Leopoldina
Nationale Akademie
der Wissenschaften

acatech
DEUTSCHE AKADEMIE DER
TECHNIKWISSENSCHAFTEN

berlin-brandenburgische
AKADEMIE DER WISSENSCHAFTEN

briefing paper

Deutsche Akademie der Naturforscher Leopoldina —
Nationale Akademie der Wissenschaften
acatech – Deutsche Akademie der Technikwissenschaften
Berlin-Brandenburgsiche Akademie der Wissenschaften
(für die Union der deutschen Akademien der Wissenschaften)

November 2010

Summary of the statement

Predictive Genetic Diagnostics as an Instrument of Disease Prevention

The early recognition of treatable diseases is playing an increasingly important role in modern medicine. Most diseases involve hereditary dispositions. For this reason, in the future, diagnostics at the DNA level will be an important part in personalised medicine, especially as in the near future it will be possible to sequence man's entire chromosome set reliably and cost-efficiently. Recently, analysis methods have quickly developed and it is hopeful that the genetic foundations of diseases – whether monogenic or multifactorial diseases – will gradually be better understood and consequently new prevention and treatment opportunities will possibly emerge as a result. Thus research should be intensified in the area of genetic medicine in Germany.

Genetic investigations are connected with value questions; many people even fear a „genetisation" of the society. This is added to by the fact that scientists, doctors and the media sometimes draw different conclusions from genetic results and methods, also partly causing false hopes or creating anxieties. Thus society should be continuously and factually informed about the options and constraints of genetic medicine including predictive genetic diagnostics.

The statement serves to inform the public and politics and extensively highlights the broad field of predictive genetic diagnostics from various perspectives. According to the latest knowledge, opportunities and constraints are considered, as well as the medical, ethical, economic and legal dimensions of predictive genetic diagnostics.

Members of the Academy Group: Prof. Dr. Peter Propping (Human Genetics, Bonn, Chairmanship), Prof. Dr. Claus R. Bartram (Human Genetics, Heidelberg), Prof. Dr. Matthias Brandis (Peditatrics and Youth medicine, Freiburg), Prof. Dr. Thomas Cremer (Biocenter, München), Prof. Dr. Detlev Ganten (Charité Foundation, Berlin), Prof. Dr. Reiner Leidl (Business Studies, München), Prof. Dr. Markus Löffler (Medical Informatics, Statistics and Epidemiology, Leipzig), Prof. Dr. André Reis (Human Genetics, Erlangen), Prof. Dr. Hans-Hilger Ropers (Max-Planck-Institut for molecular genetics, Berlin), Prof. Dr. Jörg Schmidtke (Human Genetics, Hannover), Prof. Dr. Ludger Schöls (Hertie-Institute for Clinical Brain Research, Tübingen), Prof. Dr. Karl Sperling (Human Genetics, Charité Berlin), Prof. Dr. Jochen Taupitz (Civil, International and Comparative Law, Mannheim and Heidelberg), Prof. Dr. Gerd Utermann (Medical Biology and Human Genetics, Innsbruck), Prof. Dr. Ulrich Walter (Clinical Biochemistry, Würzburg), Prof. Dr. Karl Werdan (Internal Medicine, Halle/Saale), Prof. Dr. Urban Wiesing (Ethics and History of Medicine, Tübingen)

Key recommendations

Recommendation 1: Predictive genetic diagnostics must only be carried out at the request of and in the interests of individual people.

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

Recommendations 3-5: If during genetic diagnostics more information – „excess information" – is generated than is required for the intended diagnostics, the Academy Group recommends discussion with the affected person concerning proceedings to bring about an „enlightened decision". An excess of genetic information should not appear in the medical file or any doctor's letters.

Recommendation 6: 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 nature, 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.

Recommendations 7 and 8: The newborn screening is a successful example of the use of early recognition of an illness using predictive genetic diagnostics. Surveys for other genetic illnesses should be aligned with the newborn screening. In the Gendiagnostikgesetz, newborn screening should however be regulated separately and under consideration of the particular examination situation.

Recommendations 9 and 10: A range of genetically determined and essentially treatable diseases which are highly likely to appear over a lifetime can be predicted. In the health system, organisational measures should be taken to treat patients with these kinds of diseases and persons at risk in an appropriate way. Here the further training of specialist doctors and the setting up of interdisciplinary and superregional competence centres can also play a role.

Recommendation 11: The Academy Group encourages research projects to identify the prerequisites and criteria which must be fulfilled in Germany for offering genetic screening.

Recommendation 12: The systematic investigation of healthy people for dispositions (heterozygote screening for recessive diseases) – without any family history of disease being evident – is a new situation for our society which has wide-ranging ethical and social implications. Such investigations should for the time being only be carried out within the scope of research projects.

Recommendation 13: Before predictive genetic diagnostics can be integrated into the health system, supporting evidence indicating their effectiveness and cost-effectiveness must be available. For this, scientific accompanying projects are necessary.

Recommendation 16: The Gendiagnostikgesetz stipulates that the responsible doctor is to destroy the results of genetic investigations and analyses ten years after the investigation. The Academy Group recommends: the results of the genetic diagnostics should be allowed to be stored in the interest of counselees and family members without a concrete deadline as before.

Recommendations 17 and 18: The complete sequencing of the genome can provide evidence for explaining genetic contributions to multifactorial diseases. The Academy Group recommends intensively setting up appropriate, systematic research programmes in Germany and promoting translational research and the development of medical guidelines for predictive genetic diagnostics as well as basic research.

Recommendations 19 and 20: Genetic tests, as currently offered directly via the internet – so-called DTC tests ("direct to consumer" tests) – mostly have an uncertain scientific basis and do not generally fulfil the requirements of a suitable genetic consultation. DTC tests should not be permitted because they do not fulfil the requirements of medical and ethically acceptable predictive genetic diagnostics.

Recommendations 21 and 22: Society should be informed properly and continually about the possibilities and limits of genetic medicine, including predictive genetic diagnostics. The new findings of genetic research should be presented in schools, in particular. 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.

The statement in brief

Genetic and epigenetic foundations of health and disease

The development of a human being, his/her health and the emergence of diseases are a phenotypic expression of reciprocal effects between all of his/her hereditary dispositions, the genome, packaging and composition of the hereditary dispositions in the chromatin of the cell nucleus as well as of the environmental conditions. The concurrence of these factors and their complex relationships with one another are still not yet fully understood. Epigenetics covers the characteristics of cells based on the changes in the DNA genetic make-up and are inherited in daughter cells, but are not however fixed in the DNA sequence. This can lead to a physically recognisable particularity or even disease in a human being. Monogenic diseases where the variant of a particular gene leads to a disease are not to be confused with multifactorial diseases. So-called widespread diseases such as diabetes mellitus, heart and circulation diseases, allergies or psychological diseases differ from monogenic diseases (such as cystic fibrosis or Huntington's chorea) in that they do indeed show a certain familial frequency, but there is no clear mode of inheritance. The occurrence of the disease is based on the concurrence of hereditary and environmentally determined factors.

Key words:
Genetics; history of genetics; Epigenetics; Environmental influence; Concurrence of all factors; Monogenic diseases; Multifactorial diseases
see chapter 2

Medical context of genetic diagnostics

The diagnosis of a disease pattern first and foremost depends on the clinical symptoms. A certain uncertainness can therefore never entirely be ruled out. Through molecular safeguarding, however, the clinical suspicion of a monogenic disease can be verified – in particular, this applies to the initial stage of a disease, the point at which secondary preventive measures must be taken. The optimal therapy can be achieved when one knows how the effect of a type of medication is dependent on genetic factors. In this respect, pharmacogenetics plays an important role as far as „personalised medicine" is concerned. The predictive diagnostics of monogenic diseases is to a large extent new medical territory. It is broached in detail as an issue in the report. As the results are not just of importance for the person to be examined, but also for an entire family, for example, particular care from a medical, ethical and legal perspective is necessary. In all cases, it should be ensured that every measure is preceded by a qualified consultation and counselling. In this context, the commonly controversially debated topics of prenatal diagnostics and preimplantation genetic diagnosis are briefly discussed (PIGD). Like the similarly discussed serial examinations for genetically determined diseases, they agitate in a complex ethical field and in a complicated legislative environment. Serial examinations for genetically determined diseases take place worldwide as part of the newborn screening programs. In Germany, this program covers 12 predominantly genetically determined metabolism disorders which can lead to severe diseases if left untreated.

Key words:
Molecular validation of the diagnosis; Pharmacogenetics; Personalised medicine; Predictive diagnostics; Prenatal diagnostics; Preimplantation genetic diagnosis; newborn screening
see chapter 3

Quantifying risks

A predictive statement requires a quantitative evaluation. Particular statistical methods are required to be able to make statements concerning the risk of affection for genetically determined diseases. In particular, apart from the possible genetically determined disposition of a person, the various influential factors such as environmental conditions, lifestyles or preventive measures should be considered.

Key words:
Risk assessment using; Sensitivity and specificity; Positive and negative predictive value; Age-dependent probability of disease; Relative risk
see chapter 4

The future of human genome research: importance for predictive diagnostics

New technical developments have led to advances in human genome research. High resolution DNA chips are used in research on DNA samples from large groups of patients with multifactorial diseases which are compared with healthy people. The DNA chips used to date, however, only detects genetic variants which have a certain minimum frequency among the population. To date identified genes can only account for a small proportion of heritability in all multifactorial traits. The analysis of multifactorial diseases, however, is likely to experience a qualitative advance through the new methods of analysis, although the challenge here is far greater than for monogenic characteristics. For the diagnostics of monogenic diseases, genome sequencing may soon be a simpler and cost-efficient alternative to the numerous tests used today. However, the sequencing of the entire genome of an individual can lead to a significant increase in not (yet) interpretable genetic excess information. The person examined alone is to decide about their use. This involves extensive medical, ethical and legal issues which are discussed in the report in detail. Furthermore, it must notably be ensured that the data obtained can be interpreted in a qualified way. Internet based "direct to consumer" (DTC) offers for genetic diagnostics should not be permitted as they do not fulfil the requirements for medical and ethically acceptable predictive genetic diagnostics. For predictive gene tests, an advertising ban should be legally enforced.

Key words:
New analysis methods (DNA chips; „next generation sequencing"); Genome-wide associations studies (GWAS); Qualitative advancement in the diagnosis of multifactorial diseases; Internet- based "direct to consumer" (DTC) offers; Heterozygote testing; Disease research; Implementing research results in medical practice
see chapter 5

EuroGentest-Investigation

Both the standards of medical research and numerous legislative procedures may today only be judged in a European framework. The report highlights the EuroGentest investigation of genetic serial examinations in Europe. With regards to the results of the serial examinations (updated 2006–2008), the report contains detailed charts.

Key words:
Newborn screening; Prenatal screening for chromosome dysfunctions and neural tube defects; Cascade screening
see chapter 6

Health economics aspects

Due to scientific and technical progress, medical provision opportunities are increasingly growing. At the same time, due to the aging of the population, there are continuously fewer paying members of the mutually supportive society. This means that medical provision opportunities and their financing are developing in opposition to one another. Should one wish to verify which provisions may be offered under social security, the most important deciding factor must be the benefit to the patients. This can sometimes lead to a cost-efficient result, sometimes it means that health is „bought" through higher costs. Studies concerning genetic screening show that both economic and uneconomic results are possible. Better data records could lead to greater precision here. In order to improve health in both an effective and economic way with predictive genetic diagnostics, the basis for evidence must thus crucially be improved. This also means an increased need for research in this area.

Key words:
Cost-effectiveness components; Cost-effectiveness of a diagnostic test; Cost-effectiveness of screening programmes
see chapter 7

Medical ethical aspects

For all genetic diagnostics, the fundamental, widely accepted and in many cases stipulated ethical principles of medicine must be respected. The patient to be examined must freely consent to the measure after being informed, the medical measures must serve the health of the affected person. However, the following apply and need to be considered when predictive examinations are concerned: a) The ensuring of flanked self-determination through good counselling; b) Observance of the fact that other relevant conclusions about relatives may be drawn using genetic information whereby the self-determination of several people is affected; c) All results are subject to medical professional discretion, unless the person examined acquits the doctor from his/her duty of professional discretion; d) The medical measures are subject to the requirement that they are conducive to and do not damage the health of the affected person or at least have an acceptable benefit-disadvantage ratio. Here a particular challenge arises in predictive diagnostics: Whenever this is the case, predictive genetic diagnostics should by no means ever be responded to in a trivial way. This concerns knowledge which points to diseases which may only possibly emerge in the distant future. Predictive knowledge is often probabilistic, i.e. the appearance of a disease can only be predicted as a possibility. Equal access must be ensured. Decisions both for an individual predictive examination and for a serial examination should be founded on a professional basis with regards to their effectiveness and economic efficiency and should not involve any discrimination.

Key words:
Observance of self-determination; Genetic knowledge and family members; Professional discretion; Benefit and not disadvantage; Fairness considerations
see chapter 8

The German Gendiagnostikgesetz (Gene Diagnostics Act)

The concluding chapter of the report comments in detail on the German Gendiagnostikgesetz which came into effect on 1st February 2010, whereby the main focus of attention is on the second section (genetic examinations for medical purposes). As numerous problems and inconsistencies emerge in the implementation of the German Gendiagnostikgesetz which also affect predictive genetic diagnostics, essential parts of the Act are in urgent need of amendment (§§ 8, 9, 11, 12, 14, 15).

see chapter 9

Contacts:
Dr. Kathrin Happe, Leopoldina, Department Science - Policy - Society, politikberatung@leopoldina.org, Tel.: +49 (0)345 47 239-832
Caroline Wichmann, Leopoldina, Department of Press and Public Relations, presse@leopoldina.org, Tel.: +49 (0)345 47 239-800