developed for doctors.

4 Quantification of Risks

Predictive genetic diagnostics should provide a person seeking advice with information on genetic risk factors which could lead to illnesses in the future. A series of genetic and fundamentally treatable diseases such as hereditary cancers or familial hypercholesterolemia are characterised by high penetrance: in the case of complete, i.e. 100% penetrance, all mutation carriers fall ill in the course of their lives. In such a case, when the genetic risk factor is proven, the person examined can receive the definitive information that the disease will appear in the course of their life but will not receive any information on the exact time of the outbreak of the disease. It is important to calculate the age-dependent probability of disease, both in the case of complete as well as incomplete penetrance.

Data from prospective examinations on large groups of persons is required for such calculations in order to determine the modulating factors, which can reduce or increase the age-dependent probability of disease. Some of the factors can be, for example, environmental conditions, lifestyle, preventive measures or independent genetic modulation conditions. Moreover, the comparison with the risks of disease in the general population should be considered in the risk assessment. The risk assessments of predictive genetic examinations are subject to statistical considerations, which are illustrated in the following.

Risk assessment using the example of hereditary colon cancer

The hereditary form of colon cancer (hereditary nonpolyposis colorectal cancer, HNPCC, Lynch syndrome) is used as an example in the following to show how a predictive statement can be gradually improved. This is an autosomal dominant disease and it is responsible for 2 to 3% of all colon cancers in Europe. Moreover, the risk for various other forms of cancer is also increased. The disease is caused by a germline mutation in one of the four DNA repair genes (DNA-MisMatch-Repair genes, MMR genes). However, amongst all patients with colon cancers, the number of patients with mutations in the DNA repair genes is low. The majority of colon cancers are called sporadic because the family of a patient is not burdened by a mutation in an MMR gene. It is extremely important to detect carriers of gene mutations amongst the patients with colon cancer as these patients have a considerably increased risk of falling ill with further carcinomas (not only in the colon). In addition, it is highly probable that the relatives of the patient have inherited the mutation in question. If the relatives undergo a predictive genetic examination, categorised according to the degree of relatedness (cascade examinations, see chapter 3), two results are possible. If a relative has not inherited the familial mutation, then there is no risk of them developing hereditary colon cancer. However, if the relative has inherited the familial mutation, then they have an increased risk of falling ill with colon

cancer and/or other tumours in the course of their life. The risk of disease depends on age. The risk is very low up until the age of 20 and significantly increases with age to the extent that 50% of the carriers develop a carcinoma. In order to recognise these carcinomas early, the carriers should take part in a special early detection programme.

A key problem is finding those patients affected by the hereditary form of the disease amongst all patients with colon cancer. The cause of the hereditary form of colon cancer is the failer of one of the MMR gene products in the cells of the intestinal mucosa. This failure leads to genetic changes (so-called somatic mutations) occurring in the colon cells when the DNA is duplicated during the cell division in the affected cells and these changes can be detected in the tumour tissue using molecular pathological methods. This phenomenon is called microsatellite instability (MSI). All daughter cells of such a tumour cell show MSI. The proof of MSI in a tumour tissue sample is used as an indication to identify the higher probability of a carrier of a hereditary mutation in an MMR gene. MSI can be detected in almost all patients with a mutation in an MMR gene. However, even amongst patients who have sporadic colon cancer, there are some who show the MSI phenomenon in their tumour cells.

The probability of discovering a hereditary form of colon cancer is not only increased by evidence of MSI in the tumour tissue but also through illness at a young age and through the family history of its presence.

On the one hand, performance criteria of the diagnostic test procedures and on the other hand, information on the frequency (prevalence) in the reference population are both relevant in order to quantify the probability of the presence of a genetic predisposition as a form of absolute risk specifications.

Sensitivity and specificity as a measure of test accuracy

Sensitivity indicates how many (in percent) of the genetic carriers are detected by a test. In our example, sensitivity is the ability of the diagnostic test (here the MSI-test) to correctly identify the carriers of a germline mutation (mutation carrier) (see table 4.1 in the appendix). The cancer cells of a patient with an MMR gene mutation almost always show microsatellite instability. The sensitivity is over 99%.

Specificity indicates how many (in percent) of the non genetic carriers are not detected by a test. In this example, the specificity of the diagnostic test (here the MSI-test) is the ability to correctly identify those colon cancer patients who are not mutation carriers, in other words, those who do not carry a germline mutation in any of the MMR genes and whose tumour is therefore to be described as sporadic (see table 4.1. in appendix). In the MSI test the specificity is approx. 86%, which means a microsatellite instability can be detected in a proportion of patients (14%) who do not show a germline mutation in one of the MMR genes (false positive).

The following conclusion can be made: the patient group with microsatellite instability contains almost all mutation carriers of the MMR genes, who need be detected, but also a large number of patients who do not carry any germline mutations.

Sensitivity and specificity only characterise the quality of diagnostic test procedures. These values are independent of the frequency of the disease. They also do not provide any direct information on the probability of the presence or exclusion of a mutation. The following statistical parameters are used for this purpose.

Positive and negative predictive value

The positive predictive value of a test (PPV) is a measure of its diagnostic power. It indicates the proportion (in percent) of persons with a positive test result who actually have the characteristic investigated. In an ideal situation, this value is 100%, however, in reality this only happens in exceptional cases. Using the example of hereditary colon cancer, tables 4.2 and 4.3 in the appendix explain that the positive predictive value varies greatly depending on the frequency of the disease in the group examined (prevalence), although sensitivity and specificity remain constant.[43] In the example, tumour tissue samples were examined for the presence of a microsatellite instability and mutations in the MMR genes in a group of colon cancer patients.

In the entire group of non-selected colon cancer patients, 1.7% of them have a germline mutation in one of the MMR genes (see table 4.1 in the appendix). There is, therefore, a low prevalence. Approx. 15% of all colon cancer patients show a microsatellite instability in their tumour tissue (positive MSI phenomena). For the PPV, the ratio is formed from the number of mutation carriers with MSI and the total of all MSI positive patients (see table 4.2 in the appendix). The positive predictive value is therefore 11% (=170/(1,330+170) x 100). As a result, only a proportion of these MSI positive colon cancers are really a result of a mutation in an MMR gene and approx. 10 patients must be genetically tested in order to identify a genetic carrier.

The negative predictive value of a test (NPV) is a measure of the certainty of exclusion. It indicates the proportion (in percent) of persons with a negative test result who do not actually have the characteristic investigated. In our example, the NPV indicates the probability that the person examined is not a mutation carrier if there is no MSI involved. The NPV in the example is almost 100% (=8,499/(8,499+1) x 100).

Using the MSI-analysis, the proportion of patients with a germline mutation can be increased from 1.7% (the prevalence of the mutation carriers amongst non-selected colon cancer patients) to 11%. This value can be considered as the prevalence of the mutation carriers amongst MSI positive colon cancer patients. Given the high sensitivity (almost all carriers of germline mutations are filtered out by the MSI-test), the probability that real mutation carriers are "lost" in this procedure is low.

The PPV can be increased again by taking other risk factors for the presence of a germline mutation into consideration. For example, the analysis can be restricted to those colon cancer patients who fell ill before the age of 50 or who have other family members who have the disease. To do this, either the Bethesda criteria[44] or the even stricter so-called Amsterdam criteria[45] are used (see tables 4.2 and 4.3 in the appendix). When the Bethesda criteria are used, the prevalence increases to 13% and the PPV to 52%. When preselecting with the Amsterdam criteria, a prevalence of 50.5% and a PPV of 88% is reached. In such cases, the probability of a health-related genotype rises sharply as a result of including other data.

Age-related probability of the disease

Not all patients with a predisposition to hereditary colon cancer actually fall ill. According to current data, the lifetime risk is approx. 50%. The risk of disease is very low for those below the age of 20 and increases with age.

43 Figures of the German HNPCC Consortium (*Deutsches HNPCC-Konsortium*) http://www.hnpcc.de.

44 Rodriguez-Bigas MA et al. (1997).

45 Vasen HF et al. (1991).

The age-dependent probability of disease can depend on various modulating factors. These differ between the various MMR genes. Furthermore, independent modulating genes and life style factors play a role. Calculating the age-dependent probability of disease for genetic carriers requires precise knowledge of these factors and appropriately defined and validated calculation models.

This conclusion applies to every form of predictive genetic diagnostics. The positive predictive value as well as the age-dependent probability of disease are the parameters, which are used in genetic counselling after a positive predictive genetic diagnostic. The person seeking advice can be told the probability that the disease concerned will appear at a certain age. How high the risk of disease is, must be taken into consideration in the connected strategy for the early detection of cancer.

Relative risk measures

So far, by referring to PPV, NPV and age-dependent probability of disease absolute risk measurements have been listed. In a number of situations, relative risk measures are also important. They provide comparative information on how great the difference is between various comparison groups. Risk ratios or meaures derived from them are often considered here (relative risks, odds ratios). These measures are useful for describing the influence of individual risk factors on the occurrence of a disease.

Relative risk measures also play a role in determining genetic factors, which contribute to complex diseases. In many illnesses it is assumed that it is not the change in the individual gene, which causes the disease but the fact that several changes in the genetic sequence and environmental factors together lead to the outbreak of the disease (see chapter 3). These gene variants, which influence the outbreak of the disease are called susceptibility genes.

In scientific investigations, the so-called odds ratio measures the influence of gene variatns on multifactorial diseases. It involves a measured value, which is used to describe the effect of a so-called susceptibility gene on the onset of a disease (see chapter 3).

The relative risk measures do not provide the person seeking advice with any estimation of the absolute risks. They can, however, contribute to the calculation models for absolute risks.

5 The Future of Human Genome Research: Significance for Predictive Diagnostics

Two technical developments, with the help of which the relationship between variability in the human genome and diseases can be examined with increasing efficiency, have led to a new phase in human genome research: the introduction of high resolution DNA chips (DNA arrays), which allow the typing of up to one million different single nucleotide polymorphisms (SNPs) at the same time as well as the current development of highly-efficient methods for DNA sequencing (next generation sequencing).

Genome-wide association studies (GWAS)

High resolution DNA chips are used in DNA samples of large groups of patients with multifactorial diseases who are compared with healthy persons. They allow chromosomal regions or even specific gene variants which influence the development of a multifactorial disease to be systematically named. In recent years, more than 450 GWAS have identified more than 2,000 genetic variants, which are associated with diseases or other characteristics. Not all of these findings could, however be replicated (see chapter 3). The factors of the individual genetic variants, i.e. genotypes which contributed to the onset of the respective disease or other characteristics, differed but, irrespective of a few exceptions (e.g. age-dependent macular degeneration, atopic diseases, some microdeletions in autism and other brain diseases) were usually very low (see chapter 3).[46]

If variations in different genes contribute to the development of a multifactorial disease, it is perceived that, in these patients, several synergetic factors have joined together to lead to an increased "predisposition dose". The GWAS concept is based on the hypothesis that the genetic contribution to a multifactorial disease materialises as a result of DNA variants, which are common in the human population (common disease-common variant-hypothesis). The DNA chips used so far therefore only detect variations which have a certain minimum frequency in the human population. The present findings mean it is likely that a variant common in the human population generally contributes very little to the development of a multifactorial disease. This also complies with evolutionary aspects. If a variant codes for a gene product which leads to a lower reproduction rate as a result of illness, then only those variants which have very slight effects can remain in the population. On the other hand, a variant which leads to an increased number of children as a result of an advantage would prevail. However, simultaneously considering numerous variants, each one of which only slightly influences the phenotype, can explain a large part of the variability of the phenotype. This has recently been illustrated for height (hidden heritability).[47, 48] At present, it cannot yet be confirmed whether this applies in general to multifactorial diseases and whether this is reflected in improved possibilities for disease prediction.

46 Ku CS et al. (2010).

47 Yang J et al. (2010).

48 Gibson G (2010).

Furthermore, there must be a large number of rare variants, which increase the disease probability for multifactorial diseases when combined (common disease-rare variant-hypothesis). In many cases, the rare variants will be the result of new mutations or mutations from a few generations ago. In any case, interaction between various genotypes that predispose to the illness (so-called epistasis) and interaction with environmental factors is to be expected. In addition, epigenetic modifications can also exist (see chapter 2). In conclusion, it can be stated that at present, only a small part of heritability can be explained for all multifactorial diseases.

There is great scientific interest in this field because the collection of many susceptibility genes should allow new insights into the causal framework (pathophysiology) of multifactorial diseases. It is likely that scientific research will discover corresponding combinations of parameters. This will involve unusually complex examinations, which use genetic and clinical findings, other parameters from different areas as well as characteristics of the course of the illness. Special algorithms have to be developed using bio-mathematical methods, the results of which allow statements to be made on predispositions to disease. The development of such diagnostics, which is based on large cohorts of patients, will be a research subject for many years to come. It can be expected that even high-resolution DNA chips will be replaced by possibilities of a low-priced genome sequencing in research programmes in the foreseeable future.

High throughput sequencing (next generation sequencing)

New sequencing systems, which are considerably more efficient and which reduce consumable costs, have been developed in recent years. Thanks to the rapid progress of existing second generation sequencing systems (e.g. HiSeq, Illumina), the upcoming market launch of third generation sequencing systems (SMRT^{R}, Pacific Biosciences; Ion Torrent; Starlights, Life Technologies) as well as the constantly decreasing sequencing rates of commercial suppliers (e.g. Complete Genomics, US), the costs for genome sequencing should continue to decrease, even if they do not do so as quickly as was initially expected. According to expert estimations, in three to five years it will be possible to offer sequencing for the entire human genome including sample preparation for less than 1,000 US dollars, and the costs are expected to continue to decrease as a result of the development of even more efficient sequencing techniques. As regards the interpretation of the sequence, a difference must be made between the expressed sequences (transcriptome, exon) and the entire sequence. Although the industry is somewhat more optimistic in this regard[49], it will take much longer for the significance of the entire variability of the human genome, as regards the phenotypical effects and in due consideration of epistasis, genotype/environment interaction and epigenetics (see chapter 2), to be interpreted.

For the diagnostics of monogenic diseases, genome sequencing could soon present a simpler and cheaper alternative to the multitude of specific tests used in diagnostics today. If high throughput sequencing is used in diagnostics, it is essential that the sequencing quality is tested first. Interpreting the sequencing data is much more problematic. Bioinformatic instruments must be developed as filters with regard to the connection with diseases. In this respect, it will be a matter of interpreting the sequencing information for certain questions, e.g. defined diseases, and to assess hypotheses for the interpretation. As knowledge on genotype-phenotype relationships is constantly growing and changing, the bioinformatic filter systems will have to be continually developed.

49 Interview with Jay Flatley, Illumina http://www.xconomy.com/san-diego/2010/04/06/.

The exon includes all DNA segments which carry the genetic information for proteins. For example, exon sequencing can be used to examine a large number of functional variations which contribute to the genetic predisposition to multifactorial diseases, including cancers and Alzheimer's disease. The exon contains less than 2% of the genome. Changes in many regulating DNA sequences which appear in the remaining 98% of the genome are not included in the exon sequencing. Exon sequencing has already made its way into diagnostic practice for certain groups of defined diseases.[50] Sequencing of the entire genome or its coding fragments is now offered abroad.[51,52] In Germany, the complete sequencing of the transcriptome and exon of an individual is offered.[53] Given there is still very little information on the complex conditions of gene regulation which influence the cell type-specific pattern of gene expression, it must be assumed that sequencing the entire genome of an individual leads to a significant increase in genetic excess information, which cannot (yet) be interpreted.

The regulations of the Gene Diagnostics Act in Germany are based on the concept of targeted investigation of defined genes. Should genetic excess information be generated, it is stated in the explanatory statement to section 9 that this information must be fully explained to the person examined, who must then decide whether the excess information is to be destroyed or included in the interpretation. The Gene Diagnostics Act does not specify how to proceed if the genome of a human is to be systematically examined or completely sequenced (see chapter 9).

Significance of modern genetic analysis methods for disease research

Disease research using sequencing methods and DNA chip technology can only promise to be successful if it is applied to well-characterised patients, respectively families. So far, more than 2,000 genes are known, the mutations of which cause 3,500 different monogenic diseases in humans. This is just the tip of the iceberg, however (see chapter 3). It is highly likely that, in the next few years, the new methods of DNA sequencing will provide important new insights in this field.[54] In the Western world families are often small. In many cases, the person affected by a monogenic disease will be the only one. However, in this situation it is not easy to consider a genetic disease in an individual case in the first place. The new DNA technologies could provide an important additional tool.

Although the challenge is much greater than with monogenic characteristics, the quality of the analysis of multifactorial diseases should be considerably improved as a result of the new methods. The next task will be to categorise the genes concerned in functional relationships. This information will provide research with new insights into pathophysiological relationships. In addition, the interaction between the genotype and the environment as regards the outbreak of multifactorial diseases as well as the role of epigenetics in the genetic function will be able to be analysed in a more targeted manner. Genetic and functional methods, i.e. aetiological research and pathophysiological research will merge. The analysis

50 Center for Genomics and Transcriptomics, CeGaT http://www.cegat.de/.

51 The company Knome (http://www.knome.com/) offers genome sequencing at prices of approx. 70,000 or 25,000 US $ (as of: December 2009).

52 The company Complete Genomics (http://www.completegenomics.com/) has been offering genome sequencing since January 2010 for 20,000 US dollars. This does not include analysis and clinical interpretation of the sequence data obtained.

53 In addition to the analysis of so-called diagnostic panels, the company CeGaT offers exon sequencing. Depending on the number of samples processed at the same time, the costs range between 5,600 and 8,900 Euros. This does not include interpretation of the data (http://www.cegat.de/).

54 Check Hayden E. (2009).

will be carried out both on the level of the cells or the tissue as well as on the level of the entire organism. Given the fact that multifactorial diseases are not only based on genetic factors, it cannot be expected that their development and their course can be explained by genetic research alone. Research into reciprocal relationships between genetic, epigenetic and biochemical networks and their interaction with environmental influences is necessary.

The way in which the shown development is progressing can lead to improved possibilities for detecting predispositions to disease. If a series of genetic variants is identified, which contribute to the onset of a multifactorial disease, it would be possible to collect these variants together with epigenetic information, biochemical parameters and exogenous factors as risk profiles in order to make certain predictive statements for a given person. The extent to which predictive genetic diagnostics can lead to statements on individual multifactorial diseases, which are really relevant for disease prevention in individual, tested persons and, if necessary, when this will be the case, cannot be predicted at present. However, before such information can be used for predictions in clinical routine, extensive empirical examinations must be carried out for validation.

The comparative sequencing of the entire human genome in risk and test groups offers the maximum possible amount of genetic information. It is hoped that research programmes which can be used to detect the presumably numerous alleles located in various gene loci, which contribute to the risk predisposition to certain multifactorial diseases, will soon become reality. The issue of appropriate interpretation of technically sound, genome wide sequencing results is a huge problem as such genome-wide comparisons involve quantities of data, which represent unresolved challenges for bioinformatic analyses. As the individual alleles should usually only have a slight influence on the phenotype, offering a predictive genetic diagnostic procedure too early is problematic if this only includes a small part of all alleles that predispose to a certain multifactorial disease. As soon as genome-wide sequencing analyses for certain multifactorial diseases have detected a proportion of alleles which is significant for the individual person, the sequencing can be restricted to this part of the genome. Genome-wide examinations can also be important in monogenic diseases, as in many of these cases the symptoms can vary greatly, even in relatives who have an identical mutation in the main gene responsible for the disease concerned. In the case of these diseases, identifying other genetic factors in addition to the main gene, which influence the clinical picture and the course of the illness, is also important for the prognosis and new therapy approaches.

Translation of genetic tests into better patient care

The clinical implementation of knowledge gained from research into medical care is called translation. In the context of genetically complex diseases there is considerable need for action, particularly in the following areas:[55]

1. Development of automated procedures for characterising mutations;
2. Identification of genetic findings which are relevant and suitable for clinical work;
3. Increase in the personnel capacity for integrating genetic information into care practice;
4. Evidence of the clinical benefit of genetic information;
5. Evidence of the profitability of the care drawing on genetic information.

The "Genomic Translation" Model ("Analytic validity; Clinical validity; Clinical utility; and Ethical, legal, and social implications",

55 Samani NJ et al. (2010).

ACCE), which was developed by the Public Health Genomics Department of the American Center of Disease Control also corresponds to steps 2 to 4.[56] These translation steps show what is required of patient-related research in order to improve patient care.

The specific challenges in clinical practice are illustrated using the example of the complete genome sequencing of one patient.[57] Experts highlight that, throughout the course of complete sequencing, a great deal of information is required

1. from the patient before testing,
2. for the interpretation of the test results with regard to the test methods and the correlation with a disease,
3. as regards the uncertainty in cases where the significance of the variations is unknown,
4. as regards the topicality of the interpretation[58].

In order to improve health care through predictive genetic diagnostics, basic research knowledge, the translation and the non-medical aspects such as legal and ethical framework conditions addressed in this statement must be put into practice. This is added to by the fact that the sectoral health system in Germany hampers its implementation in care and the research associated with it.

Internet-based Direct-to-Consumer (DTC) offers for genetic diagnostics

The existing high throughput technologies have very quickly led to commercial exploitation as a result of diagnostic services. Since 2006, so-called Direct-to-Consumer (DTC) companies, which offer selected DNA marker typing via the internet, have been founded in rapid succession, particularly in the US, in order to report on the personal genetic profile and especially on health risks. Today there are at least 40 companies operating on this market across the world.[59] The person interested in a test concludes a contract with the supplier over the internet, selects the characteristics or diseases they want to be examined for and sends the company a saliva sample. When the laboratory examination is complete, the customer electronically receives a password which they then use to retrieve the test results.

Some of the DTC companies limit their services to the creation of the risk profile for one or a few, usually genetically complex, diseases, while the more well-known suppliers such as Navigenics, DeCode and 23andme promise to make statements on the risk for up to 50 different characteristics or diseases. The majority of the examination offers apply to predispositions to multifactorial diseases but also to monogenic tumours, predispositions to autosomal recessive diseases, genetic reactions to medicines and characteristics with no medical relevance. A large number of the examinations offered have an uncertain scientific basis.[60] In Germany, DTC offers are prohibited based on the exclusive diagnosis by doctors or specialists regulated in section 7 of the Gene Diagnostics Act.

There are now a multitude of predominantly critical statements, for example, from the American Society of Human Genetics[61],

56 Centers of Disease Control http://www.cdc.gov/genomics/gtesting/ACCE/index.htm.

57 Ashley EA et al. (2010).

58 Ormond KE et al. (2010).

59 see list of the Genetics and Public Policy Centers, Johns Hopkins University http://www.dnapolicy.org from 28.05.2010.

60 The test offers include, for example, the following phenotypes: diabetes mellitus type 1+2, age-dependent macular degeneration, Parkinson's disease, stroke, rheumatoid arthritis, hereditary breast cancer (only individual mutations), lung cancer, life expectancy, eye colour, heroin addiction, nicotine addition, earwax type.

61 American Society of Human Genetics: Am J Hum Genet 81: 635-637, 2007. Hudson K et al. (2007). Hudson K et al. (2007).

the American College of Medical Genetics[62] and the European Society of Human Genetics[63] regarding the verification and evaluation of genetic DTC offers. Moreover, a statement was presented to the Austrian Federal Chancellery by the Bioethics Commission.[64] In the US, the Food and Drug Administration (FDA) has been requested to only have genetic tests carried out by specialists.[65, 66]

A number of points of criticism are listed in the statements:

1. The risk specifications for the most common diseases are uncertain because they are based on weak or unconfirmed findings;
2. There is a lack of information on sensitivity, specificity and on the predictive value of the tests used;
3. Often only a limited range of mutations is investigated in the gene of interest;
4. There are no independent tests for the technical quality and interpretation of the findings;
5. The results of the tests can only be usefully interpreted in the context of a medical evaluation;
6. The person examined should be informed of the test results by a human geneticist or a genetic counsellor, also in view of the significance of such information for their own private life and for family members[67];
7. The laboratory cannot control whether the sample sent in actually comes from the person who concluded the contract with the company and that it was not, for example, the sample of a child, spouse or another person which was sent.

The media has presented the weaknesses and shortcomings of DTC laboratories: risk assessments carried out by competing companies have repeatedly produced completely different results, obviously because different markers are used to determine specific genetic risks of disease.[68] As expected, the laboratory could also not detect if a sample had been intentionally sent by another person.

It is clear that a large number of the current DTC offers on the internet have uncertain scientific bases and that interpreting a test result without professional genetic counselling can lead to errors.

DTC companies partly canvass for customers by requesting that they engage a doctor themselves for the desired examination. The doctor concerned does not have to have the professional qualification necessary for the justification for a genetic examination and the interpretation of genetic data. As a result, health-related disadvantages could arise for the person examined. In analogy to the advertising ban on prescription medicines, advertising for predictive genetic examinations should be legally prohibited.

In the US genetic tests have recently started to be offered in "drug stores" ("over the counter genetic tests"). The American Society of Human Genetics has strongly criticised this.[69]

Heterozygosity testing

High throughput technologies could soon find themselves being used for diagnostic purposes

62 American College of Medical Genetics: http://www.acmg.net/StaticContent/StaticPages/DTC_Statement.pdf, 7. April 2008.

63 European Society of Human Genetics https://www.eshg.org/fileadmin/www.eshg.org/documents/PPPC-ESHG-DTC-06122009.pdf.

64 Austrian Bioethics Commission http://www.bundeskanzleramt.at/DocView.axd?CobId=39456.

65 Beaudet AL (2010).

66 Javitt G (2010).

67 The lack of such information, which is easily understandable for those who are not experts in the field, regarding the significance of individual test results was decisive for the decision of a number of American states to only allow genetic DTC tests under certain conditions or to prohibit them completely.

68 see Aldhouse P, Reilly M (2009); Ng PC et al. (2009); Pinker S (2009).

69 ASHG » Policy and Advocacy » Response to Recently Announced Availability of Over-the-Counter (OTC) Genetic Tests http://www.ashg.org/pages/statement_5_13_10.shtml.

in order to detect heterozygosity for autosomal recessive diseases, especially those which appear in early childhood. Based on the assumption that recessive diseases appear in 0.25 to 0.5% of all newborns in our society, it can be assumed that in 1 to 2% of all couples, both partners are heterozygous for mutations in the same gene. According to the Mendelian laws, every child of this couple has a disease risk of 25%.

Since February 2010, a company[70] in the US has been offering a DTC test for heterozygosity for 458 specific mutations in 105 disease genes. Although this does only detect a small number of the clinically relevant mutations[71], methods which should make it possible to investigate almost all known relevant mutations are already being developed. The American National Center for Genome Resources (NCGR, Santa Fe) has developed a universal test for heterozygosity which aims to provide the option of preventing serious genetic childhood diseases by sequencing coding fragments of 448 well-known genes.[72] A similar DTC test has also been offered in the US since March 2010 which is used to exclude mutations in most well-known genes for X chromosomal inherited mental disability.[73] These universal tests used to detect carriers for recessive diseases could be used to detect almost all parental risk constellations before the first conception and to give the couple concerned the opportunity to a make a reproductive decision based on this knowledge. Without this preconception examination, the parents will only know of their risk constellation after the birth of the child.

70 Counsyl, Redwood City, CA https://www.counsyl.com/; see also Levenson D (2010).

71 Only a third of the probands examined with this test are heterozygous for one of these mutations (Srinivasan et al). This means that only 2 to 2.5% of all clinically relevant recessive mutations can be excluded with this test as approx. 10 to 20 of recessive mutations are found in the genomes of healthy persons (incl. see Wheeler DA et al. 2008).

72 see National Center for Genome Research NCGR http:// www.ncgr.org/.

73 see Ambry Genetics http://www.ambrygen.com/.

The German Gene Diagnostics Act does not exclude carrier screening requested by individuals. The systematic preconception heterozygosity examination, however, represents a new situation with far-reaching ethical and social implications for society. For the time being, such examinations should only be carried out in the framework of research projects. They should be integrated into medical, ethical and social supplementary research in order to learn more about their personal and social effects.

This approach complies with the preconception heterozygote screening for beta-thalassemia in Sardinia and Cyprus and the Tay-Sachs disease in Israel, respectively amongst Ashkenazim Jews (see chapter 3), which has been practiced across the world for many years. The stated diseases are well-known in the respective societies. In contrast, a universal test for heterozygosity investigates the risk of diseases which are largely unknown in the population. Moreover, it predefines an indication by the fact that a certain gene has actually been included in the universal test.

Requirements in research and general further training

The developing opportunities of high throughput technologies open the door to extensive possibilities for monogenic and multifactorial disease research. This has not only been recognised in the traditional scientifically developed countries but also, for example, in the upcoming countries of Asia and Latin America. A better understanding of the causes of disease will also give new scope to research in the fields of normal functions and functional disorders (pathophysiology). All this will increase the options for the early detection and prevention of diseases.

In Germany, research should be intensified in the entire field of genetic medicine.

In this respect, it will particularly be a matter of connecting molecular genetics and clinical medicine. Large and systematically collected patient samples are required for this. Following on basic research, the public Health, health care process research right through to health economics should be taken into consideration.

The extensive possibilities of systematic predictive genetic diagnostics provide an opportunity for society to discuss the ethical, legal and social aspects of the use of genome high throughput technologies before the technical progress has created actual facts. Moreover, the present standard of doctors‘ knowledge in the entire field of genetic medicine should be improved. Society should be constantly informed on all the facts relating to the opportunities and limits of genetic medicine, including predictive genetic diagnostics. Pupils in particular should be informed of the new knowledge gained from genetic research.

6 The EuroGentest Investigation of Genetic Screenings in Europe

Genetic screenings are used to detect or exclude a genetic disease, predisposition or resistance to disease or to diagnose genetic characteristics which could cause diseases in the descendants of the person examined. Genetic screenings are becoming increasingly possible for a multitude of disorders.[74]

The term "genetic screenings" should only be used for the systematic execution of genetic examinations which are either carried out on an entire population (so-called population screenings) or on certain groups of persons within the entire population, for example, on pregnant women (prenatal examinations) or on newborns (neonatal examinations). Another important characteristic of genetic screenings is that they are normally introduced into society by representatives of the health system.[75] The expected benefits of genetic screenings must be measured against the possible damage – on the one hand there is the early detection and prevention as well as decision-making support as regards reproduction, on the other hand, and the build-up of fear, social stigmatisation, misuse of information and discrimination.

The World Health Organisation (WHO) has passed guidelines[76], which should be considered before a screening is carried out, whereby one of the fundamental conditions is that the course of the disease concerned can be influenced and that the disease must be able to be treated through early detection and early intervention. Implementing a national screening programme, therefore, represents a great challenge for the health system and politics.

The EuroGentest Investigation illustrates the present status (as of 2006-2008) of genetic screenings in selected European countries.[77] It includes examination targets and forms of organisation and is used as a basis for harmonising future trials, standards and practice throughout Europe.

In the EuroGentest Investigation, the term "programme" is understood in a broad sense. It contains all examination offers which are aimed at meeting public demand, regardless of whether they are systematically organised by the health system or are case-related but offered on a broad basis.[78]

Newborn screening

The newborn screening for genetic diseases is carried out with chemical detection techniques e.g. tandem mass spectrometry (see table 6.1 in the appendix). National programmes for PKU (phenylketonuria) (Finland only has regional programmes for immigrants) and CH (congenital hypothyroidism) exist in almost all countries. Newborn screening is restricted to PKU and CH in Estonia, Finland, Latvia, Lithuania, Norway and Slovenia. Newborns are screened for other diseases in other countries but there is no content-related consensus as to which diseases should be appropriately included here.

74 Godard B et al. (2003).
75 Stewart A et al. (2007).
76 Wilson JMG (1968).
77 Javaher P et al. (2010).
78 Rogowski W, Langer A (2007).

All countries consider newborn screening to be in the interest of the newborns themselves. Screening programmes, which are primarily aimed at detecting genetic risks of repetition for other siblings, for example, for Duchenne and Becker muscular dystrophy have not been set up in any European country on a continuing basis.

Newborn screening is considered to be a cost-effective and important health measure throughout Europe. In all 25 countries, screening is organised in such a way that complete coverage would at least be theoretically achievable. In fact, the aim is completely or almost completely fulfilled in most countries. Depending on the health system, the screening programmes are either carried out and legally regulated under direct government supervision or through the respective social security systems (see tables 6.2 to 6.9 in the appendix).

Prenatal screening for chromosomal aberrations and neural tube defects

Table 6.10 in the appendix lists prenatal examinations: ultrasound examinations for fetal developmental disorders, measuring the fetal nuchal translucency and maternal serum markers as a sign of a chromosomal aberration of the fetus, maternal serum markers as a sign of a neural tube closure disorder as well as fetal chromosome examination and biochemical examination for a neural tube closure disorder from the amniotic fluid if the prenatal diagnostic procedure is primarily being carried out for other reasons. Examination offers aimed at women with a priori increased risks of fetal chromosomal anomalies (e.g. age risk) were not recorded.

The EUROCAT[79,80] study provides a summary of all prenatal screening activities in Europe as of 2004. After this study was published, comparative reports only came from individual countries, namely Denmark[81], the Netherlands[82] and Great Britain[83]: ultrasound examinations, measurements of the fetal nuchal translucency and maternal serum markers are offered almost everywhere. This applies, to a lesser extent, to the fetal chromosome examination and the biochemical examination for neural tube closure disorders from the amniotic fluid, if an invasive diagnostic procedure was carried out for another reason. Prenatal screening for haemoglobinopathies has been offered in Great Britain since 2008.

The EUROCAT study and the reports from the individual countries provide a very inconsistent image of the organisation of prenatal screening programmes. Finland[84] and France[85,86] seem to be the only countries with nationally valid recommendations with regard to content and procedures.

Table 6.11 in the appendix lists the diseases which were the subject matter of carrier screenings in 23 European countries in the year 2006. Such programmes are offered in approximately half of these countries, especially with regard to haemoglobinopathies (9 entries) and cystic fibrosis (7 entries).

Cascade screening

Cascade screening is considered as the systematic examination of the relatives of an index case for the genetic change in question, whereby each genetic carrier identified becomes a new index case. As illustrated in table 6.12 in

79 EUROCAT http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=18410651.

80 Boyd PA et al. (1998).

81 Ekelund CK et al. (2008).

82 Wortelboer EJ et al. (2008).

83 Loeber JG (2007).

84 Government Decree 1339 (2006).

85 Décrets, arrêtés, circulaires de Ministere de la sante et des sports (2009a).

86 Décrets, arrêtés, circulaires de Ministere de la sante et des sports (2009b).

the appendix, the following diseases were the most common subjects for cascade screening in the 25 countries: cystic fibrosis, Duchenne muscular dystrophy, fragile X syndrome, hereditary haemochromatosis, beta-thalassemia, other haemoglobinopathies and hypercholesterolemia.

Cascade screening differs from other screenings primarily because it detects persons, who have an increased genetic risk from the outset. On the other hand, it is carried out systematically, just like other screenings and is not initiated by the patient themselves. In practice, patient/family initiatives and active counselling interact with one another. Cascade screening for late manifesting diseases can also be considered as a systematic predictive examination. The EuroGentest Investigation, therefore, also analysed cascade screening because never before there had been an attempt to collect data on this topic for the whole of Europe.

7 Aspects of Health Economics

Thanks to scientific and technical progress, the possibilities for medical treatment are constantly growing. At the same time, however, the potential for financing the services through the community of solidarity is decreasing as a result of an ageing population, amongst other things. Both developments mean that the possibilities of medical care and their financing are developing in different directions. A review must be carried out to determine which care services can be offered in the scope of social security. The most important decision criterion are the benefits of each service for the patient, i.e. the effectiveness of the medical service. In addition, the German Social Security Code (Sozialgesetzbuch) requests that the profitability of the services is also taken into account. The evaluation of all socially relevant consequences of a medical technology is called the Health Technology Assessment (HTA). HTA reports usually summarise the evidence on the medical effectiveness and on the profitability of all studies available. Besides effectiveness and profitability, legal, ethical and psychological aspects also play a role as decision criteria, especially in predictive genetic diagnostics.

When are diagnostics profitable?

If decisions on medical care are to be made on the basis of scientific knowledge (the so-called evidence), studies on the medical benefits and profitability are required. This also applies to predictive genetic diagnostics of diseases i.e. predispositions to disease[87]. The crucial question of profitability here is: what is the health-related utility of a diagnostic procedure per Euro spent in comparison to renouncing this diagnostic strategy? If a strategy leads to an improvement in health and even to a cost reduction, it is definitely profitable. In many cases, however, an improvement in health must be achieved by an increase in costs. Whether the additional costs of the diagnostic procedure are considered to be acceptable or not comes down the health insurance company's (or the patient's) willingness to pay for it.[88]

Components of profitability

When investigating the profitability of a predictive genetic diagnostic procedure, the costs of care and the health effects must be taken into consideration. In addition to the costs of the test, there are also the consequential costs of further investigation and the treatment. The fact that treatment costs can also be reduced through early efficient therapy must also be considered. Health-related effects primarily include improvements in life expectancy and in health-related quality of life.

In the case of a non-treatable genetic disease, predictive genetic diagnostics can also provide information, which is highly important for a number of life decisions, without having any direct effects on health. Such beneficial aspects cannot be examined in the scope

87 Khoury MJ et al. (2009).

88 Leidl R (2007).

of studies on medical effectiveness, but must be evaluated using other approaches, such as determining the individual willingness to pay for this knowledge.[89]

Profitability of a diagnostic test

The test costs are the first costs to be incurred in a diagnostic test. In analogue to the parameters of the medical test accuracy (see chapter 4), four cases can be defined:

1. In the case of a correct diagnosis, early or more targeted treatment can bring health advantages, whereby therapy costs are incurred.
2. Should incorrect treatment for a patient result from an incorrect test result (an unnecessary intervention, for example), the health-related advantages fail to materialise, while unnecessary costs arise and other consequential costs and deteriorations in health can develop.
3. No further costs are incurred in the case of the correct classification of healthy persons.
4. In the case of people requiring intervention who are not recognised by the test, the costs and effects of improved therapy do not apply.

The profitability of a test is calculated from the total costs and health effects across all four cases, weighted by the frequency of the occurrence. This can be methodically examined, particularly well using decision-theoretic models. In this respect, all profitability examinations which are collected in a current overview of newborn screening were such modelling studies[90]. The profitability of test strategies can also be compared using mathematical modelling (see example 7.1 in the appendix).

Profitability of screening programmes

Screening programmes are based on systematically selected target groups, such as all persons of a certain age and sex who live in a defined region on a given day. In addition to the test properties and costs mentioned, their profitability particularly depends on the prevalence (i.e. the frequency of the occurrence) of the disease and the genetic markers to be used in the target group, the severity and the therapy possibilities of the disease as well as the age of the probands. Previous studies on genetic screening based on DNA showed that both profitable as well as unprofitable results are possible and that the results can be influenced by an improvement in the availability of data[91] (see example 7.2 in the appendix for a comparison of cost of screening approaches).

It is particularly difficult to assess the benefit to patients and profitability if several predispositions to disease are to be diagnosed at the same time. Pooling the results of individual diagnostic strategies is only possible and recommended if costs and health effects are recorded in a methodically comparable way and the results are statistically independent of each other. These assumptions are, however, very restrictive as diseases last for differing periods of time, there is different information on the course and consequences of therapy, the information available for modelling varies greatly, and important diseases, such as diabetes mellitus and coronary heart disease, are not independent of one another. When evaluating extensive testing strategies, high methodological heterogeneity, which severely hampers an evidence-based overall assessment of utility and profitability, is to be expected.

Good model-based theoretical examinations on the effectiveness and profitability of screening strategies use the best available data on the

89 Grosse SD et al. (2008).

90 Langer A, John J (2009).

91 Rogowski W (2006).

epidemiological situation, on the test properties as well as on the costs and health-related results. High-quality medical care data for the target groups in Germany is required for a realistic assessment of the situation in Germany. In order to determine the true effectiveness and profitability of the screening programmes, this data should be compared with the data in other European countries. Furthermore, an evaluation of the programme practice must complement the model examinations. Profitability is improved if, for example, risk carriers take part in the screening on their own initiative; however, it is decreased if participants mistakenly are tested several times. Health insurance companies must also be integrated and involved in a practice-based evaluation of screenings programmes (see example 7.3 for the significance of a practice-related evaluation of screening approaches).

Functions of the research and health policy

The evaluation of patient utility and the profitability of multiple predictive diagnostic test strategies demands much more from the scientific base of information than the individual tests or screening measures have so far. In order to effectively and economically improve health with predictive genetic diagnostics, evidence must, therefore, be considerably improved. This means a significant need for further research. In particular, the scientific assessment of multiple preventive diagnostic strategies in terms of their medical effectiveness and profitability must be developed further, and the decision-making on the use of such strategies in the framework of health insurance as well as in the framework of direct use by consumers must be investigated in terms of their health-related and financial effects. The first international comparisons on the evidence-based management of genetic screening approaches are so far showing a considerable variety of foundations for evidence and decisions[92] (see example 7.4 in the appendix for differences in the newborn screening for two genetic diseases in North America and Europe).

Furthermore, converting predictive knowledge into better health can require a change in behaviour from the person concerned if predictive genetic diagnostics supplements behaviour-related knowledge.[93] If improving the knowledge on genetic risks is not sufficient to modify behaviour, better prevention strategies must be developed in order to realise the health-related potential of the improved genetic knowledge[94] (see example 7.4 in the appendix for relations between genetic tests and health-related behaviour).

Today many countries also regularly draw upon economic evidence when making decisions about the payment of drugs by health insurance companies. For efficient care, however, the profitability of all areas must be taken into consideration, including of course, prevention.[95] In order to promote efficiency right from the development of the technology and then later in its use, profitability must be taken into consideration at an early stage in a new, rapidly expanding area such as predictive genetic diagnostics (the consequential costs of which are still unclear) . This is particularly true if statutory health insurance services are used. However, predictive genetic diagnostic procedures paid for "out of one's own pocket" can also lead to medical care services from health insurance companies, especially as a result of the consequences of incorrectly verified test results.[96] In this respect, the evidence-based management of predictive genetic diagnostics also presents a new challenge in the field of health policy.[97]

92 Grosse SD et al. (2010).
93 Humphries SE et al. (2007).
94 Heshka JT et al. (2008).
95 Leidl R (2008).
96 McGuire AL, Burke W (2008).
97 Rogowski WH et al. (2009).

8 Medical Ethics Aspects

In the performance of any genetic diagnostic procedure, the fundamental, widely accepted and, in many cases, stipulated medical ethical principles must be observed. This also applies to the examination of phenotypically healthy persons. The person to be examined must provide voluntary consent to the procedure following a detailed explanation of its purpose, nature and associated risks and the medical measures must promote the health of the person concerned. Specific features must be observed when applying these principles to predictive examinations.

Safeguarding autonomy

The autonomy of the person being examined must be respected each time predictive medicine is applied. This has numerous consequences. Every human being has the right to seek information about their genetic constitution as well as the right to bypass the respective examinations. However, respecting autonomy infers that the individual has not only a negative right to inactivity but also a positive right to support in order to enable the individual to make a well-founded decision. The autonomy of the person to be examined must be fostered through reflective and comprehensible counselling which should be commensurate with state of the art scientific knowledge. Good counselling must not only clarify all available information, but also the limits of objective knowledge. The offer of a predictive genetic examination should only be made if this is guaranteed. The person to be examined must provide voluntary and informed consent.

Predictive genetic diagnostics should only be carried out in combination with appropriate counselling. Since predictive genetic diagnostic procedures often generate knowledge that is difficult to interpret and which can entail major biographical consequences, the counsellor must be appropriately qualified. The counselling should be non-directive in order to allow the person to make a sustainable decision. The offer of support must continue after the results have been communicated. The further consequences of a predictive genetic examination also require informed consent.

Genetic knowledge and family members

Since genetic information may provide relevant information concerning relatives, the atonomy of several persons is affected by the performance of a genetic test. The unasked for confrontation with genetic findings can mean that the right of relatives to remain ignorant is violated and that they irrevocably lose their “genetic innocence“. This is true, for example, in the case of a man who wishes to undergo a predictive examination for Huntington’s disease on the grounds that his grandfather had been affected by the disease. If he proves to be a carrier of a mutation which leads to Huntington‘s disease, then his mother is also certain to be a carrier of the mutation. In this case, the examination of the grandson also provides information concerning the predisposition of his mother, regardless of whether or not she wished to be informed of her genetic status. In

principle, informed consent must be obtained from each of the individuals concerned before genetic information is disclosed to a person. Should one relative refuse to consent to a procedure that would provide a benefit for the person requesting the examination, a conflict arises between the autonomy of the various persons concerned. In such a case, priority is given to the autonomy of the person who has consulted the doctor to determine his/her genetic predisposition.[98]

Medical confidentiality

Since the autonomy of the person examined must be respected, the person in question can decide on how their results are used. This may have implications for family members. All results are subject to medical confidentiality, unless the person examined releases the doctor from their obligation to this. Furthermore, a breach of confidentiality can be permitted, or may even be necessary, in the interests of a higher-ranking legal consideration, e.g. if another person could be provided with the option of prevention or treatment. In such cases, a conflict with Section 11 of the Gene Diagnostics Act may arise (see chapter 9).

Benefit and non-maleficence

Medical measures are subject to the requirements that they promote the health of the person concerned, and that they do not harm or that they at least have an acceptable benefit-risk ratio. However, it is often difficult to determine whether these requirements are met within the context of predictive genetic diagnostics, which indicates diseases that may only manifest in the distant future. Predictive knowledge is often probabilistic, i.e. the occurrence of a disease can only be predicted with a certain level of probability. However, the extent to which different individuals wish to reduce the uncertainty of their future through such examinations varies greatly.

Predictive genetic examinations may have consequences which have a weak scientific backing and the benefits of which may also be considered low in comparison with the costs. Not every preventive measure against a possible future disease is considered acceptable by the person examined, particularly if decisions have to be made concerning drastic preventive measures in the absence of certainty. An examination may be helpful in the sense that it enables prevention or allows certain biographical decisions to be made. However, it can be harmful if it arouses fear, generates an undesired change in a person's self-image, or paves the way towards genetic discrimination. Thus, when determining the medical benefits, the preferences and attitude of the person to be examined must be taken into consideration prior to testing. Which statements will be possible and with what level of probability; which options for prevention and other consequences may result; and how should the person to be examined evaluate these? All this must be discussed before an examination is conducted in order to ensure that the measure will provide an advantage for the person concerned.

The various levels of responsibility

Professionals working within the various levels of the health system carry differing responsibilities. The responsibility for implementing a genetic screening programme differs from the responsibility of a doctor who advises an individual patient concerning the performance a predictive genetic examination. While, in individual cases, the doctor must base his/her advice on the will and welfare of the patient,

98 Chadwick R et al. (1998).

professionals responsible for implementing a screening programme must also consider the possible social benefits and harm that may ensue from the decision to screen or not to screen for a particular disease.

Considerations of justice

All measures must be carried out in accordance with the principle of equality. Equal access must be guaranteed. Decisions concerning an individual predictive examination or the implementation of a screening programme should be based upon scientific evidence of their effectiveness and profitability and should not be discriminatory. Such decisions must be reinforced with comprehensible and ethically acceptable arguments as to why screening for a particular disease should be performed. There must be reference to specific disease and hope that intervention can be successful. The persons responsible for the design of screening programmes must take the potential for discrimination into account.

9 The German Gene Diagnostics Act (*Gendiagnostikgesetz*)

The act on human genetic examinations (Gene Diagnostics Act – *Gendiagnostikgesetz* GenDG)[99] came into force on 1st February 2010 in order to "prevent any discrimination and disadvantages based on genetic characteristics, especially with regard to the duty of the state to protect human dignity and to ensure the individual right to autonomy via sufficient information" (Section 1, Gene Diagnostics Act[100]). The Gene Diagnostics Act is divided into eight parts, whereby this chapter primarily focuses on the second part (Genetic examinations for medical purposes).

Personal and professional area of application

The Gene Diagnostics Act regulates genetic examinations and human genetic analyses carried out in the scope of genetic examinations.

Only living humans as well as living embryos and foetuses during pregnancy are included in the personal scope of protection (Section 2, Paragraph 1). Genetic examinations on the deceased as well as on dead foetuses and embryos including the handling of corresponding genetic samples and genetic data are not included in the law.[101] The problem areas of preimplantation genetic diagnosis (PGD) as well as the (preconceptual) polar body diagnosis are also excluded from the scope of regulation, too. This is due to the fact that PGD does not take place in the embryo during pregnancy and the polar body diagnosis is already carried out before the embryo has developed.[102]

The area of application of the Gene Diagnostics Act is objectively restricted to the enumerative and, thus, conclusively listed areas of genetic examinations for medical purposes, for determining descent as well as in the insurance and employment sectors. Genetic examinations and analyses as well as the handling of genetic samples and data for research purposes are explicitly not included in the regulations of the Gene Diagnostics Act (Section 2, Paragraph 2, No 1), which is surprising in view of the original drafts and discussion.[103] If genetic data is gathered and processed for research purposes, the research bodies are not bound to the strict requirements to inform according to Section 7 et seq. According to Section 2, Paragraph 2, No. 2, examinations based on the regulations of criminal proceedings and the German Protection Against Infection Act (*Infektionsschutzgesetz*) are also excluded.

The numerous legal definitions in Section 3 highlight the special status the legislator assigns to genetic information. The law considers genetic examinations to be all examinations which are used to provide a reliable diagnosis of human genetic characteristics using genetic analysis (Section 3, No. 1 a]) or a prenatal risk

99 Taupitz J, Pölzelbauer C (2010).

100 Sections without a name are hereafter those of the Gene Diagnostics Act.

101 BT-Drs. 16/10532, P. 19 f.

102 See also BT-Drs. 16/10532, P. 20.

103 The draft (BT-Drs. 16/3233) presented by the parliamentary group BÜNDNIS 90/DIE GRÜNEN on 3rd November 2006 contained its own section for „genetic examinations for scientific research purposes" (Sections 26-33 Gene Diagnostics Act-E). In the draft (BT-Drs. 16/10532) of the Gene Diagnostics Act (announced on 31st July 2009), which was presented by the German Federal Government on 13th October 2008, this section was deleted.

assessment (Section 3, No. 1b])[104]. When carrying out postnatal examinations, only differing laboratory examination methods are included in the scope of protection (see Section 3, No. 2 a] to c]), namely cytogenetic analyses, molecular genetic analyses and gene product analyses, while phenotype examinations (sometimes carried out using imaging techniques) are also included in the area of application in prenatal risk assessment.[105] It must be highlighted that according to Section 3, No. 2 c], the Gene Diagnostics Act also includes the analysis of the gene products of DNA and RNA, i.e. the tandem mass spectrometry, provided it is possible to directly determine the genetic properties through gene product analysis.[106] The non-discrimination principle laid down in Section 4, Paragraph 1 of the Gene Diagnostics Act, which is substantiated again in Section 21 of the Gene Diagnostics Act for the employment sector, also illustrates the genetic exceptionalism emphasised by the legislator.[107] In contrast to the regulations of the German General Act on Equal Treatment (*Allgemeines Gleichbehandlungsgesetz*), any form of discrimination as a result of genetic characteristics must be considered as unjustified, whereby objective reasons can also not justify a restriction.[108]

Genetic examinations for medical purposes (Sections 7 to 14)

The law defines both diagnostic as well as predictive examining as genetic examinations for medical purposes (Section 3, No. 6). Institutes and persons, who carry out genetic analyses for medical purposes in the scope of genetic examinations must comply with certain quality standards and quality assurance measures but are, in contrast to institutes which carry out genetic analyses to determine descent, exempt from a general accreditation requirement (Section 5, Paragraph 2 in conjunction with Paragraph 1, Sentence 2, No. 1 to 4)[109].

A key element of the law with regard to genetic examinations for medical purposes is the detailed regulation on the requirement to inform the person concerned and to provide genetic counselling. The Gene Diagnostics Act defines specific prerequisites for prenatal as well as predictive genetic examinations.

In Section 7, the Gene Diagnostics Act provides for an extensive medical doctor reservation, which applies to all genetic examinations for medical purposes. For predictive genetic examinations, the responsible doctor must also have a special qualification. In addition to specialists for human genetics, only doctors who have received training which included information on hereditary diseases in accordance with the respective training regulation, may carry out predictive genetic examinations in their respective specialist area.[110] Apart from human geneticists, the law also concerns pediatricians, gynaecologists, internists and neurologists. In accordance with Section 7, Paragraph 2, the genetic analysis may only be carried out by the medical person responsible or by the persons or institutes they commissioned.

Following this, the Gene Diagnostics Act regulates the requirements for the informed consent of the person concerned (Sections 8, 9). According to Section 9, only the doctor,

104 BT-Drs. 16/10532, P. 17.

105 BT-Drs. 16/10532, P. 17.

106 BT-Drs. 16/10532, P. 21.

107 See only BT-Drs. 16/10532, P. 16: „The law assumes the special feature of genetic data“ (*„Das Gesetz geht von der Besonderheit genetischer Daten aus.“*).

108 For criticism of this see: Kiehntopf M, Pagel C (2008); Taupitz J (2007).

109 The draft from the Federal Government planned such an accreditation requirement for all institutes which carry out genetic examinations (see Section 5 Gene Diagnostics Act-E, BT-Drs. 16/10532, P. 9). On 1st January 2010, the Federal Republic of Germany, represented by the BMWi (Federal Ministry of Economics and Technology), set up a national accreditation body (*Deutsche Akkreditierungsstelle GmbH (DAkkS)*), implementing the EU regulation No. 765/2008 2010 (www.dakks.de).

110 BT-Drs. 16/10532, P. 25.

who arranges the genetic examination (and not the person who carries out the genetic examination on their behalf) is obliged to inform the patient and to obtain a written declaration of consent for the examination and the acquisition of samples. In accordance with Section 8, Paragraph 1, Sentence 2, the consent includes both, the decision on the scope of the genetic examination as well as the decision as to whether and to what extent the result of the examination is to be disclosed or destroyed. Therefore, it must be emphasised that the only options are either to be informed of the results or to destroy the results (or certain parts of them). It is therefore not possible for the person concerned to firstly be notified of the results and then to have them destroyed with the result that they would not be part of the treatment documentation.[111] Once the consent has been given, it can be revoked in writing or verbally at any time with effect for the future, whereby a verbal revocation must be documented immediately (Section 8, Paragraph 2). Should the genetic analysis be delegated to a laboratory, both the consent as well as a possible revocation must be provided as evidence to this laboratory by the responsible medical person (Section 8, Paragraph 1, Sentence 3, Paragraph 2, Sentence 3).

A requirement for effective consent from the person concerned is that they are sufficiently informed by the responsible doctor in accordance with the detailed requirements of Section 9. The duty to inform, which must be documented in accordance with Section 9, Paragraph 3, includes information on the purpose, type, scope, validity and consequences of the examination (including possible health-related risks through disclosure of the results) in accordance with Section 9, Paragraph 2, No. 1 to 6. The person concerned must also be informed about the retention of samples, the use of samples and the examination results, about the revocation possibility as well as about the right to remain ignorant, including the right to have the examination results destroyed. In addition, the legislator demands, as evidenced by the explanatory memorandum, that in certain situations, the patient must also be informed of the possibility of an unexpected examination result, especially if "according to the generally accepted status of science and technology, it is possible that during the planned genetic examination to clarify genetic features, certain unexpected genetic characteristics, which are not included in the purpose of the examination, can be detected".[112] After the person concerned has received the information, they must be granted "suitable time to think" (Section 9, Paragraph 1, Sentence 2). How appropriate the length of time is depends on "the type and significance of the possible expected diagnosis and the effects the examination could have on the person concerned and their family".[113] The Gene Diagnostics Act does not contain any explicit regulation on the option of renouncing the waiting time or the consent itself. The legislator, however, considers the option possible of renouncing the duty to inform or parts of it, in accordance with the "generally accepted right to waive the duty to inform".[114]

Section 10 regulates the requirements for genetic counselling, which from 1st February 2012 may only be carried out by doctors qualified for genetic counselling (Section 7, Paragraph 3, Section 27, Paragraph 4) and which, in turn, must be documented in writing according to Section 10, Paragraph 4. Genetic counselling does not necessarily have to be carried out by the responsible medical person, but can also be carried out by another medical

111 BT-Drs. 16/10532, P. 26.

112 BT-Drs. 16/10532, P. 27.

113 BT-Drs. 16/10532, P. 27.

114 BT-Drs. 16/10532, P. 27. For criticism of this see: Genenger A (2010).

person qualified for genetic counselling.[115] The content of the genetic counselling goes beyond the information on the examination methods and examination results and their medical and psychological significance presented in the scope of the duty to inform.[116] In addition to the general intelligibility and value neutrality of the counselling, in Section 10, Paragraph 3, Sentence 1 the legislator highlights the requirement for non-directive counselling.[117] The psychological and social consequences in connection with a (non-)implementation of the genetic examination and its (possible) results as well as the support possibilities for coping with physical and mental stress must be discussed with the person concerned in an open-ended manner (Section 10, Paragraph 3, Sentence 2). The person concerned may also be advised to recommend a genetic examination to genetic relatives (Section 10, Paragraph 3, Sentence 4). Section 10 provides a graduation in counselling obligations in line with the various counselling requirements in diagnostic and predictive genetic examinations. According to Section 10, Paragraph 1, counselling in a diagnostic genetic examination can be waived in individual cases upon availability of the examination results (for example, if no other implications for the person concerned are expected in view of the diagnosis result) [118]. However, in predictive genetic examinations (and prenatal examinations, Section 15, Paragraph 3), it is obligatory, according to Section 10, Paragraph 2, that genetic counselling is offered before the respective examination has been carried out as well as after the examination results have been made available. According to Section 10, Paragraph 2, however, the person concerned still has the option to present a written renouncement of the genetic counselling (as is the case with the duty to inform).

Sections 11 to 13 contain important regulations on disclosing the results as well as on retaining and destroying the results and samples. According to Section 11, the results of the genetic examination may only be disclosed by the responsible doctor after explicit written consent of the person concerned. This also applies if the genetic analysis was delegated to a commissioned person or institute.[119] In the case of a revocation or a request to destroy the results, the person concerned must not be informed of the results, Section 11, Paragraph 4.

Following medical professional law (see Section 10, Paragraph 3 MBO-Ä, the professional code of doctors), Section 12, Paragraph 1, Sentence 1 defines a ten year obligatory retention period for the results of genetic examinations and analyses in the treatment documentation concerning the respective person. After this period has expired and if the individuals decide they want the data to be destroyed instead of being informed about this or if they have revoked their consent in due time, the results must be immediately deleted by the responsible doctor or the body commissioned (Section 12, Paragraph 1, Sentence 2, 4, Paragraph 2). However, should the protective interests of the patient oppose this or should the patient request in writing that the data should be stored for longer, it must be retained and blocked.[120] The explanatory memorandum does not specify in which cases such a blockage of data in the interest of the patient is advisable.[121]

115 BT-Drs. 16/10532, P. 26. The extent and content of the necessary qualification of the medical person carrying out the counselling is to be defined in more detail by the Gene Diagnostics Commission established in the Robert Koch Institute according to Section 23, Paragraph 2, No. 2 a).

116 BT-Drs. 16/10532, P. 28.

117 BT-Drs. 16/10532, P. 28.

118 However, genetic counselling is obligatory for a diagnostic examination for a genetic characteristic which should clarify the existence or non-existence of a non-treatable disease.

119 According to Section 11, Paragraph 2, only the person or institute commissioned may inform the responsible doctor about the results.

120 According to Section 7, Paragraph 2, the commissioned body (but not the patient) must be informed about the blocking of data. For criticism of this see: Genenger A (2010).

121 BT-Drs. 16/10532, P. 29.

The Gene Diagnostics Act does not contain a legal obligation to retain the genetic sample. According to Section 13, Paragraph 1, it is rather a matter of principle that, provided it is no longer required within the scope of its intended use or the person concerned has revoked their original consent, the sample is immediately destroyed. Using the sample for purposes other than those originally intended is, according to Section 13, Paragraph 2, only possible if this is permitted according to the other legal regulations (for example, to prosecute a crime or breach of the law according to Sections 25 and 26) or the person concerned was explicitly informed about the further use and agreed to this in writing.[122]

A genetic examination of a person lacking the full capacity to understand and consent to the intended genetic examination is, according to Section 14, Paragraph 1, strictly only permitted if the genetic examination direclty benefits the concerned and if the examination is associated with as little risks and burdens as possible. In addition to the legal representative, the person lacking the full capacity to consent must be informed "as far as possible". The person concerned has the right to reject the examination or the acquisition of the genetic sample required for it, whereby their natural wish is decisive.[123] Section 14, Paragraph 2, however, makes an exception to the requirement for an immediate benefit, if a genetic disease or health-related disorder in the family can only be diagnosed through the genetic examination of the person lacking the capability to consent.

Prenatal examinations and genetic screenings (Sections 15 and 16)

A feature of prenatal risk detections is that the area of application not only includes chromosome analyses or molecular genetic analyses, but also non-invasive screening tests, for example, measuring the nuchal translucency using ultrasound or the triple test as well as the prenatal phenotypical characteristic screening of a genetically (co-) determined syndrome (Section 2, Paragraph 1, Section 3, No. 1 b], No. 3, No. 4).[124] According to Section 15, Paragraph 1 and Paragraph 3, not only does the person have to be provided with information in accordance with one of the criteria listed above, but a genetic counselling session must be carried out before and after the examination by appropriately qualified staff.[125] In addition, the responsible doctor must advise pregnant women of their right to a detailed psychosocial counselling session according to Section 2 of the Pregnancy Conflict Act (*Schwangerschaftskonfliktgesetz*).[126] According to Section 15, Paragraph 1, Sentence 1, prenatal examinations are restricted to medical purposes. Section 15, Paragraph 2 was added at the last minute, whereby the prenatal diagnosis of late manifesting diseases which first appear in adulthood is prohibited.[127]

According to Section 16, Paragraph 1, genetic screenings in terms of Section 3, No. 9 are only permitted if the onset of the disease to be diagnosed with the examination can be avoided or the disease is at least treatable, should the persons to be examined have the corresponding genetic characteristics.[128] Heterozygote screenings, i.e. genetic examinations with regard to a genetic predisposition for recessive diseases (e.g. beta-thalassemia, cystic fibrosis) which are only permitted as genetic

122 BT-Drs. 16/10532, P. 30.

123 BT-Drs. 16/10532, P. 30.

124 Krones T et al. (2009); BT-Drs. 16/10532, P. 17.

125 For doubts as to whether the resulting need for genetic counselling can be covered by sufficient staff within the two year transition period see: Krones T et al. (2009); Richter-Kuhlmann E (2010).

126 For possible implications with regard to the various aims of the counselling according to the Gene Diagnostics Act and Pregnancy Conflict Act: see Krones T et al. (2009).

127 For criticism of this: see Krones T et al. (2009).

128 BT-Drs. 16/10532, P. 33.

examinations for medical purposes, but not in the framework of a screening programme are therefore excluded.[129] According to Section 16, Paragraph 2, genetic screenings which are introduced after the enactment of the law require an additional evaluation by the Gene Diagnostics Commission established in the Robert Koch Institute, the opinion of which, however, is not legally binding; it only has an advisory nature.[130]

Genetic examinations in the field of employment and insurance (Sections 18 to 22)

Sections 18 to 22 restrict the rights of insurance companies and employers to ascertain or use the results of genetic examinations in connection with the conclusion of an insurance contract or in the scope of an employment contract. Section 18, Paragraph 1 contains the explicit prohibition against insurance companies demanding genetic examinations or analyses before or after the conclusion of an insurance contract (Section 18, Paragraph 1, No. 1) or demanding or accepting the findings from genetic examinations already carried out (Section 18, Paragraph 1, No. 2). Exceptions to this are, according to Section 18, Paragraph 1, Sentence 2, provided for in various insurance branches if the insurance benefit exceeds €300,000 or if an annuity of more than €30,000 was agreed upon. However, according to Section 18, Paragraph 2, previous illnesses are also subject to the obligation to notify in line with the general obligation to disclose information, even if they were detected using a diagnostic genetic test.

According to the regulations in the insurance sector, an extensive ban on collecting and using genetic information also applies in the employment sector (Sections 19, 20). According to Section 20, Paragraph 2, only diagnostic genetic examinations on a gene product level in the scope of occupational health medical examinations and under certain conditions are permitted, however, only subordinate to other occupational safety measures. Diagnostic genetic examinations through cytogenetic and molecular genetic analysis can be permitted under strict conditions in the case of activities which are hazardous to health according to Section 20, Paragraph 3 through a statutory instrument of the Federal Government. According to Section 22, the employment regulations accordingly apply to public employment on the federal level.

Policy-making powers of the Gene Diagnostics Commission (Section 23)

Section 23 transfers the task of creating guidelines in relation to the general status of science and technology, which is declared as decisive in numerous regulations of the Gene Diagnostics Act, to the Gene Diagnostics Commission (*Gendiagnostik-Kommission*) established in the Robert Koch Institute. In this respect the interpretation of the legal provision is largely outsourced to an independent body. The Gene Diagnostics Commission must determine and publish guidelines in relation to, amongst other things, the fundamental evaluation of the significance of genetic characteristics for diseases or health-related disorders as well as for the effect of a medicine (No. 1 a] and b]), for the qualification to carry out a genetic counselling session as well as in the field of descent determination (No. 2 a] and b]), in relation to the content of the information and genetic counselling (No. 3), in relation to the various analysis methods including the quality assurance measures (No. 4) as well as to the requirements for carrying out prenatal examinations and screenings (No. 5 and 6). The areas listed

129 BT-Drs. 16/10532, P. 33.
130 BT-Drs. 16/10532, P. 33.

in Section 23, Paragraph 2, No. 1 to 6 must not, however, be considered as exhaustive, according to the explanatory memorandum.[131]

Legal consequences (Sections 25 and 26)

Outside of the labour law prohibition of discrimination which, in Section 21, Paragraph 2 of the Gene Diagnostics Act, guarantees the person concerned entitlements to compensation and damages from Section 15, Paragraph 1, Paragraph 2 of the General Act on Equal Treatment, the Gene Diagnostics Act standardises numerous sanctions and fines for infringements of certain regulations of the law. Section 25 includes terms of imprisonment of up to two years for the infringements named there; according to Section 26, Paragraph 2, the maximum fine is €300,000. Furthermore, infringements of the regulations of the Gene Diagnostics Act can result in legal consequences based on the general provisions (e.g., Section 134 of the German Civil Code, nullity due to an infringement of a prohibition law).[132]

Policies of professional organisations

The law created by the legislator is supplemented by policies in many different ways. These policies are created by professional organisations with different degrees of obligation. As regards predictive genetic diagnostics, the chair of the German Medical Association (*Bundesärztekammer*) passed various guidelines, which claim to represent the opinion of the medical profession in the area concerned. Please refer to the "Guidelines on the diagnostics of the genetic predisposition to cancers" from May 1998[133], the "Guidelines on prenatal diagnostics of diseases and predispositions to disease" from December 1998[134] as well as the "Guidelines on predictive genetic diagnostics" from February 2003[135]. These guidelines contain instructions for the human genetic diagnostics and the associated counselling. Provided medical associations transform the guidelines into their own (statute) laws, they are professionally binding for the doctors in the respective medical association.

In addition, there are also numerous principles from scientific professional associations, especially those which are merged in the Association of Scientific Medical Associations in Germany.[136] They claim to embody the respective state of medical knowledge.

Need for amendment of the Gene Diagnostics Act

The Gene Diagnostics Act pursues goals which find a broad consensus in our society and require a legal regulation. These include the protection of human dignity, the right to informational autonomy, the right to remain ignorant in connection with genetic diagnostics, the principle of non-discrimination in genetic tests and the medical doctor reservations for genetic examinations.

Numerous problems and contradictions, which also concern predictive genetic diagnostics, however, arise when implementing the Gene Diagnostics Act. Fundamental parts of the law urgently need to be updated (Sections 8, 9, 11, 12, 14, and 15).

131 BT-Drs. 16/10532, P. 39.

132 Genenger A (2010).

133 German Medical Association (*Bundesärztekammer*), Guidelines on the diagnostics of the genetic predisposition to cancers (1998).

134 German Medical Association, Guidelines on the prenatal diagnostics of diseases and predispositions to disease (1998).

135 German Medical Association, Guidelines on predictive genetic diagnostics (2003).

136 Human genetic principles can be found at http://www.uni-duesseldorf.de/AWMF/ll/ll_078.htm.

Section 9: Handling genetic excess information

The Gene Diagnostics Act does not stipulate how extensively a person being examined has to be informed if the genome is to be systematically investigated, for example, through the complete exon sequencing already available now (see chapter 5). The explanatory statement to Section 9, Paragraph 2, No. 1 only addresses the handling of genetic excess information, which is generated as a secondary finding. In this respect, it is requested that the person examined is completely informed about this and that they decide on whether the excess information should be destroyed or included in the interpretation. The Gene Diagnostics Act does not, however, specify how to proceed if the genome of a human is to be systematically examined, i.e. completely sequenced.

Section 11, Paragraph 3: Communicating the results of genetic examinations and analyses

If, in the case of a patient with a treatable genetic disease which has autosomal dominant inheritance, for example, breast/ovarian cancer or hereditary colon cancer, the causal mutation is proven, then the patient is recommended a special early detection programme. Healthy relatives of the patient, e.g. children and siblings have an increased risk of having the same mutation and consequently developing the cancer in question. The patient is instructed to point out the particular risk to their relatives and to pass on the recommendation for genetic counselling. All aspects of a predictive genetic examination are discussed in the framework of genetic counselling.

The doctors who have looked after the patient and provided them with genetic advice, have no opportunity to check whether the patient has passed the information on to their relatives. It may also be that a patient intentionally does not pass the information on within the family. According to Section 11, Paragraph 3, the responsible medical person may only inform others about the result of a genetic examination or analysis with the explicit, written consent of the person concerned. Without exception, the law considers confidentiality for patients to be of a higher significance than the medical fiduciary duty towards relatives that have a high risk of a disease, which can be effectively treated if detected early enough.

In the case of a treatable hereditary disease, the medical fiduciary care should, in principle, not be subordinate to confidentiality. In individual cases, the doctor should weigh up which of the two legally protected interests should be categorised higher. This should always apply if the risk persons amongst the relatives are also patients of the doctor concerned, which means the doctor has an obligation as a legal guarantor towards them. But even in the cases in which the family members are treated by different doctors, in specific cases and if there are clear medical benefits, the doctor should have the opportunity to appropriately highlight the risk to risk persons amongst the relatives of the patient with a treatable hereditary disease and to recommend genetic counselling to them e.g. through sending them an information sheet. Section 11, Paragraph 3 of the Gene Diagnostics Act should be modified in this regard.

Section 12, Paragraph 1: Obligation to destroy examination results

In Section 12, Paragraph 1 No. 1, the law stipulates that the responsible medical person must retain the results of genetic examinations and analyses for ten years, after which the responsible medical person must destroy this data. The genetic data can or must, however, be retained if there is reason to assume that destroying the data would have a negative effect on the protected interests of the person concerned or if the person concerned requested in writing that it be retained for longer. On the other hand, the person concerned can demand that the examination results are destroyed at any time. In addition, the explanatory memo-

randum states how the destruction of the data should be approached if genetic relatives of the person concerned were also examined, but these relatives do not want to be informed of their own data.

The legal regulations are not appropriate for the purpose and are not practical in an everyday medical context. Before the ten year period has expired, the significance a certain genetic finding may have for the person concerned at a later point in time cannot always be assessed. It is possible that genetic data can still be interpreted differently years after the analysis, given the acquisition of new insights. This can be important for the health of the person examined at that time. In contrast to medical analyses which determine the present condition of health, genetic diagnostics investigates unalterable characteristics. Moreover, at the time of the examination, the person concerned cannot determine themselves whether they should request that their examination results be retained for more than 10 years. The legal requirement that the responsible medical person should refrain from destroying the examination results after 10 years means that all data have to be evaluated again by the doctor in the medical context before being destroyed. This is not practical.

Irrespective of the practicality, it is not wise to have to destroy the examination results after 10 years. Genetic analysis results are often also relevant for family members. If a deceased patient was the index case in a family, the results would be irretrievably lost.

There is also another aspect to this. Even if the doctor complies with the regulation to destroy the data, the result of an examination is by no means reliably deleted. As is the case with other medical findings, the results of genetic examinations are generally sent to other treating doctors in examination/medical reports with the patient's consent. The medical report usually contains a statement on the interpretation of the result. This is in the interests of the patient's treatment, for example, if the genetic finding has therapeutic or preventive consequences.

It is neither possible nor desirable to subsequently identify and destroy the findings filed in the various patient documents. In this regard there are no grounds for the legal regulation. Therefore, it is both in the interest of the person examined as well as in the interest of the family members that the results of the genetic diagnostic may be retained without a specified period, as it was previously the case. Only in this way can it be guaranteed that later research information can be used in the interests of the person examined to interpret the (unchangeable) DNA sequence once collected. For the rest, it is a recurrent experience in human genetics practice that previously examined persons or their family members inquire about their collected genetic findings long after 10 years because new viewpoints have arisen.[137]

In future, excess genetic information will be generated more often in the framework of genetic diagnostics (whether it be obtained as a secondary finding or intentionally using a systematic method) from which predictive statements can potentially be deduced. Together with the person to be examined, a decision as to whether this information should be a) immediately used in a specific manner (primary information), b) destroyed, or c) stored without being used for the time being must be made.

The various options must be appropriately taken into consideration when informing the person concerned. An extensive explanation, as required in the explanatory statement for Section 9, will be almost impossible in reality. Storing the genetic information can be useful because in future it may become important for the health of the person being examined.

137 The „Guidelines on predictive genetic diagnostics" from the German Medical Association (*Bundesärztekammer*) (Dtsch Ärztebl 2003) recommend retaining the cross-generation documentation obtained in the scope of predictive genetic diagnostics for at least 30 years.

Genetic information is subject to the power of disposition of the donor. In order to be able to use new genome research knowledge, the donor should have the option of a secondary analysis of the stored sequence information at a later point in time, for example, with regard to defined diseases or predispositions to disease (see chapter 5). The type of storage has both technical and legal aspects. The law should take the aspects of storage and future analysis possibilities into account.

Section 14: Systematic genetic examination of persons lacking the capacity to consent

In Section 14 and its explanatory statement, the Gene Diagnostics Act states that a diagnostic or predictive genetic examination on a person lacking the capacity to consent is only permitted if it opens up opportunities for prevention or therapeutic intervention possibilities with regard to a disease or health-related disorder. In future, it may be necessary to carry out a systematic genetic examination as part of a genetic diagnostic procedure in the interests of the health of a person lacking the capacity to consent (for example, exon sequencing) in order to accurately diagnose an existing genetic disease. This can generate a significant amount of excess genetic information. After the diagnostic aim has been achieved, the excess genetic information collected should, however, not be allowed to be interpreted for a child or an adult temporarily unable to consent because the opportunity to remain ignorant is then taken away from the person examined. The genetic excess information should, however, be blocked and stored so that this group of people is not disadvantaged compared to an adult with the capacity to consent. As soon as the capability to consent is bestowed, in the case of an examined child once they have reached their 18th birthday, the person concerned should be able to decide on their own free will and after genetic counselling whether the information should be a) immediately used in a specific manner (primary information), b) destroyed or c) stored without being used for the time being. If a person is deemed incapable of consent on a permanent basis due to a severe and irreversible impairment to their intellectual abilities, their legal representative should decide whether the information should be used immediately in a specific manner (primary information), destroyed or continued to be stored for the time being.

Sections 14 and 16: Newborn screening

The law considers the newborn screening, which has been successfully carried out for decades as a genetic survey (explanatory statement to Section 16). This means that the parents must receive a genetic counselling session before the blood test. Baby nurses and midwives, who previously took the blood are no longer allowed to do this on their own responsibility. There are already indications that since the Gene Diagnostics Act came into force, newborn screening has not been carried out for some babies, for example, in the case of home births or with parents, who do not speak sufficient German, although this was by no means the parents‘ wish. For a series of people affected, this will lead to life-long disabilities which could have been prevented with earlier diagnosis and appropriate therapy. The Gene Diagnostics Act should therefore be amended so that the person who takes the blood as part of the newborn screening, e.g. the baby nurse or the midwife, is allowed to inform the parents about the aim of the examination. The examination should then be dependent on whether the parents provide written confirmation of their consent. If a normal result is provided, the parents would not need to be contacted again. If the findings, on the other hand, were abnormal, the parents should then be provided with extensive information and genetic consultation from the responsible doctor.

Section 15, Paragraph 2: Prenatal genetic examinations for late manifesting diseases

Section 15, Paragraph 2 prohibits the prenatal diagnosis of a disease which "will only appear after the 18th birthday of the child in accordance with the generally accepted state of medical science and technology".

The formulation of the law is incomprehensible. It is not wise to connect the appearance of an illness with the "general state of medical science and technology". Late manifesting hereditary diseases usually follow an autosomal dominant mode of inheritance. The clinical manifestation of most of these diseases can appear across a wide age range. There are clinical manifestations, for example, of Huntington's disease, cystic kidneys or familial adenomatous polyposis, before the 18th birthday. In this respect, symptoms of the later disease, which are often discrete and clinically not yet relevant, can be determined even earlier. The legislator does not determine the criteria which must be met in order to define the outbreak of a disease. The formulation of Section 15, Paragraph 2, suggests that the legislator no longer wants to prohibit a prenatal genetic examination of a late manifesting disease as soon as more sophisticated analytical methods have succeeded in objectifying the appearance of the illness from very early on.

It is known from experience in genetic counselling that due to a higher risk pregnant women very seldom request prenatal genetic examinations for a late manifesting disease anyway. There are also no indications that something has changed in this respect in recent years. Section 15, Paragraph 2 should be deleted given the fuzzy definition of the age of onset of a late manifesting hereditary disease. Moreover, the Gene Diagnostics Act also touches upon the regulation of Sections 218 et seq. of the German Penal Code (*Strafgesetzbuch* - StGB) in this connection.

Section 18: Genetic examinations in connection with the conclusion of an insurance contract

It is conceivable that in future, the applicant will have more predictive knowledge at the point the insurance agreement is concluded because systematic genetic examinations are being carried out more frequently. Given the fact that Section 18 of the Gene Diagnostics Act prohibits taking existing results or data from genetic examinations under certain amounts into consideration, an increasing number of applicants with an above average health risk can conclude insurance contracts, for example, in additional private health insurance, term life insurance, occupational disability insurance, incapacity insurance or nursing care insurance. Such an adverse selection can considerably restrict the functionality of the insurance market concerned. No need for action is considered necessary at present. The development should, however, be observed.

Sections 8 and 9: Analysis of samples from abroad

The law fails to mention other important aspects in practice. This applies, for example, to the question as to whether or to what extent the person must be provided with information in accordance with Sections 8 and 9 of the Gene Diagnostics Act before giving the required consent, if a German laboratory is to carry out a genetic analysis of samples which were obtained abroad and were sent to the laboratory by a doctor practicing abroad. The law does not contain any explicit regulations on this issue. It could therefore be assumed that the law is also to be applied strictly in this respect, which would however lead to the Gene Diagnostics Act being used de facto abroad, too. Neither the law nor the explanatory statement suggest whether the legislator wanted the German Gene Diagnostics Act to be extended abroad with international connections in this way.

If we consider this in purely practical terms, a strict application of the regulations of the Gene Diagnostics Act in an international context proves to be very problematic. Foreign patients are rarely provided with extensive information in accordance with the detailed regulations of Section 9 by a foreign doctor abroad. Vice versa, it cannot be assumed that the German legislator wanted to downgrade an existing higher level of explanation, which might be legally required abroad, to German law if the samples are to be analysed in Germany.

All in all, the law should make clear that providing information and obtaining consent "on site" in accordance with foreign law is sufficient. This corresponds to the view whereby constituent elements of domestic law can be implemented abroad in accordance with the applicable law there, provided there is functional equivalence. The genetic analysis of a sample obtained abroad by a German laboratory should therefore be permitted if the doctor, who sent the sample confirms that the person concerned has been provided with information about the nature, scope and significance of the genetic examination in accordance with the legal regulations in the sample's country of origin and the person has subsequently granted their consent. If the German laboratory has doubts about the assignment of the sample to the person concerned or a substantiated suspicion that there has been insufficient information provided or even misuse, then the laboratory must refuse to examine the sample sent.

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11 List of Abbreviations

ADPKD	Autosomal dominant polycystic kidney disease
ARPKD	Autosomal recessive polycystic kidney disease
CNV	Copy number variants
DNA	Desoxyribonucleic acid
DTC	Direct-to-Consumer
GenDG	*Gendiagnostikgesetz* - Gene Diagnostics Act
GWAS	Genome-wide association study
HTA	Health technology assessment (Evaluation of all socially relevant consequences of a medical technology)
MMR	(DNA-)Mismatch-Repair gene (i.e. a DNA repair gene)
MSI	Microsatellite instability
NPV	Negative predictive value
PPV	Positive predictive value
RNA	Ribonucleic acid
SNP	Single nucleotide polymorphism

12 Glossary

Allele	An exact or different copy of a defined DNA fragment, whereby it can either be a gene or a functionally irrelevant variation. Two alleles are contained in each autosomal locus as a result of the diploidy of the human set of chromosomes.
Amino acids	Class of chemical compounds which are the building blocks of proteins
Association	In genetics, a statistical connection of a genetic variation to a multifactorial determined characteristic
Autosome	One of the 22 non-sex chromosomes
Blastomere	Individual cell in early embryonic development
Cascade screening	Systematic examination of the relatives of a patient (index case) with a monogenic disease for the genetic change concerned
Chromosomes	Carriers of genetic information located in the nuclei, which can be examined using a light microscope and which consist of DNA and proteins
Codon	A set of three successive nucleotides which contain information for an amino acid or a translation signal (start/stop).
Cohort	A group of persons in medical epidemiological research who are examined at recurrent intervals with regard to specific characteristics e.g. diseases
Cystic fibrosis	Also called mucoviscidosis. Autosomal recessive disorder of the chloride channel anchored in the cell membrane which leads to the formation of a thick mucous in the lungs, pancreas and intestine.
Cytogenetics	Sub-area of genetics which examines chromosomes and their disorders using a light microscope
Diabetes mellitus	A group of multifactorial, autosomal dominant or mitochondrial metabolic diseases in which a person has high blood sugar
Diploidy	Two sets of chromosomes (2 x 23 = 46 chromosomes), normal genetic status of the somatic cells
DNA	Desoxyribonucleic acid: Carrier of genetic information
Dominant	Phenotypical characteristic of a (mutated) allele i.e. the phenotype can be recognised in the case of heterozygosity
Duchenne muscular dystrophy	Muscle disease caused by X-chromosomal inheritance
Epigenetics	Field of science which investigates mechanisms in the phenotypical transfer of cell properties which are not determined in the DNA sequence to the daughter cells. The genetic activity of DNA fragments is influenced as a result of changes (epigenetic change)
Exon	All of the DNA fragments expressed in a cell
Expression	Type or degree of intensity of a gene
Gene	Fragment of DNA which codes for a functional product or has a regulatory function
Genetic markers	Polymorphism the exact chromosomal position of which is known and the different alleles of which appear so often that they are suitable for population screenings
Genome	The total genetic make-up of an individual

Genotype	Combination of both alleles in a gene locus
Gonosome	Sex chromosomes X and Y
Haemochromatosis	Disease caused by excess iron in the body
Haploidy	Single set of chromosomes (23 chromosomes), normal genetic status of germ cells
Heritability	Genetic proportion (in percent) of the overall variability of a steadily distributed characteristic observed in a population, e.g. height
Heterozygosity	So-called mixed inheritance. Two different alleles appear in one gene locus (e.g. mutation/normal allele (wild type)
Histones	Strong alkaline proteins which are closely associated with the DNA in the chromosomes
Homologous chromosomes	The chromosomes belonging to a chromosome pair
Homozygosity	So-called single inheritance. A pair of identical alleles appear in one gene locus (e.g. mutation/ mutation or wild type/ wild type)
Huntington's disease	Huntington's chorea; autosomal dominant neurodegenerative disease, which usually appears between the age of 40 and 60
Hypercholesterolemia	High blood cholesterol, usually has a multifactorial cause, an autosomal dominant form leads to a pronounced increase in the cholesterol concentration
Hypertension	High blood pressure, usually has a multifactorial cause
Index patient	The person through whom a genetic disease is identified in a family
Karyotype	Formalised description of the chromosome constitution of a cell (number and structure)
Mendelian Laws	The rules named after their discoverer, Gregor Mendel, describe the inheritance of characteristics caused by a mutation in a gene
Methylation	Transfer of methyl groups; in genetics it generally refers to the methylation of the DNA building block cytosine or individual amino acids of histones in the scope of the epigenetic inactivation of a gene
microRNA	Small RNAs which do not code and which have an important role in the gene regulation network
monogenic	A characteristic determined by a mutation of an individual gene
Multifactorial inheritance	A phenotype caused by the interplay between many genetic factors and environmental influences
Mutation	Hereditary change in the DNA in a cell i.e. in all cells of an individual. The term can be used for sequence changes irrespective of their phenotypical effect. In medical genetics it is usually used for sequence changes with phenotypical consequences
Nephrectomy	Operative removal of a kidney
Nucleotide	Basic building block of the nucleic acids DNA and RNA; in the DNA genetic material it consists of a base (adenine, guanine, cytosine or thymine), the sugar desoxyribose and a phosphate
Penetrance	Proportion of the mutation carriers (in percent) who are phenotypically affected by the mutation
Pharmacogenetics	Field of science which examines the influence genetic make-up has on the effect of medicines
Phenotype	Recognisable characteristic of a genotype in comparison to the characteristic of another genotype
Phenylketonuria	Autosomal recessive metabolic disorder which leads to a serious developmental disorder if left untreated in childhood
Polymorphism	Sequence variation. Position in the DNA sequence, where two or more alleles exist; usually used for those variations which do not have any functional significance
Preconceptual	Period before an oocyte is fertilised by a sperm cell
Preimplantation genetic diagnosis	Genetic examination of the individual cells of an embryo in the 8 cell stage for a monogenic disease or a chromosomal disorder after in vitro fertilisation
Prevention	Precautionary measures for avoiding a disease or prevention of the onset of a disease

Recessive	Phenotypical characteristic of both (mutated) alleles of an autosomal gene locus i.e. the phenotype can only be recognised in the case of homozygosity. In the case of an X-chromosome coded allele it is only the male sex which is phenotypically characterised
RNA	Ribonucleic acid (RNA): different types of molecules which are important for converting the genetic information from DNA into proteins (mRNA = messenger RNA) or have various functions (e.g. microRNA)
Screening	Systematic survey of all persons of a certain age/sex for a disease or a risk of disease
Sectoral health system	Areas of patient care divided by organisation and financing e.g. inpatient and outpatient treatment
Sequencing	Demonstration of the base sequence of the DNA or RNA
SNP	Single nucleotide polymorphism. Variation of an individual base pair in a DNA strand
Spinal muscular atrophy	Autosomal recessive disease which leads to muscle deterioration but is a result of a disorder of the nerve cells in the spinal cord
Susceptibility gene	Genetic information which increases or decreases the susceptibility for a certain disease
Transcription	Synthesis of RNA using a DNA template so that the genetic information is transcribed
Transcriptome	Set of all RNA molecules created in a cell
Translation	Synthesis of the proteins in the cells using the genetic information copied to mRNA molecules
Tumour supressor gene	Genes which code for proteins which negatively control the signal transmission in cells i.e. the cell cycle and thus prevent an excessive cell division as the cause of a tumour formation

13 Appendix

Appendix to chapter 4

For reasons of clarity, the empirically determined numbers in the following example are illustrated in the form of 10,000 persons examined.

Table 4.1: MSI analyses and mutation analyses in MMR genes in non-selected colon cancer patients

	Negative (no mutation in MMR Gene)	**Positive (Mutation in MMR Gen)**
Negative (no MSI)	True negative No mutation - no MSI 8,499	False negative Mutation - no MSI 1
Positive (MSI present)	False positive No mutation - MSI 1,330	True positive Mutation - MSI 170

Sensitivity: 170 / (170+1) x 100 = 99.4 %
Specificity: 8,499 / (8,499+1,330) x 100 = 86.5 %
Positive predictive value: 170 / (1,330+170) x 100 = 11.3 %
Negative predictive value: 8,499 / (8,499+1) x 100 = 99.9 %

Table 4.2: Frequency distribution in the MSI analysis for colon cancer patients who meet the Bethesda* criteria

	Negative (no mutation)	**Positive (mutation present)**
Negative (no MSI)	True negative 7,500	False negative 10
Positive (MSI present)	False positive 1,200	True positive 1,290

Sensitivity: 1,290 / (1,290+10) x 100 = 99.2 %
Specificity: 7,500 / (7,500+1,200) x 100 = 86.2 %
Positive predictive value: 1,290 / (1,200+1,290) x 100 = 51.8 %
Negative predictive value: 7,500 / (7,500+10) x 100 = 99.9 %
Note:
* Rodriguez-Bigas MA et al. (1997).

Table 4.3: Frequency distribution in the MSI analysis for colon cancer patients who meet the Amsterdam criteria*

	Negative (no mutation)	**Positive (Mutation present)**
Negative (no MSI)	True negative 4,250	False negative 50
Positive (MSI present)	False positive 700	True positive 5,000

Sensitivity: 5,000 / (5,000+50) x 100 = 99.0 %

Specificity: 4,250 / (4,250+700) x 100 = 85.9 %

Positive predictive value: 5,000 / (700+5,000) x 100 = 87.7 %

Negative predictive value: 4,250 / (4,250+50) x 100 = 98.8 %

Note:

* Vasen et al. (1991).

Appendix to chapter 6

Table 6.1: Diseases targeted in neonatal screening programmes by MS/MS in 10 EU member states (data from 2006)

Countries	Diseases
Austria	PKU, MSUD, TyrI, Cit, ASLD, Homocyst, MCADD, LCHADD, VLCADD, CPT ID, CPT IID/CACT, CTD, KTD, HMG-CoA LD, MMA, PA, IVA, GA I, 3-MCCD
Belgium	PKU, MSUD, TyrI, MCADD, LCHADD, VLCADD, CPT ID CPT IID/CACT, CTD, KTD, HMG-CoA LD, MMA, PA, IVA, GA I, 3-MCCD
Denmark	PKU, MSUD, Cit, ASLD, Arginase D, MCADD, LCHADD, VLCADD, CPT ID CPT IID/CACT, CTD, KTD, HMG-CoA LD, MMA, PA, IVA, GA I, 3-MCCD (pilot study, not 100% population coverage)
Germany	PKU, MSUD, MCADD, LCHADD,VLCADD, CPT ID, CPT IID/CACT, IVA, GA I
Greece (parents decide for or against testing)	MSUD, TyrI, Cit, ASLD, Homocyst, MCADD, LCHADD, VLCADD, CPT ID, CPT IID/CACT, HMG-CoA LD, PA, IVA, GA I, 3-MCCD, Malonic aciduria, and some others
Netherlands	MCADD (regional pilot programme)
Poland	PKU, MSUD, Cit, MCADD, LCHADD, VLCADD, CPT ID, CPT IID/CACT, CTD, IVA, GA I (pilot study with 30% of population covered)
Portugal	PKU, MSUD, TyrI, Cit, ASLD, Homocyst, MCADD, LCHADD, VLCADD, CPT ID, CPT IID/CACT, CTD, KTD, HMG-CoA LD, MMA, PA, IVA, GA I, 3-MCCD, Tyrosinemia type II, Hyperargininemia, Malonic aciduria, Multiple Acryl-CoA Dehydrogenase Deficiency (MADD)
Spain	PKU, MSUD, MCADD, LCHADD, VLCADD, CPT ID, CPT IID/CACT, IVA, GA I
UK (except Scotland)	PKU, MCADD (currently being rolled out nationwide)

Source: Javaher P et al. (2010).

Legend:

PKU	= Phenylketonuria
MSUD	= Maple syrup urine disease
TyrI	= Tyrosinaemia type I
Cit	= Citrullinaemia type I (II)
ASLD	= Argininosuccinate lyase deficiency
Homocyst	= Homocystinuria (CBS deficiency)
MCADD	= Medium-chain acyl-CoA dehydrogenase deficiency
LCHADD	= Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
VLCADD	= Very long-chain acyl-CoA dehydrogenase deficiency
CPT ID	= Carnitine palmitoyltransferase I deficiency
CPT IID/CACT	= Carnitine palmitoyltransferase II deficiency
CTD	= Systemic carnitine transporter deficiency
KTD	= ß-ketothiolase deficiency
HMG-CoA LD	= 3-hydroxy-3-methylglutaryl-CoA lyase deficiency
MMA	= Methylmalonic aciduria
PA	= Propionic aciduria
IVA	= Isovaleric aciduria
GA I	= Glutaric aciduria type I
3-MCCD	= 3-methylcrotonyl-CoA-carboxylase deficiency

Table 6.2: Newborn screening in Europe (2004)

Countries	Population (Million)	Children screened	Percentage of children screened*
Austria	8.17	79,022	109
Belgium	10.35	95,318	87
Cyprus	0.77	8,421	86
Czech Republic	10.25	97,664	105
Denmark	5.41	67,169	107
Estonia	1.34	13,886	106
Finland	5.21	53,000	96
France	60.42	817,388	110
Germany	82.42	726,973	104
Greece	10.65	106,655	103
Hungary	10.03	100,000 (estimation)	100 (estimation)
Ireland	3.97	62,000	108
Italy	58.06	577,351	110
Latvia	2.35	20,340	98
Lithuania	3.60	29,153	99
Luxembourg	0.46	5,652	101
Malta	0.40	3,887	97
Netherlands	16.31	194,781	105
Poland	38.58	354,973	99
Portugal	10.52	108,564	99.3
Slovakia	5.43	52,293	91
Slovenia	2.01	18,249	102
Spain	40.28	452,125	111
Sweden	8.99	101,450	104
UK (2005-2006) England Northern Ireland Wales	52.20	 544,179 22,568 32,917	 98.6 99.9 No data
Total	**432.70**	**4,645,928**	**92.7**

Source: Loeber JG et al. (2007), from Javaher P et al. (2010)

* over 100% is usually due to duplicate testing or duplicate data entry

Table 6.3: Newborn screening: number of phenylketonuria (PKU) cases detected (2004)

Countries	Number of children screened	Number of cases detected	Prevalence
Austria	79,022	10	1 : 7,902
Belgium Flanders	65,466	2	1 : 32,733
Belgium Wallonia	61,994	4	1 : 15,499
Cyprus	8,421	No data	No data
Czech Republic	97,664	7	1 : 13,952
Denmark	67,169	5	1 : 13,434
Estonia	13,886	1	1 : 13,886
France	817,388	46	1 : 17,769
Germany	726,973	85	1 : 8,553
Greece	106,655	3	1 : 35,552
Hungary (2001)	50,756	4	1 : 12,689
Ireland	62,000	10	1 : 6,200
Italy	577,351	158	1 : 3,654
Latvia	20,340	3	1 : 6,780
Lithuania	29,153	3	1 : 9,718
Luxembourg	5,652	No data	No data
Netherland	194,781	15	1 : 12,985
Poland	354,973	44	1 : 8,068
Portugal	108,564	11	1 : 7,714
Slovakia	52,293	10	1 : 5,229
Slovenia	18,249	6	1 : 3,042
Spain	450,125	8	1 : 18,000, hyperphenylalaninaemia ≈ 1 : 10,000
Sweden	101,450	8	1 : 12,681
UK (2005-2006) England Northern Ireland Wales	 544,179 22,568 32,917	 67 7 3	 1 : 8,122 1 : 3,224 1 : 10,972
Total	**4,669,989**	**581**	**1 : 8,076**

Source: Loeber JG et al. (2007), from Javaher P et al. (2010).

Table 6.4: Newborn screening: number of congenital hypothyroidism (CH) cases detected (2004)

Countries	Number of children screened	Number of cases detected	Prevalence
Austria	79,022	27	1 : 2,927
Belgium Flanders	65,466	16	1 : 4,092
Belgium Wallonia	61,994	14	1 : 4,428
Cyprus	8,421	5	1 : 1,684
Czech Republic	97,664	33	1 : 2,960
Denmark	67,169	21	1 : 3,199
Estonia	13,886	1	1 : 13,886
France	817,388	287	1 : 2,848
Germany	726,973	246	1 : 2,955
Greece	106,655	80	1 : 1,333
Ireland	62,000	23	1 : 2,696
Italy	577,351	328	1 : 1,748
Latvia	20,340	6	1 : 3,390
Lithuania	29,153	3	1 : 9,718
Luxembourg	5,652	4	1 : 1,413
Malta	3,887	1	1 : 3,887
Netherlands	194,781	66	1 : 2,951
Poland	354,973	115	1 : 3,087
Portugal	108,564	43	1 : 2,525
Slovakia	52,293	15	1 : 3,486
Slovenia	18,249	6	1 : 3,042
Spain	452,125	235	(currently accepted - acumulated data - ≈ 1 : 2,500 - 1 : 2,700)
Sweden	101,450	32	1 : 3,170
UK (2005-2006) England Northern Irleland Wales	 544,179 22,568 32,917	 309 15 12	 1 : 1,761 1 : 1,504 1 : 2,743
Total	**4,625,120**	**1.943**	**1 : 2,504**

Source: Loeber JG et al. (2007), from Javaher P et al. (2010).

Table 6.5: Newborn screening: number of congenital adrenal hyperplasia (CAH) cases detected (2004)

Countries	Number of children screened	Number of cases detected	Prevalence
Austria	79,022	3	1 : 26,341
Belgium Flanders	65,466	6	1 : 10,911
Belgium Wallonia	22,736	2	1 : 11,368
France	817,388	45	1 : 18,164
Germany	726,973	70	1 : 10,385
Italy	129,206	11	1 : 11,746
Luxembourg	5,652	1	1 : 5,623
Netherlands	194,781	10	1 : 19,478
Slovakia	52,293	10	1 : 5,229
Spain	112,914	7	1 : 16,131
Sweden	101,450	1	1 : 101,450
Total	**2,420,795**	**166**	**1 : 14,583**

Source: Loeber JG et al. (2007), from Javaher P et al. (2010).

Table 6.6: Newborn screening: number of cystic fibrosis (CF) cases detected (2004)

Countries	Number of children screened	Number of cases detected	Prevalence
Austria	79,022	23	1 : 3,436
Belgium Wallonia	30,036	4	1 : 7,509
France	784,663	179	1 : 4,384
Germany	45,822	20	1 : 2,291
Italy	434,101	94	1 : 4,618
Spain	136,298	48	(currently accepted ≈ 1 : 4,000)
Total	**1,509,942**	**368**	**1 : 4,103**

Source: Loeber JG et al. (2007), from Javaher P et al. (2010).

Table 6.7: Newborn screening: number of galactosaemia cases detected (modified after Loeber (2004)

Countries	Number of children screened	Number of cases detected	Prevalence
Austria	79,022	20	1 : 3,951
Belgium Wallonia	61,994	4	1 : 15,499
Germany	726,973	17	1 : 42,763
Ireland	62,000	2	1 : 31,000
Italy	176,360	6	1 : 29,393
Spain	38,348	2	1 : 19,174
Sweden	101,450	0	1 : 100,000
Total	**1,246,147**	**51**	**1 : 24,434**

Source : Loeber JG et al. (2007), from Javaher P et al. (2010).

Table 6.8: Newborn screening: number of biotinidase deficiency cases detected (2004)

Countries	Number of children screened	Number of cases detected	Prevalence
Austria	79,022	2	1 : 39,511
Belgium Flanders	33,324	1	1 : 33,324
Belgium Wallonia	44,651	No data	No data
Germany	726,973	16	1 : 45,436
Italy	105,471	1	1 : 105,471
Luxembourg	5,652	1	1 : 5,623
Spain	20,420	1	1 : 20,420
Sweden	101,450	3	1 : 33,817
Total	**1,111,311**	**24**	**1 : 46,305**

Source: Loeber JG et al. (2007), from Javaher P et al. (2010).

Table 6.9: Newborn screening: number of medium-chain acyl-coenzyme A dehydrogenase deficiency (MCAD) cases detected (2004)

Countries	Number of children screened	Number of cases detected	Prevalence
Austria	79,022	6	1 : 13,170
Belgium Flanders	33,324	3	1 : 11,108
Belgium Wallonia	46,108	3	1 : 15,369
Germany	726,973	69	1 : 10,210
Italy	16,519	No data	No data
Spain	20,420	2	1 : 10,210
Total	**922,366**	**83**	**1 : 11,113**

Source: Loeber JG et al. (2007), from Javaher et al. (2010).

Table 6.10: Prenatal screening programmes in 25 EU member states (data from 2006)

Countries	Ultrasound for fetal abnormalities	Nuchal translucency	Maternal serum markers	Maternal serum-alpha-fetoprotein	Fetal karyotyping[1]	ACE/AFP from amniotic fluid[2]	others
Austria	N	N	N	N	N	N	
Belgium	N	N	N	N	N	N	
Czech Republic	N	N	N	N	N	R	First trimester MS screening
Cyprus	N	N	N	Not routinely	Not routinely	Not routinely	
Denmark	N	R	R	R	N	N	
Estonia	N	R	N	N	N		
Finland	R	R	R	R	R	R	
France	N	N	N	N	R*	R*	
Germany	N	N	N	N	N	N	
Greece	N	N	N	N	R	R	
Hungary	N	N	R	N	R	R	
Ireland	R	R	R	R	R	R	All limited to women's request
Italy	N	N	N	N	N	N	
Latvia	N	rarely	rarely	rarely			
Lithuania	N	Selective screening for high risk pregnancies	Selective screening for high risk pregnancies	Selective screening for high risk pregnancies	N		
Luxembourg	R	R	50% of pregnant women	50% of pregnant women	R		
Malta	N	N	N	N			
Netherlands	R	R	R	R	N	N	
Poland	N	N	N	N			
Portugal	N	N	R	R	N	R	
Slovakia	N		N	N	N	R	
Slovenia	N	N	For high risk pregnancies	For high risk pregnancies			

Table 6.10 (continued): Prenatal screening programmes in 25 EU member states (data from 2006)

Countries	Ultrasound for fetal abnormalities	Nuchal translucency	Maternal serum markers	Maternal serum-alpha-fetoprotein	Fetal karyotyping[1]	ACE/AFP from amniotic fluid[2]	others
Spain	N	N	R	R	R	R	
Sweden	N	R	R		R		
UK (without Scotland and Wales)	N	N	N	Not recommended	N	Not recommended	

Source: Javaher P et al. (2010).

Legend:

R = regional

N = nationwide

ACE = Acetylcholinesterase

AFP = Alpha-fetoprotein

Blank spaces in the fields indicate “no programme”

[1] In case an invasive prenatal diagnosis was performed for reason other than primarily detecting fetal aneuploidy (e.g. a single gene disorder)

[2] In case an invasive prenatal diagnosis was performed for a chromosomal or sinlge gene disorder

* In France, “R” reflects diverse approaches to these issues in the absence of a defined nationwide policy for these measures

Table 6.11: Diseases targeted in population-based carrier screening programmes in 23 EU member states (data from 2006 in comparison with data from 2003)

Countries	Population-based carrier screening	Comments
Austria	None	
Belgium	Local screening for haemoglobinopathy, CF, FXS, and SMA	
Cyprus	Screening for haemoglobinopathy - offered only if they have not undergone preconceptual screening beta-thalassemia screening is offered to all couples prior to marriage, nationwide	Offered through the public thalassemia centres. Very high uptake.
Czech Republic	Screening for CF in pregnancy	Both non-systematically
Denmark	None	
Estonia	None	
Finland	No carrier screening for haemoglobinopathy and CF in pregnancy or preconceptual, congenital nephrosis (R)	
France	Regional Screening for haemoglobinopathy and CF	
Germany	Haemoglobinopathy in pregnancy, depending on ethnic background	
Greece	Haemoglobinopathy in pregnancy and preconceptual, upon request for CF	
Hungary	None	
Ireland	None	
Italy	Haemoglobinopathy, CF and FXS in pregnancy, hearing loss CX26	
Latvia	None	
Lithuania	Screening for CF - selective screening for high risk pregnancies	
Luxembourg	None	
Malta	None	
Netherlands	Rarely haemoglobinopathy in pregnancy or precon-ceptual	
Poland	None	
Portugal	Screening for haemoglobinopathy	by red blood cell count and indices
Spain	None	
Sweden	None	
UK	National screening programme for sickle cell and thalassaemia based on routine bloods indices, family origin questionnaire and variant screening or testing	

Source: Loeber et al. (2007), cited in Javaher P et al. (2010).

Table 6.12: Diseases targeted in cascade screening in 25 EU member states (data from 2008)

Countries	Cascade screening	Comments	Type of initiation
Austria	Hypercholesterolemia, Fabry Disease, DMD, FXS and other dominant disorders		1
Belgium	On a case by case basis but not organized or compulsory, screening for CF, DMD; FXS, HH, haemoglobinopathy and beta-thalassemia		3
Cyprus	Offered to the whole population through specialised clinics, Screening for CF, DMD; FXS, HH, haemoglobinopathy and beta-thalassemia	Molecular tests performed mainly at the Cyprus Institute of Neurology and Genetics. Genetic counselling offered through the Genetics clinic and/or the Thalassemia centre.	No data
Czech Republic	Principally all hereditary conditions	http://www.uhkt.cz/nrl/db/index_html?lang=en	1 and exceptionally 2
Denmark	Screening for hypercholesterolemia (A) HNPCC (B) FXS (C) CF (D)		A: 3 B: 2 C: 1 D: 1
Estonia	Not on a systematic basis, only on a case by case basis or in families with history for CF, DMD/BDM, FXS, nonsyndromic Deafness, trombophilia (Leiden mutation, factor II), any genetic disease with high penentrance where there is an index person with a known disease-causing mutation		1
Finland	On the initiative of the family or the professional screening for any recessive disorder with a reasonably good founder mutation, HNPCC, BRCA1 and other conditions like DMD, FXS, HH, factor V, and familial y hypercholesterolemia		1, sometimes 3
France	Cascade screening mandatory by law whenever it is necessary	A law since 2004 to propose cascade screening whenever necessary, Obligation for the consultant to convince the patient to contact the family and patient‘s declaration in case of refusal as protection of the physician	1, mandatory by law
Germany	Principally all hereditary conditions		1
Greece	Nationally for haemoglobinopathy, regionally for CF; DMD and FXS		1
Hungary	Nationwide screening for CF, regional screening for FXS and CAH		No data
Ireland	Nationally for CF, DMD, FXS, haemoglobinopathy, beta-thalassemia and many others		1
Italy	On a case by case basis, but not organized or compulsory, screening for CF, DMD, FXS, HH, haemoglobinopathy, beta-thalassaemia and nonsyndromic deafness due to connexin 26		3, a combination of both with direct contact by professionals after proband-initiation
Latvia	No response	No response	No response
Lithuania	Screening for CF - selective screening for high risk pregnancies	Centre for Medical Genetics, Vilnius University Hospital Santariškių klinikos	No data

Table 6.12 (continued): Diseases targeted in cascade screening in 25 EU member states (data from 2008)

Countries	Cascade screening	Comments	Type of initiation
Luxembourg	No response	No response	No response
Malta	No response	No response	No response
Netherlands	Nationwide cascade screening programme for familial hypercholesterolaemia. Index patients are advised to inform their family on a systematic basis for hereditary tumours and on a case-by-case basis for other diseases		3, for familial hypercholesterolaemia 1, for hereditary tumours etc.
Poland	Molecular screening recommended and offered in relevant inborn errors of metabolism including CF, galactosaemia, DMD, SLO, NBS, LCHAD, SCO2 gene mutation, SURF1 gene mutation, mtDNA mutations and familial hypercholesterolemia	Hemochromatosis occurance in Polish population not established, Haemoglobinopathy and beta-thalassemia for Polish population irrelevant	1, performed by 12 regional genetic clinics and national metabolic clinics
Portugal	If proper referral occurs nationwide screening for CF, DMD, FXS, HH, haemoglobinopathy, beta-thalassemia and other late-onset neurological disorders like: SCAs, Huntington, familial amyloidosis etc.		1
Slovakia	On family request, screening for CF		a combination of both with direct contact by professionals after proband-initiation
Slovenia	No response	No response	No response
Spain	Nationwide screening for CF, DMD and HH		No data
Sweden	Nationwide screening for CF, DMD, FXS, HH, haemoglobinopathy, beta-thalassemia and any genetic disease with high penetrance where there is an index person with a known disease causing mutation on a case by case basis		1
United Kingdom	CF, family members at their request		3

Source: Javaher P et al. (2010).

Legend:

1: Proband-initiated contact of at risk relatives

2: Direct contact by professionals of at risk relatives

3: A combination of both with direct contact by professionals after proband-initiation

CF = Cystic fibrosis

DMD = Duchenne muscular dystrophy

FXS = Fragile X syndrome

HH = Hereditary haemochromatosis

CAH = ongenital adrenal hyperplasia

HNPCC = Hereditary nonpolyposis colorectal cancer

BRCA1 = Breast cancer 1

SLO = Smith-Lemli-Opitz syndrome

NBS = Nijmegen Breakage syndrome

SCO2 = Synthesis cytochrom c Oxidase 2 gene

SURF 1 = Surfeit locus protein 1 gene

SCA = Spino cerebellar ataxis

Appendix to chapter 7

Example 7.1: A modelling study on autosomal recessive hereditary haemochromatosis showed that a national screening programme consisting of a combination of phenotypical and genetic diagnostics costs three times as much and a simple genetic screening costs approx. four times as much as the strategy with the combined approach for only testing male offspring of known haemochromatosis patients per each year of a person's life. The study also showed that carrying out the genetic tests directly after determining the transferrin saturation is much more cost-effective than carrying out a second transferrin saturation test as provided for in the German guidelines[138].

Example 7.2: A review[139] published in 2006 found 21 evaluations of genetic screening programmes. It found that genetic tests were much more cost-effective than liver biopsies for confirming hereditary haemochromatosis. Moreover, it was also cheaper to identify the first and subsequent mutation carriers through DNA in order to screen first-grade relatives of patients with familial adenomatous polyposis than to carry out an intensified colonoscopy for each person. The cost advantages developed through the reduction in colonoscopies for mutation negative relatives. In the case of familial hypercholesterolemia, however, phenotypical tests proved to be more effective and cheaper than the DNA test in an economic modelling of various screening strategies. There are, however, no current reviews.

Example 7.3: The effectiveness and profitability of a screening for amblyopia in children was examined using literature-based modelling and the evaluation of a practical programme. Amblyopia is a non-direct genetic visual disorder. It involves a functional disconnection of an eye or both eyes, particularly in childhood, which can lead to blindness. The causes can be diverse, for example, a squint, overhanging eyelid = ptosis, haze over the cornea, which leads to poor activation of the nerve cells in the visual cortex of the brain. Relevant deviations between the theory and practice appeared through differences in the frequency of the disease, in the programme participation by patients and doctors as well as in the organisation costs[140].

Example 7.4: The review mentioned[141] showed that in the genetic screening of newborns for the autosomal recessive diseases cystic fibrosis (mucoviscidosis) or adrenogenital syndrome (inability to synthesise cortisol), in North America both diseases are usually examined. Three groups of countries could be found in Europe: in the first two groups it was either only cystic fibrosis or adrenogenital syndrome which was tested, the countries in the third group test both diseases. Detailed studies on the frequency of the appearance of the disease and on early mortality are required in order to be able to accurately assess the effectiveness of the screening strategies.

138 Rogowski WH (2009).
139 Rogowski W (2006).
140 König HH et al. (2002).
141 Grosse SD et al. (2010).

Example 7.5: In a review by Heshka et al. 2008[142] on 16 studies which include behavioural aspects, persons with predispositions to colon cancer (HNPCC) had higher participation rates in the cancer screening, while the participation rate for those with a predisposition to breast cancer (BRCA1/2) (screening participation was generally high) was not so distinctive. Furthermore, the review showed that persons with a predisposition to breast and ovarian cancer (BRCA1/2) improved their lifestyles to the same extent as persons without this predisposition through a healthy diet, more exercise and not smoking. In comparison, however, carriers of a predisposition to Alzheimer's disease (APOE ε4) changed their diet and exercise routine more often in the hope of minimising the risk. New genetic information can have different effects on health-related behaviour. Irrespective of this, the effect of behavioural changes on health is still to be clarified.

142 Heshka JT et al. (2008).

Text genesis

The Academy Group "Predictive genetic diagnostics as an instrument of disease prevention" was set up in September 2009 by the Standing Committee of the German National Academy of Sciences. A content-related concept for the preparation of the Academy Group had been being developed since March 2009.

The statement was developed by the members of the Academy Group in a total of 9 meetings between September 2009 and July 2010. An international Academy symposium was held in Bonn on 7th and 8th February 2010 as well as an expert hearing in Frankfurt (Main) in order to take all important aspects and, in particular, experiences from abroad into account.

Programme of the International Academy Symposium, 7th - 8th February 2010, Bonn

International Symposium "Predictive genetic diagnostics as an instrument for disease prevention"

Sunday, 7th February 2010	
Welcome address	Heinz Schott, Bonn, Member of the Leopoldina Presidium
A. Scientific background	
Why this symposium?	Peter Propping, Bonn, Germany
Genetic screening criteria in the age of genomics	Martina C. Cornel, Amsterdam, NL
Epidemiological prerequisites for screening	Thomas F. Wienker, Bonn, Germany
Evaluation of genetic susceptibility testing	Caroline Wright, Cambridge, UK
Epigenomics for risk prediction?	Winston Timp, Baltimore, US
B. Established screening procedures	
Newborn screening in Germany and Europe	Georg Hoffmann, Heidelberg, Germany
Carrier screening for haemoglobinopathies	Antonio Caro, Cagliari, Italy
Cascade screening for hypercholesterolemia in the Netherlands	Peter Lansberg, Amsterdam, NL
Cascade screening for hereditary disorders in France	Ségolène Aymé, Paris, France
C. Experimental/controversial screening procedures	
Comprehensive carrier screening	Hans-Hilger Ropers, Berlin, Germany
Hereditary breast and colon cancer: predictive testing and genetic screening	John Burn, Newcastle, UK

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C. Experimental/controversial screening procedures (continued)	
Pharmacogenetic screening and personalised medicine.	Matthias Schwab, Stuttgart, Germany
Screening for thrombophilia	Saskia Middeldorp, Leiden, NL
Genetic and biochemical screening for metabolic diseases	Joachim Thiery, Leipzig, Germany
D. Questions of value	
Health economic analysis of screening for haemochromatosis	Wolf Rogowski, München, Germany
Captious certainties: makings, meanings, and misreadings of consumer oriented genetic testing	Norbert Paul, Mainz, Germany
Health risk communication	Ulrich Hoffrage, Lausanne, Switzerland
Concluding remarks	Peter Propping, Bonn, Germany

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