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**TAB**

# Genetic diagnostic - status and prospects

Summary



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## SUMMARY

The international project to fully sequence the human genome is close to completion. We can expect that the resulting information will greatly expand the possibilities for diagnosing genetic traits (at least partly) responsible for the incidence of diseases. There are also signs of technological developments which could considerably simplify the use of »genetic tests« in medical practice (DNA chips). This potentially opens up the prospect of routine use of genetic tests in many areas of health care. These prospects and the emerging medical and ethical problems already apparent in the current use of genetic diagnosis, together with the many dangers of misuse are the reasons why TAB, at the suggestion of the rapporteurs for Technology Assessment in the German Bundestag Committee for Education, Research and Technology Assessment, has returned to the topic of »the status and prospects for the use of genetic tests« within the framework of its monitoring activities (TAB submitted an earlier report on genetic diagnostics in 1993).

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## THE STATUS OF HUMAN GENOME RESEARCH

Sequencing of a base or reference genome will bring us closer to the declared goal of international human genome research of using the structure of the human genome to explain the function of individual genes, but will still leave us well short of achieving it. The »reference genome« describes the genetic material common to humans and allows for comparison with the genome of other organisms. However, to understand the function of individual genes, and particularly the mutations involved in the etiology of disease, genetic differences between human beings – i.e. the variation within the genome – are more important. In medical and pharmaceutical terms, disease-related genetic variations are particularly important. To understand such variations and their medical significance, a number of different research strategies are currently being pursued internationally.

There is scientific agreement that mere knowledge of the sequence of genes or proteins has little explanatory value on its own, even if, at times, this was hardly ever mentioned in the debate on genome research, as a result of the concentration on sequencing. With the progress in the international human genome project, the focus is increasingly on the complexity of the actual task, explaining the function of genes. One question here is the fundamental suitability of the systematic »big science« projects with their primarily quantitative approach for reaching a basic understanding e.g. of the pathological processes.



## SUMMARY

Systematic genome research generally is accordingly in a relatively early stage. The overwhelming majority of the drugs and therapies on the market in any case are still not based on the actual Human Genome Project (HGP). The most concrete methodological-technical and »material« inspirations and influences have been in the field of genetic diagnostics.

Major advances have been made in diagnosing infections and tumours, and these already have great practical significance. DNA analysis techniques have gained broad acceptance in the field of pathogen diagnostics and have probably had the most concrete benefits for medicine in this area to date. There are also diverse possibilities for using DNA analysis in differential diagnosis of cancers. As cancer always involves changes at the level of DNA, chromosome and DNA analysis techniques are suitable for early identification, progress monitoring and controlling the success of therapy.

For some years pharmacogenomics and toxicogenomics have figured in professional circles as highly promising applications of genome research in other areas of research and possibly medicine. The goal of this research area is to detect genetically-caused differences in metabolising drugs and toxins, in order to utilise them to improve prevention and therapy. The vision of pharmacogenetic research is to use analysis of genetically-caused differences concerning the ability to metabolise chemical substances with the goal to develop drugs for specific groups of patients, or to select from the available drugs those which are optimal for individual patients – i.e. which have the maximum effect along with minimum side effects. Despite the overall minimal state of knowledge at this stage, the pharmaceutical industry is showing great interest, given the substantial economic potential in pharmacogenomics.

In the narrower field of genetic diagnostics, the main focus of hopes and fears is diagnosis of multifactorial diseases affected by a number of genes and environmental influences. Most of the widespread diseases – cancer, cardiovascular, metabolic (including diabetes) and neurodegenerative diseases (Alzheimer) – have multifactorial etiology. It is expected that research into the human genome will open up a new dimension of understanding of the role of genes in the incidence of the diseases listed. In clinical practice, however, diagnosis using human DNA is still very largely limited to single-gene inherited diseases. Examples of real use of possible tests for multifactorial diseases are still limited at present to a small number, the most frequently cited being proof of mutations in the BRCA genes causing breast cancer and the association of ApoE variants with a risk of Alzheimer's. Hopes are focused particularly on diagnosing genetic disposition to cancer.

A typical feature of all forms of genetic diagnosis for multifactorial diseases or disposition to disease is the limited information they provide, as they show only an increased risk of a disease and not a reliable prognosis. The value of the typical information from gene tests – a corresponding genetic characteristic means that the patient has a certain probability of contracting disease x by a given age – appears highly doubtful, at least where no reliable or tolerable therapy is available.

It is, however, not unlikely that genetic testing will be extended in future to multifactorial disposition to disease. First, the next few years will probably see growing research into dispositions which it makes sense to test for, i.e. are amenable to preventive therapy. Second, it must realistically be expected that largely pointless tests may also establish themselves. Past experience shows that many diagnostic and therapeutic procedures are used (and also funded by the health insurance schemes) whose purpose has never been scientifically convincingly demonstrated or even evaluated.

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## HUMAN GENETIC COUNSELLING AND DIAGNOSIS

The number of diseases and handicaps with known genetic causes has grown steadily in recent years. A range of new genetic tests is also used in genetic counselling at university institutes and by human genetics specialists in private practice. The overwhelming majority of these are (still) tests for relatively rare single-gene inherited diseases. However, genetic tests for breast cancer and Alzheimer's are also being used. The problem of using tests like these, which can only identify an increased risk of the disease, is being intensively debated by the professional associations and the Federal Medical Council, as there are generally only drastic preventive measures (in the case of breast cancer) or no useful measures at all available if the diagnosis is positive. The general expectation in professional circles is that the range of predictive diagnostic products available for multifactorial diseases will increase in future. This will increase the number of questions about the value or otherwise of using such test products. Because of the limited information provided by such tests, qualified human genetic counselling is regarded as essential.

Whether qualified counselling can be ensured in future is doubtful if the test possibilities continue to expand and tests become so technically simple and cheap that they can be used by non-specialists working with private diagnostic laboratories. The technological prerequisite for this is met by the development of the DNA chip, which potentially permits several hundred genetic tests to be carried



out in a single automated process. Whether genetic tests will become routine in general medical practice (other than genetic counselling) is highly doubtful, given the limited informational value of many tests. The current problems in test practice do, however, give grounds for concern that genetic tests may come to be used on the principle that »if it can be diagnosed, it should be«.

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## PRENATAL DIAGNOSIS

This is particularly applicable to prenatal diagnosis of genetically caused diseases and handicaps in the foetus as part of preventive examinations in pregnancy. Prenatal diagnosis (PD) using amniocentesis and chorionic biopsy has steadily developed into a routine procedure for pregnant women since the end-70s. The original age indication limiting prenatal diagnosis to women over 35 has now largely disappeared in practice, so that every pregnant woman is notified of the possibility of PD by her gynaecologist. The expansion of the use of PD has been driven by the so-called »triple test«, which makes it possible to identify an increased risk of chromosomal anomalies in a foetus from an examination of the mother's blood. Although this test is under severe criticism from human geneticists for its lack of validation and frequent false positive (and negative) results, it is offered by many gynaecologists as a »safety first« test, which is often followed by a (frequently unnecessary) amniocentesis.

The use of genetic diagnostics in PD is already revealing substantial problems with the quality of counselling. In the overwhelming majority of cases the diagnosis is ordered by the gynaecologist, and in part carried out in his own laboratory. The quality and scope of counselling are often deficient. A free, individual decision for or against performance of a genetic tests requires comprehensive information of the patient. There is general agreement that this is often not available in PD practice.

Women's associations and many self-help groups for the handicapped reject PD as a standard part of preventive medicine in pregnancy. They claim it is not medically justified, leads to unnecessary stress on women and harbours a trend towards discrimination against the handicapped. The demand for an improvement in counselling (including psycho-social counselling) is often linked to the desire for independent (rather than human genetic) counselling services for women.

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## PRE-IMPLANTATION DIAGNOSIS

A new potential application for genetic diagnosis is in vitro fertilisation. In so-called pre-implantation genetic diagnosis (PGD) artificial insemination is combined with examination to identify genetic alterations not in the foetus in utero but in egg-cells or in vitro in embryos in an early stage of development. Embryos or egg-cells in which the target genetic characteristic is found are selected, while those without the target characteristic are transferred to the woman's uterus.

The procedure, which has now been used in several hundred cases worldwide, has led to a debate in Germany about the Embryo Protection Act. While PGD was previously regarded unanimously as prohibited by the Embryo Protection Act, an increasing number of comments have recently either cast doubt on the relevance of the Act's provisions (which would mean that PGD is allowed) or called for reforms to the Act (to make possible PGD in Germany). The procedure – according to the proponents of PGD – could save parents who are aware of the genetic risk and (possibly) have already terminated a pregnancy after a positive result from a prenatal diagnosis, from having to terminate another pregnancy. Critics of PGD point to the right of the embryo to protection against any kind of manipulation, and regard PGD as opening the door to selective positive eugenics.

It is to be expected that technical advances will make it possible to perform PGD at a stage of embryonic development where the provisions of the Embryo Protection Act no longer apply. A point to be clarified is whether the claims of parents with an acknowledged risk justify abandoning the fundamental protection of the human embryo against »exploitative« interference which is the intent of the Embryo Protection Act.

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## GENE TESTS IN EMPLOYMENT

Genetic tests at DNA level to predict individual risk of disease and vulnerability are not performed in occupational medicine, as far as is known. However, there are tests available at the gene product level which demonstrate reduced capacity to break down toxins. In addition, analyses at the DNA and chromosome level are being used to identify previously incurred injury do to the workplace environment.

The debate about the use of genetic tests at the workplace centres primarily on the danger that subjective workplace safety, i.e. excluding individuals with ge-



netically-caused hypersensitivities from jobs, could take priority over objective workplace safety, i.e. removing hazardous materials from the work process. The practice of biomonitoring for early identification of already incurred damages in hazardous jobs can be regarded as in the interest of the employee and is not at issue.

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The central question in a precautionary regulation could then be how potential benefits of these test technologies can be achieved for workplace safety without justifying concerns about employee selection, discrimination and nullification of objective workplace safety.

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## GENE TESTS FOR INSURANCE

The use of genetic testing in connection with health insurance and life insurance has been a matter of controversy for years. In practice, no use has so far been made of information from genetic tests in issuing insurance policies, at least in Germany.

Views differ on the question how far it makes sense for insurance companies to modify insurance premiums for an individual on the basis of »genetic risk« as shown by genetic test results. Insurers claim that there is no actuarial point in partitioning the group of policy holders into small groups by risk, so that active use of genetic diagnosis is not intended. However, they reserve the right to demand disclosure of results from genetic diagnosis if these should reveal that applicants are using their knowledge of personal genetic risk to take out large policies.

The critical response to this is that it could very well make sense for insurance companies to set premiums on the basis of (genetically caused) risk of disease, and that there is at least a danger that applicants with presumed high risk would only be able to take out a life or health insurance policy on unfavourable terms,



or would be forced out of the private health insurance schemes and into the statutory health insurance schemes.

Reports from the UK, claiming that local insurers have abandoned their former reservations about the use of genetic tests and intend to ask applicants if genetic tests are available, indicate that the situation could change rapidly in Germany as well. Currently, there is no legal obstacle in Germany to any demand by insurance companies for disclosure of genetic data. The possibility cannot be ruled out that with growing use of genetic tests in medicine as a whole, applicants will exploit their knowledge of their genetic constitution either to demand favourable premiums or to conceal their knowledge of genetic risks to take out large policies.

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## NEED FOR REGULATION

Advances in human genome research will put the question, debated back in the early 90s, concerning statutory regulation of the use of genetic diagnostics in a new light. First, there are the problems which emerged during the 90s of ensuring the quality of human genetic counselling and diagnostics (particularly in the context of prenatal diagnosis), and second there are the increasingly concrete possibilities for using genetic tests for widespread diseases (even if – or because – the medical benefit of tests for multifactorial diseases is doubtful), all of which indicate the need for federal statutory regulation. Given the pace of development in the field of genetic diagnostics, the professional regulations currently applying in Germany could require backing and closer definition through a Genetic Diagnostics Act, to ensure that genetic diagnostics is limited to medical purposes and that the quality of diagnosis and counselling is ensured by licensing laboratories and counselling services, tying their performance to the right of self-determination, preventing abuse of genetic data by third parties, and preventing discrimination against the handicapped.

In the insurance sector, regulation is indicated to prevent discrimination against individuals who have had genetic tests carried out. An issue of central importance in terms of the use of genetic tests at the workplace is statutory definition of the right of the employer to request information, the restriction of testing practice to tests which are in the interests of the employee or necessary to protect third parties, and ensuring data protection and voluntary participation in testing.



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