

The background of the cover features a large, faint, circular seal of the Berlin-Brandenburg Academy of Sciences and Humanities. The seal contains an eagle with spread wings and the text 'BERLIN-BRANDENBURGISCHE AKADEMIE DER WISSENSCHAFTEN UND KUNSTEN'.

Interdisciplinary Research Group „Gene Technology Report“
Berlin-Brandenburg Academy of Sciences and Humanities (Ed.)

**GENETIC TESTING AND
GENETIC DIAGNOSIS IN GERMANY.
STATUS QUO AND CONTROVERSIAL ISSUES.**

SUPPLEMENT OF THE GERMAN
GENE TECHNOLOGY REPORT

SUMMARY

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Contents

Introduction	5
Summary and core statements	6
Need for Action	13
at the European level	13
at the German level	13

Introduction

Genetic diagnosis is one of the main areas of application of gene technology. The spectrum ranges from differential and prenatal diagnosis or predictive gene tests to its use in forensic medicine, genealogical tests, and screening programmes for entire sections of a population. Some of these procedures have already been in use for decades and have meanwhile become routine; others are being introduced or discussed. Specific applications and their introduction are accompanied by public debate on their evaluation and their place within society. These discussions have always been characterized by obvious fragmentation and plurality of opinion. Specific areas of application have to be constantly re-negotiated, taking into account the various problem areas and future prospects, the arguments and positions proposed, and their politico-scientific and social complexity.

It is not only new scientific-technological developments or the multitude of established applications that demonstrate the cutting-edge nature and explosiveness of the issue of genetic diagnosis, but also the current political debate on specific legislation concerning genetic diagnosis: In May 2007, the German Parliament discussed a bill proposed by Bündnis 90/Die Grünen (the German Green Party) and referred it to the parliamentary committees for further debate. Thus it appears that a legal settlement of important questions is in sight within the current legislative period. In this context, the supplement "Genetic Testing and Genetic Diagnosis in Germany" offers not only an overview of current developments and tendencies in the context of genetic diagnosis in Germany; it also takes up the socio-political dimension and discussion. It therefore links directly to the chapter on molecular genetic diagnosis in the first Gene Technology Report from the year 2005.

In order to present the issue of genetic diagnosis in all its current aspects, the book will focus on five main points: Part 1 provides a summary, formulates core statements and calls for action considered necessary by the interdisciplinary Research Group 'Gene Technology Report' of the Berlin-Brandenburg Academy of Sciences and Humanities on the issue of genetic diagnosis in Germany. Part 2 of the supplement is devoted to the current state of the technology and legislation in the field of molecular genetic diagnosis in Germany. In continuation of this, part 3 discusses specific areas of application such as forensics, preimplantation genetic diagnosis or potential screening programmes. The status and regulation of genetic data is covered in part 4. The specific approach employed by the interdisciplinary Research Group 'Gene Technology Report' is presented in part 5; this section also presents data on selected indicators that attempt to quantitatively assess various problems.

Summary and core statements

The publication "Genetic Testing and Genetic Diagnosis in Germany" refers to the chapter 'Application in medicine the example of molecular genetic diagnosis' in the 2005 Gene Technology Report. On the one hand, issues are dealt with that have not been covered in the first volume, such as forensic medicine, preimplantation genetic diagnosis or the question of genetic exceptionalism. On the other hand issues are presented that document the extraordinary technical progress within the field, take into account important developments in the areas of quality assurance and legislation and update selected indicators.

The number of monogenic diseases for which the responsible mutations have been identified and which can therefore be diagnosed molecular-genetically currently stands at about 3500. By contrast, the number of identifiable genetic risk factors for complex illnesses with a low prognostic value is uniformly small. However, due to the availability of high-resolution DNA chips, increasing numbers of these factors will be detected in future. In view of specific therapeutic interventions it is thus implied that so-called 'blockbuster drugs' will only assume a subordinate role.

Other chips, so-called array CGH chips, have already increased the resolution of microdeletions and microduplications compared to optical microscope analysis by a factor of 100. This has made it possible to explain the molecular cause of numerous unsolved medical cases, for example cases of mental disability or congenital heart defects, and has also underlined the significance of the role played by new mutations. At the same time, the cost of DNA sequencing has fallen considerably, and the complete sequencing of a human genome for 1000 dollars could become a reality in the next five to ten years.

These technological developments have opened up new possibilities for genetic diagnosis. Prerequisite for this are, however, standardized examinations of large groups of patients and adequate monitoring. In view of the large number of genetically caused diseases, implementation in medical practice also requires an intensification of genetic treatment in large clinical genetics centres.

The technological requirements for forensic diagnosis are not fundamentally different to medical diagnosis. However, the available volume is often small and analysis is limited to non-coding, highly polymorphic gene sequences. Moreover, the standardization and automation of medical findings plays a central role in national and trans-national cooperation. Parallel to this, so-called DNA databases are being established as a tool for police investigation. Between September 1998 and November 2006 it was possible to trace DNA material found at crime scenes to suspects in more than 30,000 cases in Germany. (Figure 1)

Forensic DNA analyses are undisputed in clear-cut cases. However, serious questions are raised concerning the dissemination of databases containing personal information and the inclusion of other markers that can, for example, give information about the ethnic origin of a person, their gender or physical characteristics. Indeed, the proof of biographical origin has already found its way into forensic diagnostics, for example to set priorities in the case of screenings. In general, the primary goal of all applications must be to maintain a high level of public acceptance.

Figure 1: Police DNA-databases in Europe

Country	Population	Persons			Traces	Success			Date		
		s	c	Total		Person/Trace		Total			
						s	c			Total	Trace/Trace
Austria	8 100 000			94 550	24 600			7 255	3 208	10 463	01.01.07
Belgium	10 400 000		6 883	6 883	9 375	137	134	271	697	968	01.06.06
Croatia	4 600 000			13 041	2 301			1 114	311	1 425	31.12.06
Czech Rep.	10 300 000			12 639	4 740			4 537	5 587	10 124	31.12.06
Denmark	5 500 000			10 112	9 875			2 370	1 951	4 321	01.11.06
Estonia	1 500 000			15 096	5 533			1 392	455	1 847	01.01.07
Finland	5 200 000			45 526	8 463			6 919	1 271	8 190	01.12.06
France	59 300 000	212 191	119 157	331 348	16 624			4 551	1 190	5 741	01.12.06
Germany	82 400 000			438 574	102 831			35 169	12 448	47 617	01.12.06
Hungary	10 200 000			43 375	263			22	12	34	31.12.06
Netherlands	16 100 000	10 176	16 880	27 056	29 534			10 078	4 029	14 107	12.06.06
Norway	4 500 000		8 698	8 698	2 005			747	272	1 019	30.06.06
Portugal	10 300 000				2 160				57	57	01.01.07
Slovenia	2 000 000			5 782	2 744			523	108	631	01.02.05
Spain	44 400 000			11 926	20 420			2 032	8 772	10 804	31.12.06
Sweden	9 000 000	15 183	8 549	23 732	15 848	8 354	1 495	9 849	11 090	20 939	06.12.06
Switzerland	7 360 000			83 390	13 973			12 701	3 272	15 973	01.12.06
Ukraine	47 600 000			1 723	176					22	01.01.07
UK	59 600 000			3 790 551	312 958			762 280	45 697	807 977	01.12.06
Total	398 360 000			4 964 002	584 423			861 810	100 427	962 259	

s = suspect; c = convictable

Source: www.enfsi.org/ewg/dnawg/bd/dnadatabases, 21.06.2007

The same molecular markers are used in paternity tests. Such tests are carried out on more than 100 laboratories in Germany, although the large number of DNA samples from children obtained clandestinely by suspicious fathers presents a fundamental problem, since this occurs without the consent of those affected (that is, the child and its mother). Several passages in the supplement deal with the resulting, and as yet unresolved, legal aspects.

In Germany, prenatal diagnosis (PD) is considered an inherent part of medical care. However, pre-implantation genetic diagnosis (PGD) of blastomeres is legally prohibited by the 'Embryonen-

schutzgesetz' (the German Embryo Protection Law), although it is permitted in most other European countries. One of the concerns about an increased use of PGD is raised by the possibility of choosing between different embryos before the implantation is carried out. It is apparent that examinations are increasingly being carried out for late-onset disorders that are of little significance within the context of prenatal diagnosis. At this point in time in Germany, the decision as to what happens to the embryo before implantation is not taken by the parents, but after the implantation they are granted full rights of decision. In view of this contradiction in the applied values and additional reasons not to deprive women of a PGD when certain indications are present, the Bioethics Commission of the German federal state Rheinland-Pfalz has spoken out for a relaxation of the embryo protection law.

Should the categorical prohibition on PGD be lifted, the operating framework would be of decisive significance. Examinations should be restricted to a small number of medical centres that are bound to strict accreditation and whose working practices are transparent.

In future the imposition of new regulations upon the usage and financing of molecular genetic diagnosis will be unavoidable. Health insurers in Germany have already made a start by restructuring the so called "Einheitlicher Bewertungsmaßstab (EBM)" (evaluation standard for doctors' fees). One of the decisive issues relating to this is the validity and benefit of genetic tests from a clinical standpoint, an issue that has been mentioned in the first volume of the report. A new foundation for this has been laid by the EUROGENEST project's report and various systematic evaluation processes (Figure 2). As one would expect, evaluation standards for common diseases will be more readily available than for rare diseases.

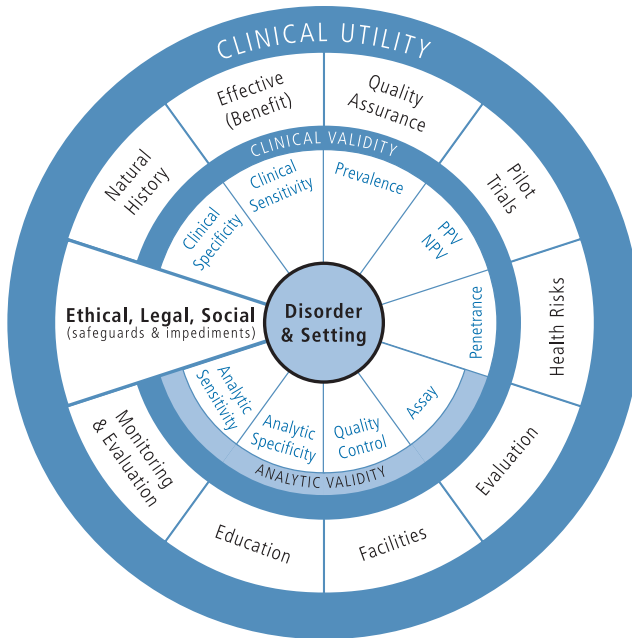
One of the central problems is the definition of risk levels below which genetic tests cannot be financed by our health care system. This presents particular difficulties, because risks-assessments have to encompass the probability of actual illness and the severity of the illness, and at the same time its psychological and social dimensions must be taken into account. Structured evaluations of genetic tests should therefore serve a fair balance of interest within the community of insured persons.

In the context of future prioritizing and rationing within the health care system, the health-economic aspect, especially in connection with genetic screenings, assumes an important role. Various types of economic evaluation are compared using as examples eight diseases such as familial breast- and ovarian cancer, retinoblastoma or cystic fibrosis. Only one study, on hereditary haemochromatosis, has been carried out in Germany. According to this comparison the efficacy of such a screening programme is not proved up to now, thus its profitability has not yet become an issue. In the supplement it is also discussed whether it is possible to translate results from other countries to a German context.

Very few genetic screening programmes provide a proof of profitability which meets the established international requirements. However, if the costs of genetic testing continue to fall, the situation might change.

Independently of the economic perspective, the question arises whether genetic examinations might actually be used as preventive measures which suspend the balance between social re-

Figure 2: ACCE – A model process for evaluating data on genetic tests



ACCE = Analytic validity, Clinical validity, Clinical utility and Ethical, Legal and Social Issues

sponsibility and personal freedom, for example by forcing an individual to undergo genetic testing in order to prevent disease more effectively. It is widely accepted that public health is a communal asset that, in principle, justifies encroachment on the freedom of the individual. The 2005 Gene Technology Report dealt at length with the possible social consequences of prenatal diagnosis in this context. In the supplement the possibility of disease prevention through public health genetics is discussed. The evaluation of various genetic examination procedures leads to the conclusion that it is improbable, in view of social values and the legal and political culture in Germany and Europe, that obligatory genetic examination will be permitted as a strategy in public health policy.

In the opinion of the Research Group there are no grounds for fears that people in our country will be forced, to any mentionable extent, to undergo genetic tests within the framework of regular health care. In a liberal society one instead tends to inform and convince people while attempting to set incentives for health-conscious behaviour.

In this context, the question arises as to what extent a genetic diagnosis law is actually necessary. In a liberal, constitutional state, any encroachment on the freedom of the individual requi-

res justification. Genetic diagnosis would have to be associated with serious dangers, from which individuals are not sufficiently protected by existing laws, in order to justify such a law. One can even go a step further and ask whether the diagnosis of genetically caused diseases differs so greatly from other diseases that one can talk of 'genetic exceptionalism', which itself requires special legal regulation. They point out the great potential for discrimination resulting from genetic examinations, in particular concerning their validity as a predictive tool. At the same time it is emphasized that due to the massive publicity genetic research has attracted, the general public has become highly sensitive to its potential abuse and dangers. Indeed there is no clear demarcation between genetic and non-genetic information which would justify its granting of special status. This becomes evident when considering the example of the debate on HIV exceptionalism, where the discussion leads from exceptionalism to normalization.

The Research Group has reached the conclusion that one may not really talk of genetic exceptionalism. The potential for discrimination is not limited to genetic information in terms of DNA diagnosis: it is present in all types of sensitive medical and social information.

In view of the ethical aspects of predictive genetic tests the supplement points out their undisputed benefits, but also addresses the common opinion that due to the increase of test applications, which are in some measure of dubious quality and increasingly available over the internet, legislation could be required. Since genetic information pertaining to an individual always contains information about his family members as well, two fundamental legal rights of equal status compete against each other: the right of self-determination of an individual to acquire genetic information and the right of self-determination of biological relatives. An essential part of the ethical debate about the risks concerns the psychological stress caused by a test result and the burden of the genetic knowledge as well as the danger of genetic discrimination in the workplace and in the insurance sector.

If one summarizes the ethical discussions related to these aspects, it is clear that a (limited) reservation (referring to a test that can only be carried out by a doctor), particularly for tests in which a disposition to serious diseases can be proven, must be favoured as the basis for any proposed regulation. It is likely that the individual would only be in a position to exercise his right to self-determination in terms of genetic information with the support of governmental regulation.

As was described in the 2005 Gene Technology Report, German law still lacks universally binding legislation for genetic testing. Of direct relevance are, among others, the data protection act and the occupational regulations for the medical profession, the laws concerning hospitals and the embryo protection law. The legal position of the European Union is of particular significance. The supplement also deals with the draft genetic diagnosis law introduced by Bündnis 90/Die Grünen, which was discussed in parliament following the first reading in May 2007. The authors speak out for an extended version, particularly in regard to research on humans and the establishment of biobanks.

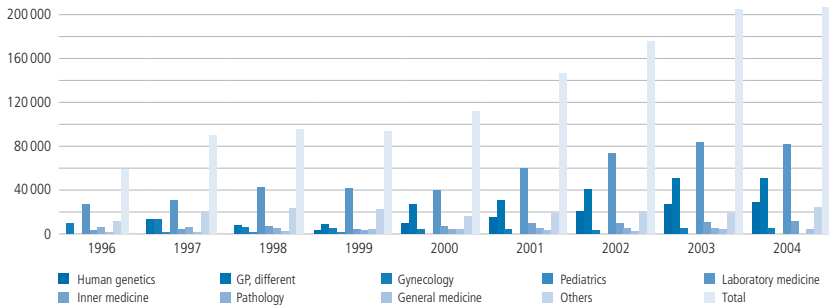
The Federal Constitutional Court of Germany has in the meantime unambiguously stated that clandestine paternity tests are unlawful. At the same time, the court has enjoined the legislature to ensure a procedure through which the right to know and determine fatherhood can be demanded, without allowing it to be contested at the same time. However, there are thus far no court decisions

on doctors' liability pertaining to predictive genetic tests and tissue donations for research purposes.

Legal regulation of genetic examinations should strive – taking into account the diverse national regulations and experiences – to carry the existing social consensus into the future and thus minimize unfounded public fears.

The concluding part of this supplement provides an overview of the so called “problem fields” of genetic diagnosis, and also of the indicators with which the developments in this field can be summarized and assessed. This approach will then be exemplified using selected indicators: An important criterion for usage of human-genetic medical services which are financed by state health insurance is the number of people who have undergone such a diagnosis. This is assessed by using the EBM number 4977 which is used by doctors to claim the fee for the performance of DNA extraction from human tissue. Since the year 2000 this has been increasing constantly, although it slowed considerably in 2004.

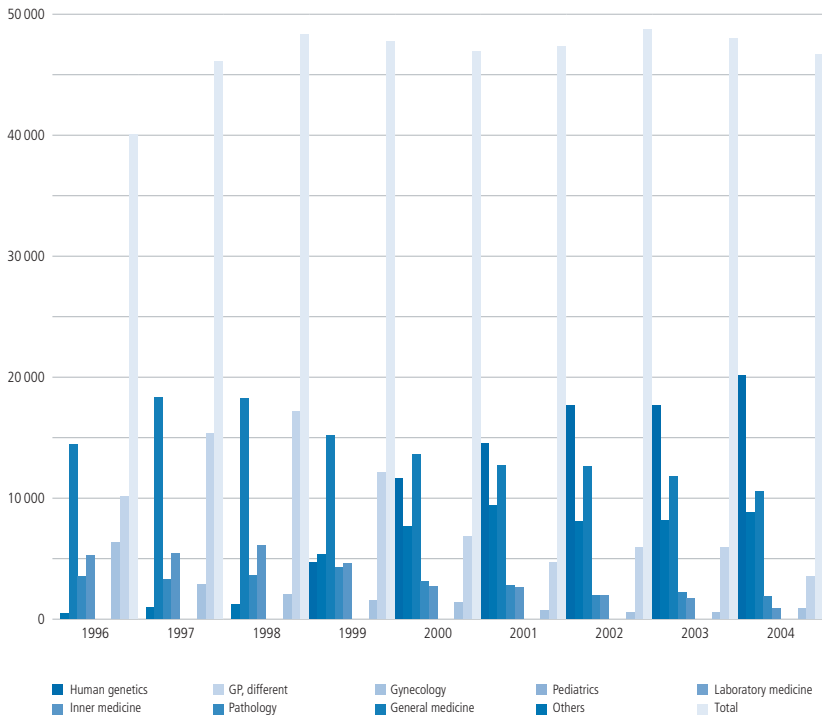
Figure 3: DNA-extraction at human tissues



Source: Fallzahl EBM 4977

With the introduction of EBM 2000 plus (the new doctors' fees regulation) in the year 2005, this service will not be paid for as an individual service, thus this parameter will no longer be available in the future. One can also observe a continual increase in the number of polymerase chain reaction and DNA sequencing procedures, but a decrease in prenatal chromosome testing. This is probably attributable to improved non-invasive prenatal diagnosis. The number of postnatal chromosome tests appears to have levelled out at about 60,000 per year. The number of human genetic consultations has remained relatively constant over the same period at around 50,000. These procedures will be given a higher rating in the new fees regulations, but at the same time will be carried out only by a 'specialist for human genetics' and a doctor with the additional title 'of medical genetics'.

Figure 4: Utilisation of genetical consultation



Source: Fallzahl EBM 173

There is no significant data available with regard to the use of commercial services for genetic diagnosis – however it is unlikely that these services will be used to any considerable extent. If an available test makes medical sense, it is usually medically indicated and thus it is a service that can be claimed by public and private patients.

The number of identified genes responsible for diseases serves as an indicator for the acquisition of knowledge. According to this, scientists from Germany were involved in nine percent of all cases in the years 2000 to 2006. In an international comparison of the three-year periods from 2001 to 2003 and from 2004 to 2006 it becomes apparent that the number of findings from Germany, Great Britain, and The Netherlands are increasing and those from the USA, France, Japan, Belgium, Italy, and Canada are decreasing, in some cases significantly. Within Germany, researchers from university institutes, particularly from institutes for human genetics, play a leading role in finding new disease genes; the large-scale research institutes play a less important role.

The German Research Foundation (DFG) acts as the main financial partner in this context. The considerable additional expenditure for the Human Genome Project in Germany made by the Federal Ministry of Education and Research (BMBF) has little direct significance regarding the number of identified genes responsible for diseases.

Need for Action

The responsibility for public health care in the European Union lies with individual member states. Nonetheless, concepts for quality assurance have already been developed on a pan-European level. Thus, these measures in particular should be managed on the European level. The areas requiring action are compiled separately here at the European and German levels.

Need for action at the European level

The following considerations should be pursued and elaborated upon at the European level - the EU-funded 'EuroGentest' Network of Excellence and the European Society of Human Genetics (www.eurogentest.org and www.eshg.org):

Quality assurance of genetic laboratories

- ▶ Analytical validity of tests
- ▶ Accreditation, certification
- ▶ Accreditation of interlaboratory comparisons and reference materials

Quality assurance of clinical findings

- ▶ Clinical validity of tests
- ▶ Clinical value of tests

Process control

- ▶ Implementation of research- and technological developments in clinical practice

Need for action at the German level

The European quality assurance systems should be adopted in Germany and adapted to its specific needs. Criteria for the assessment of the clinical relevance of genetic diagnosis developed on the European level should be applied in shaping the services catalogue of state health insurance systems

(Einheitlicher Bewertungsmaßstab) and private health insurance (doctors' fees regulation). Moreover, there is a need for faster adaptation of these catalogues to reflect medical-genetic progress and technological developments. Medically relevant measures (genetic screening programmes) must undergo thorough health-economical evaluation; in so doing, prioritisation criteria should be developed reflecting a fair balance of interests within the community of insured persons.

In the area of professional self-regulation and within the framework of general legislation there is a need for

- ▶ the creation of regulations to prevent genetic discrimination,
- ▶ the creation of regulations for adequate management of predictive tests for severe diseases (tests carried out by doctors only),
- ▶ the creation of regulations for medical-genetic research and biobanking,
- ▶ the approval of preimplantation genetic diagnosis within a strict legal framework.

The basic research and research in the field of health sciences (health services research) required for further development in the field of genetic diagnosis has to be promoted more vigorously in order to ameliorate Germany's position in relation to international standards. In the field of health services research, the necessary changes in our health system for the creation of genetic diagnosis centres should be examined. In forensic genetics, the trend towards a softening of the current legal criteria for DNA analysis used for solving crimes has to be countervailed and the principle of commensurability has to be accounted for in the extension of forensic databases.

The operation and access of databases has to be evaluated by an independent party concerning the number and type of crimes solved. The creation of new legal regulations for genealogical tests is required. It is a matter of some urgency that quality assurance in this field has to be advanced.

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