

Interdisciplinary Study Group "Gene Technology Report"
Berlin-Brandenburg Academy of Sciences and Humanities (Ed.)



SECOND GENE TECHNOLOGY REPORT

SHORT VERSION



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1. Introduction: Motivation and objective of the proposal

Since the publication of the first German Gene Technology Report in 2005, gene technology has continued to develop at a rapid pace. Four years on, this alone should be sufficient reason to provide an update of the report. Gene technology, however, is more than simply a technological development, such as photovoltaics or telecommunications technology, which unquestioningly have also developed tremendously in recent years. Gene technology, the targeted intervention into the genome, affects and unsettles people in a particular way. It allows people direct access to the foundations of all organic life. The time scale is no longer the long years of the evolutionary process, or the changes that occur in plants and animals over many generations through breeding. Even us human beings are theoretically open to direct access.

Immense responsibility arises from such far-reaching and complex possibilities, particularly in the case of gene technology. It is, for one thing, from today's perspective often impossible to foresee the short-term or, even more often, the long-term consequences. For another thing, the consequences can continue to be effective beyond the lifespan of an individual person, and plants, animals, or bacteria, can rarely be retrieved once released into nature. In other words, gene technology, more than other technological developments, throws up the question of whether humans should, or indeed must, set their own boundaries for their own technical progress. Meanwhile, not using the possibilities offered by gene technology could also have unforeseen, even fatal consequences. This particularly highlights the characteristic Janus-faced nature of technical progress in gene technology, and makes it all the more imperative to objectively take stock of the situation.

The opportunities offered by gene technologies even today, or promised for the future, in their multifarious areas of application, polarise people and divide society into at times irreconcilable camps: while one side gives particular emphasis to the incalculable risks that are detrimental to humans, the other side points primarily to the scientific and technical opportunities that benefit humans. Discussions of this kind are, indeed, typical of today's pluralistic society, where diverse interests and beliefs co-exist and find expression. At the same time, they can be understood as a social reaction to developments and problems that are getting more complex and increasingly elude personal actions. In addition, people often have very different opinions as to what should actually be discussed. Should the focus be primarily on individual aspects, such as technical options, or should it encompass all relevant aspects in their entirety – thereby also including social, ethical, ecological, and economic consequences? Should alternative strategies, which offer similar solutions to gene technology, not also be considered? To fully evaluate gene technology, would it not be more use looking at greater problem areas, such as the nutritional or psychosocial causes of diseases, or the general orientation of agriculture?

In the case of gene technology these aspects and viewpoints are very closely interwoven. This is particularly apparent in public debates, where not least individual beliefs and attitudes characterise the evaluation carried out of individual applications as "beneficial" or "detrimental". No intensive debate should end in such a simple opposition; rather, it requires a differentiated picture with many subtle shades of grey, doing justice to the complexity of

knowledge, and its position in society and public communication. However, the media, and society at large, are dominated by highly simplified images. Furthermore, statements continue to be partially non-specific, purely speculative, and lacking any verifiable explanation. The interdisciplinary research group 'Gene Technology Report' of the Berlin-Brandenburg Academy of Sciences and Humanities (BBAW) aims to break out of this situation, and to present a more detailed picture. This research group conceives of itself as an "observatory" that identifies developments and trends in the wide field of gene technology in Germany.

As a starting point it takes the respective level of scientific and technical development in the various fields of application of gene technology. It then presents the resulting consequences, considering as widely as possible heterogeneous viewpoints and comments. With this type of report, the research group wants to contribute towards moderating the multifaceted debates about gene technology. The research group adopts a particularly unique approach: rather than simply reviewing individual topics, this report considers as many fields of application of gene technology as possible, while covering and processing all cross-sectional dimensions. Thereby, the research group complements the numerous approaches and institutions that usually only address questions within branches of gene technology.

The research group being located at the BBAW is of great value in this respect. The chosen task of providing an "observatory for gene technology" involves respecting various prerequisites. For one thing, the observers should not consist of unilaterally interested parties. Additionally, their outlook should be as broad as possible, seeing beyond the narrow scope of the scientific-technical fields concerned. Thirdly, there must be long-term and continuous monitoring rather than a one-off snapshot of the situation; distinct trends only become apparent in the course of time. The BBAW fulfils the key requirements for providing the "observatory": the members in their entirety do not represent any particular interests, at least none that go beyond their interests as scientists. It offers the required interdisciplinary expertise in the different areas of application of gene technology. It is also in a position to carry out long-term monitoring. Thus, it suited the self-understanding of the BBAW to take on this complex task eight years ago (in 2001). Meanwhile it has been taken on as a long-term mission (since 2007).

The second German Gene Technology Report discusses, as did its predecessor, the fields of basic research, molecular diagnosis in human medicine, and green gene technology, i.e., the application of gene technology in plant breeding and agriculture. New additions are research on pluripotent human stem cells, as well as the field of somatic gene therapy, to which individual volumes have already been dedicated in the last years. Also new is the inclusion of a comprehensive chapter on ethics, which is unique in describing in this form a system of general ethical categories for all applications of gene technology, thus departing from the classical method of "ethical domains" for individual forms of application.

Methodological "brackets" for the subject areas are generated by analysing, on the basis of indicators, the "problem areas", which are presented in detail in the following chapter. The overall objective here is to put the multitude of individual pieces of information into an overarching context, thus ensuring thorough monitoring. The following subjects are dealt with in detail:

Figure 1: Disease-Specific iPS Cell Lines

Disease	iPS Cells Derived from Somatic Cells
ADA SCID	2 ¹⁾
Amyotrophic lateral sclerosis (disposition)	1 ²⁾
Amyotrophic lateral sclerosis (diseased)	7 ²⁾
Down syndrome	3 ¹⁾
Gaucher disease	2 ¹⁾
Huntington disease	2 ¹⁾
Juvenile diabetes mellitus	2 ¹⁾
Lesch-Nyhan syndrome	2 ¹⁾
Becker muscular dystrophy	2 ¹⁾
Duchenne muscular dystrophy	2 ¹⁾
Parkinson disease	2 ¹⁾
Sickle cell anemia	3 ³⁾
Swachman-Bodian-Diamond syndrome	2 ¹⁾
12 Diseases	32

Sources: 1) Park, I. H. et al. (2008): Disease-specific induced pluripotent stem cells. In: Cell 134:877–888.

2) Dimos, J. T. et al. (2008): Induced pluripotent stem cells generated from patients with ALS can be differentiated into motor neurons. In: Science 321:1218–1221.

3) Mali, P. et al. (2008): Improved efficiency and pace of generating induced pluripotent stem cells from human adult and fetal fibroblasts. In: Stem Cells 26:1998–2005.

Subject area stem cells: pluripotent human stem cells

In addition to human embryonic stem cells, we present, in particular, the discovery of the reprogrammability of somatic cells as so-called induced pluripotent stem cells. This development has recently caused much sensation. Overall, this chapter demonstrates how pluripotent stem cell research very much constitutes an up-and-coming, highly competitive, and internationally networked research area, which is developing into a key technology in biomedicine. Furthermore, we show how cell replacement therapies based on pluripotent human stem cells are just one of several possible areas of application. Human embryonic stem cells, and other human pluripotent stem cells, also possess great potential in other fields of medical research, such as, for example, pathogenesis research, drug research, pharmacology, and toxicology (figure1).

Subject area genetic diagnosis: molecular diagnosis in human medicine

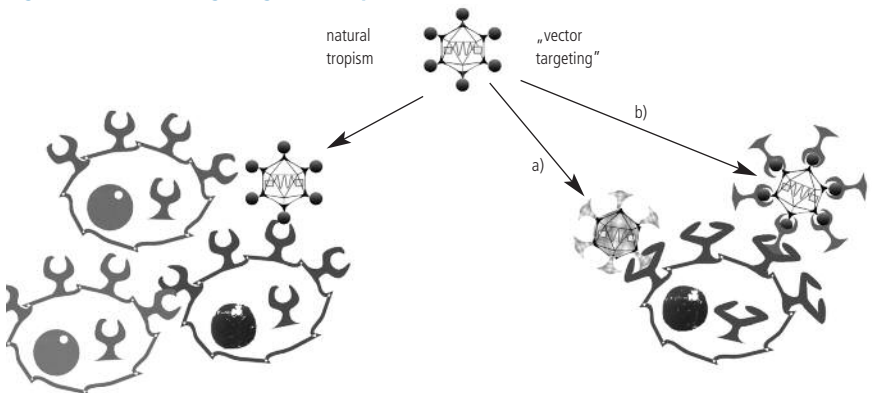
Four years ago the Gene Technology Report predicted that molecular diagnosis would gain in significance; this prediction has, in the mean time, proven to be completely accurate. During the past nine years, the number of identified genes that cause monogenetic diseases has more than doubled. At the same time, the number of known predisposing loci for complex diseases has also risen.

In the near future, rapid technological progress should further accelerate development in various fields. Chip diagnosis allows us, even today, to identify a rapidly growing number of new DNA variants. Here, what remains problematic is distinguishing DNA variants that are pathogenetically relevant from those that are functionally neutral. Resolving this issue will require the serial examination of large cohorts of patients and a healthy control group. At the same time, the costs of DNA sequencing should continue to fall drastically, so that re-sequencing a human genome for only \$1000 seems a realistic prospect for the near future. This development will also change the role of genetic consultation. On a related note, this chapter of the report will introduce the new German Law on Genetic Diagnosis. This extends into areas that were previously regulated by the doctors' code of professional conduct, and attributes particular importance to genetic consultation.

Subject area gene therapy: somatic gene therapy

The focal point of gene therapy research continues to be the development of vector and gene transfer technologies. At the same time, new technologies are displaying improved levels of efficiency in targeted gene repairs (figure 2), and could become clinically mature in the near future. After experiencing setbacks ten years ago, substantial progress has been made in therapy, for example, in the case of ADA-SCID disease and various ocular diseases. For complex diseases, such as cancer or cardiovascular diseases, it is conceivable that these therapies will be used in conjunction with conventional therapies. Against the backdrop of possible gene doping, enhancement continues to represent a relevant problem, for legal and ethical reasons. The authors continue to adamantly oppose germ-

Figure 2: "Vector targeting" techniques



Vectors often have the capacity to transduce many different cell types. "Vector targeting" allows vectors to be modified in such a way as to transduce the desired cell type only. One option is to apply a coupling module that connects the vector to the target cell, such as bispecific antibodies (a); alternatively, ligands can be incorporated into the plasma membrane, transmitting this interaction (b). In all cases, it is important to prevent a natural ligand-receptor interaction.

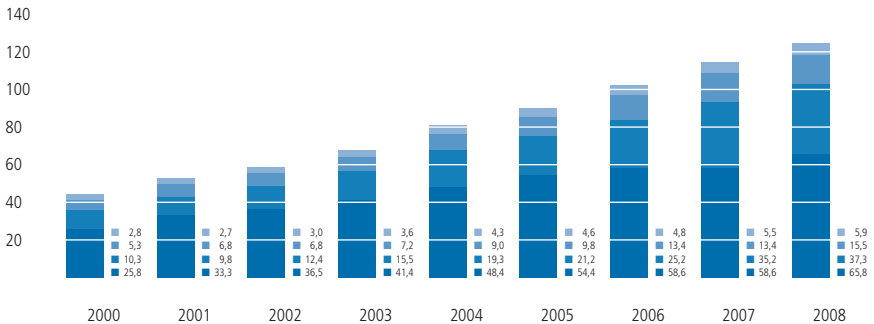
Source: Zweiter Gentechnologiebericht, 2009:176.

line intervention. Also discussed is the role of the German Research Community and the Federal Ministry of Education and Research, which are attributed a crucial importance, due to the lack of private funding for clinical studies.

Subject area green gene technology: plant breeding and agriculture

Few application areas of gene technology are as socially controversial as its use in farming and food. Even five years after the end of the moratorium on cultivating GM crops, no new varieties were approved for cultivation. Over the same period, the area used for cultivating genetically modified plants world-wide has grown by approximately 50% to 125 million hectares (figure 3). The EU only has a small share, and Germany no share of this. Restrictive legislation and the sceptical attitude of the population make the cultivation of genetically modified plants in this country de facto impossible. The research field of plant gene technology continues to evolve dynamically. Its outcomes go beyond transgenic plants to include transcriptome, proteome, and metabolome research, the sequencing of complete plant genomes, and smart breeding. Potential innovations in farming are wasted due to the lack of consistent policies in Germany, and even research itself is obstructed. Already, German research on the level of research into application is in danger of being disconnected from international research programs.

Figure 3: Hectarage of GM crops (worldwide)



in mio ha. top - down: canola cotton corn soya.

Source: www.isaaa.org; Zweiter Gentechnologiebericht, 2009:262.

Cross-sectional survey of basic research: current developments in science and technology

This section focuses on four areas that are of fundamental importance for the development of gene technology. Genome research and systems biology are a key to solving many of the medical and economic problems faced by contemporary societies. In the area of DNA sequencing, technical progress makes it possible to decode, with increasing speed and cost-efficiency, not only the human genome. In the field of RNA technologies, the application spectrum extends beyond basic research in the narrower sense of the word, and comprises amongst other things the advancement of nucleic

acid chips, the industrial manufacture of protein products, cancer therapy, and nucleic acid pharmacology. A further central field of current basic research is epigenetics. Research in this field enables greater understanding of genetically-regulated molecular processes, and opens the horizon to applications in the production of anti-bodies, epigenetic therapies, as well as the generation and use of stem cells.

Cross-sectional survey of ethics:

argumentative dimensions in the ethical evaluation of gene technology

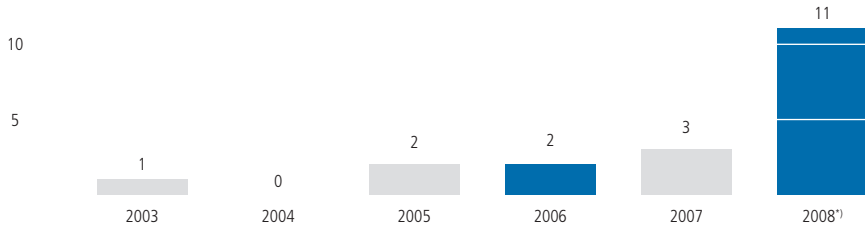
Ethical problems in the field of gene technology are usually dealt with by discussing pertinent ethical problems and questions for the respective forms of application. The chapter of this report dealing with ethics chose a different path: the central focal point is the question of which fundamental positions and opinions form the structure of the diverse ethical discourse on the multifarious options for action that are associated with gene technology. The chapter aims to cover the types and lines of argument that determine the numerous individual ethical questions. For this purpose, we define the key terms and viewpoints of the conflicting evaluations of options for action in gene technology, through compiling a grid of confronting pairs of opposites: deontological versus teleological forms of argument, human dignity versus animal dignity, bioconservative versus bioliberal, natural versus artificial. These pairs of opposites have very different meanings for each case in terms of logical or categorical status. When applied to problem areas in gene technology, they result in contradictory ethical positions, and produce antithetical answers to the question of whether certain developments in gene technology should be permitted or not with respect to ethical considerations.

With these focus points, the Gene Technology Report develops a systematic approach to the immensely confusing mass of facts and data. It is not concept-driven, in the sense of following a particular philosophical-ideological approach. Rather, the report wishes to promote impartial and open-ended debate. Target audiences include decision-makers from politics, from professional, trade, and pressure groups, as well as from non-governmental organisations, in addition to interested members of the general public, i.e., all citizens, as well as experts from other scientific disciplines, who deal with the multifaceted themes and problems of gene technology. In presenting the Gene Technology Report, the BBAW would like to offer a means of contributing towards objectifying the debate.

2. Subject area stem cells: pluripotent human stem cells (Core statements and recommended action)

This contribution gives an overview of current aspects of pluripotent human stem cell research. In this sense, the study focuses on human embryonic stem cells (hES cells) as well as further pluripotent human stem cell types, especially those which can be generated through reprogramming adult human somatic cells, so-called human induced pluripotent stem cells (hiPS) (figure 4).

Figure 4: Publications in alternative methods to establish pluripotent human stemcell lines



¹⁾ till october 2008.

Source: Zweiter Gentechnologiebericht, 2009:82.

Figure 5: Alternative procedures for establishing pluripotent human stemcell lines

Procedure	Country	Number of publications	Years
Production of hES cell lines from individual blastomeres ¹⁾	USA	2	2006, 2008
Production of hES cells from parthenogenetically activated embryos	Korea	1	2005 ²⁾
	USA	1	2007
Induction of pluripotency through fusing somatic and pluripotent cells	USA	1	2005
Induction of pluripotency through fusing somatic cells with hES cell cytotlasts	USA	1	2006
Transfer of genes whose products are associated with pluripotency (human iPS cells)	Japan	2	2007, 2008
	USA	7	2007, 2008
	China	1	2008
Induction of pluripotency through somatic nuclear transfer to animal egg cell	China	1	2003
Derivation of human adult germline stem cells with properties of pluripotent stem cells from human testicular tissue	Germany	1	2008

1) Although the German embryo protection law considers blastomeres to be embryos, this method is described as “undisturbed” in the relevant international literature because that literature does not usually consider individual blastomeres to be embryos.

2) This deals with the SCNT-hES-1 cell line. This line was publicised in 2005 as generated by SCNT. The publication turned out to be a fraud and had to be withdrawn. However, it later transpired that SCNT-hES-1 is in fact a parthenogenetically activated human cell line (Kim, K. et. al. (2007): Recombination signatures distinguish embryonic stem cells from neonatal mouse testis. In: Cell Stem Cell 1:346-352).

Source: Zweiter Gentechnologiebericht, 2009:81.

We present parameters for the characterisation of hES cells and describe the international efforts being made in order to achieve standardisation, registration and long-term banking. This data, together with all the countries active in the field of hES cell research worldwide, the number of currently available hES cell lines, and publications on hES cells and hiPS cells, are recorded in an up-to-date database (figure 5).

The study demonstrates that pluripotent stem cell research is an up-and-coming, highly competitive and internationally networked research area that is developing into key technology in biomedicine.

This contribution shows that cell replacement therapies based on pluripotent human stem cells are – despite a first licensed clinical study based on human ES cells – just one of several possible areas of application and that they also have a longer-term perspective. Human ES cells, as well as other human pluripotent stem cells, also possess great potential in other fields of medical research, e.g., pathogenesis research, drug research, pharmacology, and toxicology.

The discovery of the reprogrammability of somatic cells into induced pluripotent stem cells (iPS cells) has, in addition, demonstrated that embryonic stem cell research overall opens up the potential for brand new and unexpected insights, which in turn can lead to the establishment of new fields of research, e.g., induced pluripotency.

Recommended action

1. Research on human ES cells as a branch of stem cell research is an up-and-coming scientific discipline, which is at present located almost exclusively in basic research. The application of any cell therapy involving pluripotent human stem cells on humans requires intensive prior examinations on the effectiveness and safety of cell therapy products. This is not surprising, given that the development of adult stem cell-based therapies, as, for example, bone marrow stem cells, also required decades of pre-clinical research before a therapeutic application of adult stem cells was possible. Applied research on human ES cells, meanwhile, is becoming increasingly important in drug research, pharmacology and toxicology.

2. Human iPS cells or alternative pluripotent stem cells that have been generated without using embryos or egg cells cannot at present replace hES cells. We can rather assume that hES cells will continue to be needed as a standard for research purposes. Beyond that, we cannot yet assess from today's perspective which of the pluripotent stem cell types presented will be applied in future stem cell therapies. Therefore, research on all stem cell systems is necessary, as parallel investigations into different stem cell types can yield insights that will advance stem cell research in general.

3. Unlike the generation of hES cells, the production of hiPS cells does not involve the use of human embryos or egg cells, and is, in this respect, ethically unobjectionable. Developing future cell therapies based on human iPS cells is unproblematic, in that pluripotent cells would only be reproduced in

culture dishes and used for producing specialised somatic cells and tissues. As well as taking into account the potential for development of cell lines (see point 3.1), it is important here to distinguish between the in vitro production and experimental examination of hiPS cells and their in vivo application.

In regard to the use of human iPS cells, we propose the following recommendations:

3.1 The use of iPS cells should, besides its application in basic research, pharmacology and toxicology, be restricted to in vitro procedures to generate specialised cells for tissue regeneration and cell therapy. This means that human iPS cells must not be used for aggregation experiments following the “sandwich technique” (Beier, 2001; Wobus, 2008), which aim to create a complete viable organism. Generally, neither in vitro fertilised egg cells (IVF embryos), nor nuclear blastocyst transfers (or iPS/ES cell constructs) could develop into an individual, without manipulative interventions or human actions, implantation into the uterus, and development within the mother’s organism.

3.2 Research into the in vitro development of gametes from human iPS cells must be subject to ethical norms. It is assumed and suggested in some recent studies (Park et al., 2009) that in future it will also be possible to generate germ cells in vitro from human in vitro iPS cells. For this, experimental in vitro examinations for analysing germ cell developments or gamete aberrations should not be subject to any limitations, as long as they take place under in vitro conditions (in a culture dish). In contrast, the potential use of gametes derived from hiPS cells for reproductive purposes cannot be justified, simply for the reason that the safety of this method would have to be tested on humans beforehand, involving currently incalculable medical risks.

3.3 Stem cell research – including works on induced pluripotency and epigenesis – is a field of biomedical research that offers far-reaching and novel possibilities for regenerative medicine and medical care. At the same time, its significance for commercial applications also becomes apparent, as this field will take on great economic relevance for enterprises developing cell and tissue transplants or pharmacological and toxicological testing methods. Therefore, this type of research into basic and applied health sciences needs increased levels of funding. Furthermore, it becomes evident that the general conditions for the economic application of hiPS cell derivatives for commercial purposes have not yet been established.

3.4 The medical application of donor cells that in future will be generated from human iPS cells requires a high level of scientific-technical and material input, and should be conducted only on the basis of the strictest quality criteria. We suggest – at least in the initial phase – to confine therapeutic procedures on humans based on reprogrammed human iPS cell derivatives to certain centres that are subject to strict accreditation/licensing. At the same time, the work should be made transparent, in the same way, for example, as required by the regulations of the German Medical Association. For instance, prior to introduction of the German embryo protection law (Embryonenschutzgesetz EschG) the German Medical Association decreed a restrictive code of conduct for this domain. A central, interdisciplinary commission accountable to the public controlled its observance. A comparable com-

mission could ensure transparency in this field, or respectively document work carried out, in cooperation with the ZES (Central Ethics Commission for Stem Cell Research).

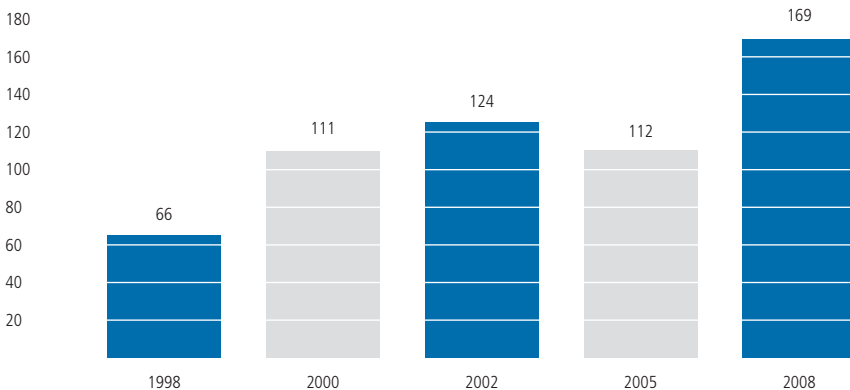
Independently of this, the monitoring system established by the BBAW (Berlin-Brandenburg Academy of Sciences and Humanities) with its Gene Technology Report, will observe developments in this field.

3. Subject area genetic diagnosis: molecular diagnosis in human medicine (Core statements und recommended action)

The first German Gene Technology Report of 2005 noted that in medical practice both at present, and in the foreseeable future, molecular diagnosis is taking on a central importance. Now, approximately five years later, this statement has not only proven to be true, but has become even more valid (figure 6), even for the near future, given the rapid advance in technological development.

The number of identified genes, which are the predominant cause of mainly monogenetic diseases, has more than doubled by mid-2009 from one thousand in January 2000. At the same time, chromosomal diagnostics is undergoing a profound change. The use of light microscopy as a method of examining chromosomes is being replaced increasingly by a method using chip diagnosis (array-CGH) with a resolution more than one hundred times higher, and the option of making the process

Figure 6: Number of institutions realize genetic testing (in Germany)



Source: Zweiter Gentechnologiebericht, 2009:141.

to a large extent automatic. In the coming years this technology will largely replace the conventional Karyotype analysis.

With the help of chip technology, a large number of new DNA variants have been identified, the so-called copy number variants (CNVs). These encompass between a few thousand and several million base pairs and can vary significantly from one individual to another. However, determining pathogenetically relevant and functionally neutral CNVs presents a great problem, which can probably only be resolved through serial examinations of large cohorts of patients and a healthy control group.

The costs of DNA (re-)sequencing will continue to fall dramatically over the coming years, so that sequencing a human genome for \$1000 seems a realistic prospect in just a few years' time. This will have a profound impact on genome research and on the molecular diagnostic of known gene defects. It is already apparent that individual differences on the DNA level are substantially greater than previously assumed; this will add a further significant complicating factor to the identification of sequence alterations.

In adopting the Law on Genetic Diagnosis in April 2009 the legislative body stipulated that genetic diagnosis can only be carried out by qualified and certified doctors, and prescribed the accreditation for laboratories that conduct genetic analyses. The law gives particular weight to genetic consultation. With prenatal and predictive diagnosis, in particular, consultation is compulsory before and after examination. The law prohibits clandestine paternity tests. In respect to employment and insurance law, existing practices are in essence now legally prescribed. One new item is the explicit prohibition of antenatal examinations for diseases that manifest later in life. The planned Commission for Genetic Diagnosis is given a high level of responsibility and will be granted extensive authority.

Recommended action

In the future, priorities will inevitably have to be established in respect to the application and financing of molecular genetic diagnosis. To enable a fair balance of interests within the social solidarity network of insured parties, this should occur on the basis of a structured evaluation of genetic tests.

The Law on Genetic Diagnosis extends into domains that were previously regulated by the doctors' code of professional conduct. For example, it stipulates that examinations for genetically conditioned diseases are available to all doctors, irrespective of their level of qualification on the professional scale, and that the Commission for Genetic Diagnosis should determine the qualification requirements for genetic consultation. The implementation of the law will therefore depend decisively on maintaining existing standards of qualification.

The "\$1000 genome" opens up new horizons in research and will change genetic diagnosis profoundly. In view of this, we propose the following recommendations to the Federal Government and the funding organisations:

- ▶ To address the consequences that the rapid advances in the field of genome sequencing have had for health research and medical care and, furthermore, measures should be adopted which

will ensure a degree of participation in the international developments commensurate with Germany's economic power and research potential;

- ▶ To place emphasis, within the spectrum of examinations concerning the genetically conditioned variability of humans, on the study of pathogenetically relevant modifications, on promoting the establishment of pertinent cohorts of patients as well as their families, and on identifying already existing, suitable cohorts. Here we recommend following the British model, and setting up a committee comprising representatives from relevant fields of research (human genetics/genome research, epidemiology, clinical research, infection biology, and pharmaceutical research);
- ▶ To clarify, at the same time, the general framework for society and data protection laws vis-à-vis human genetic research that uses biobanks. As the use of these samples is often transnational, the aim should be legislation on the EU level;
- ▶ To concentrate clinical genetics in large (university) centres, following the model of other European countries such as Great Britain, the Netherlands, Belgium, and Denmark, to create networks among them and to greatly strengthen them, in order to accelerate the identification of genome modifications that are relevant to disease, to guarantee uniform quality standards for genome diagnosis, to create additional capacity to convey this information within the context of genetic consultation, and to address the looming acute shortage of skilled specialists.

For individuals, the causes for genetically conditioned diseases are beyond influence. Therefore, the principle of solidarity achieved through distributing the financial risk among the shoulders of many must not be undermined, not even, for example, by offering lower insurance premiums to individuals with a lower level of genetic risk. Thus, efforts to simplify and standardise the health insurance system must be intensified, with the aim of creating collective insurance for the entire population covering all risks of disease.

Furthermore, genetics and genomics must feature more prominently than to date in the medical curricula. In addition, it seems important that the foundations for this should already be conveyed at school. Although the Law on Genetic Diagnosis has just recently been passed, the discussion about how to deal with genetic data is not over. It should not remain confined to the experts involved, because the topic is multifaceted and affects every single individual. For instance, due to the new possibilities in diagnosis it will become increasingly easier, in the future, to obtain detailed information about one's own genetic disposition. This gives rise to a conflict between the individual right to knowledge and the right to withhold knowledge from third parties, from relatives through to members of the same section of the population. This conflict will intensify in the future. Society, in order to be able to deal with this issue, must be comprehensively informed about the consequences of genome research and gene diagnosis. On this front, Germany is clearly lagging behind neighbouring countries, and we call for the Federal Government to adopt appropriate measures to improve the situation.

4. Subject area gene therapy: somatic gene therapy (Core statements and recommended action)

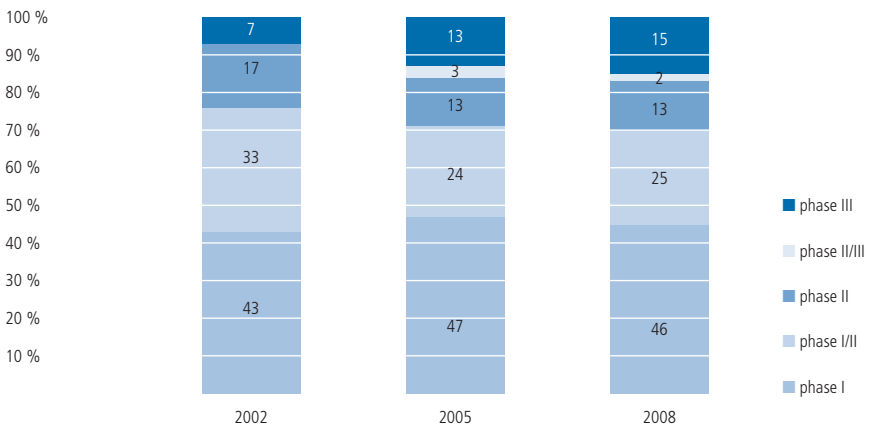
Somatic gene therapy

The development of vector and gene transfer technologies continues to be a central theme within gene therapy research. At the same time, there is growing diversification in regard to different applications and their respective appropriate vectors. New technologies for targeted gene repair display improved levels of efficiency and could, in the near future, become clinically mature, especially since it is becoming apparent, that the risks of side effects can also be significantly reduced.

Meanwhile substantial advances have been made in clinical applications, for example in the case of the ADA-SCID disease (long-term clinical effect, i.e., more than ten years without any side effects caused by the therapy). Positive results were also achieved in the case of macular degeneration. As a monotherapy, gene therapy could potentially become the chosen course of treatment for some monogenetic diseases in the near future. For more frequently treated, complex diseases (cancer, or cardiovascular diseases) it is more conceivable that these therapies will continue to be used in combination with conventional therapies.

Germany at present is witnessing a stagnation of clinical studies in the field of gene therapy (figure 7). As such, research in these directions is in competition with other new approaches to therapy (e.g., small molecules, anti-bodies). Also of essential significance in this respect is the progress made in cell therapy, in (stem cell) biological basic research, in imaging procedures, or in toxicology. Advances in the development and application of induced pluripotent stem cells (iPS) are foreseeable. Such advances may open up, for instance, new perspectives in respect to combining approaches using gene therapy with tissue engineering. Implementing the approaches involving gene therapy

Figure 7: Gene therapy clinical trials (in Germany)



pilot study = phase I.

Source: DeReG-Datenbank; Zweiter Gentechnologiebericht, 2009:220.

Figure 8: Public funding for gene therapy (in Germany)

	Duration	Total funding volume in EUR	Average funding volume per year in EUR
BMBF programmes			
1) TreatID joint research project: treatment of serious immune deficiencies with genetically modified stem cells			
Subproject 6a – expression of secreted peptides for gene therapy for HIV infection, and subproject 6b – examinations into gene therapy for chronic granulomatosis	01. 10. 2005– 31. 12. 2008	543.319	167.175
Subproject 5 – “genotoxicity of retroviral vectors”	01. 01. 2006– 31. 12. 2008	327.380	109.123
Subproject 4 – clonality analysis of in vivo GM cells	01. 01. 2006– 31. 12. 2008	2.712.674	904.225
Subproject 4 – clonality analysis of in vivo GM cells	01. 04. 2006– 31. 03. 2009	128.704	42.901
2) DeReG - German Registry for Somatic Gene Transfer Trials	01. 08. 2002– 31. 10. 2008	902.076	144.332
3) Joint research project: gene immunotherapy for advanced prostate carcinoma			
Gene therapy for the selective induction of apoptosis through TRAIL (TP 1)	01. 10. 2006– 30. 09. 2009	266.070	88.690
DFG programmes			
Focus 1230: mechanisms of gene vector entry and persistence/priority programme	since 01. 04. 2006	3,3 Mio.	
Principles and applications of adoptive T-cell therapy	since 2006	2006: 1,1 Mio. 2007: 2,0 Mio.	

Source: Zweiter Gentechnologiebericht, 2009:216.

into clinical practice would require establishing the technological conditions (so-called good manufacturing practice (GMP) technologies) for universities and the private sector.

Enhancement

Enhancement continues to be a relevant problem, especially against the backdrop of possible gene doping. The increasing safety of vectors and efficiency of control mechanisms for conventional do-

ping substances in high performance sports could make gene doping more attractive in the future. Irrespective of developments in technology, the legal and ethical arguments against genetic enhancement remain as valid as before.

Germline intervention

The development of technologies that reduce side effects could move germline intervention more sharply back into focus in other countries. Germline intervention, even if technically possible, continues to be categorically rejected by the research group 'Gene Technology Report' of the Berlin-Brandenburg Academy of Sciences and Humanities (BBAW) for ethically justified moral reasons.

Public and private funding

Attempts are being made by the German Research Community and the Federal Ministry of Education and Research to promote the field of clinical implementation through targeted sponsoring of clinical studies (figure 8); there is, however, a perceptible lack of private funding. The infrastructure is also inadequate, for example in the provision of GMP centres. Both these aspects are of immediate importance for gene as well as cell therapy; the current situation could therefore in the near future lead to a decline in clinical research and application.

5. Subject area green gene technology: plant breeding and agriculture (Core statements and recommended action)

The research field of green gene technology continues to develop at a highly dynamic rate, and researchers are at present working on second and third generation of genetically modified plants (GM plants). Accompanying this work is a comprehensive review of cell biological activities (transcriptome, proteome, and metabolome research), and the complete sequencing of an increasing number of plant genomes.

The contributions of gene technology to modern plant breeding go beyond transgenic plants. Gene technology techniques have contributed significantly to advancing knowledge about single genes and their significance for the phenotype, and to establishing smart breeding technologies.

Smart breeding, like cisgenic plants, does not constitute an equally valid alternative to transgenic processes. Especially for plants used in the manufacture of plant made industrial products or plant made pharmaceuticals, smart breeding cannot be used in most cases, because of being confined to crossable species. Even approaches to improve the use of plant biomass (e.g., second generation bio-fuels) continue to require cross-species gene transfer.

At present these examples reflect primarily the theoretical potential of green gene technology, and are mainly still located, with some exceptions, in the initial stages of basic research. In Germany, ap-

plications such as these, in particular, and other future-oriented applications of green gene technology, such as improvements in the composition and use efficiency of nutrients, or the optimisation of cultivated plants from third world and emerging countries, should be publicly funded and further developed.

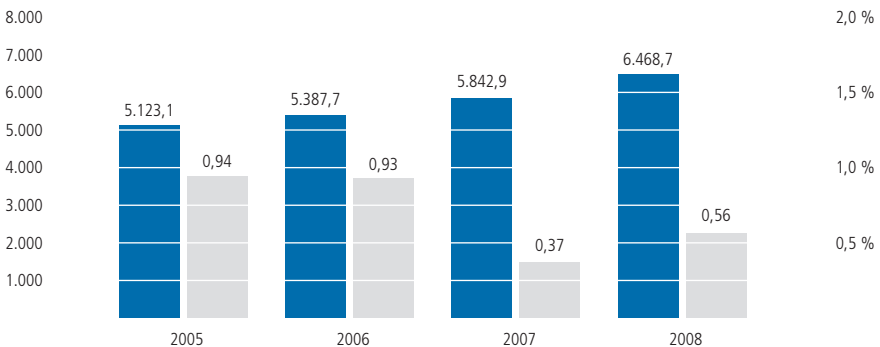
Germany continues to lack consistent policies in this respect: while the Federal Ministry of Education and Research (BMBF) funds technological developments and research into safety (figure 9), the Federal Ministry of Food, Agriculture, and Consumer Protection (BMELV) slows down the concrete application of the results. Any potential opportunities for innovation in agriculture are wasted, and even research itself is obstructed.

For the development of new GM varieties and for ecological research into safety, where Germany is among the international leaders, outdoor trials are absolutely indispensable. The destruction of authorised outdoor trials is neither a legitimate form of protest nor tolerated by the law.

Even now, on the level of research into application, German research is on the verge of being disconnected from international research programs into green gene technology. This must be prevented, just as the continued migration abroad of industrial research and the next generation of scientists, which means the permanent loss of scientific expertise, must be halted. Scientific and human resources knowhow in the field of green gene technology must be secured in the long term as the motor for future innovation in Germany.

Fundamental objections to the safety of green gene technology cannot form the basis of the central argument against the use of transformation techniques in plants.

Figure 9: BMBF public research expenditure



■ Total BMBF research expenditures in million EUR.
 ■ Percentage of the following programmes of the overall BMBF research expenditures in %: Nachhaltige BioProduktion (sustainable biological production), Netzwerke der molekularen Ernährungsforschung (networks of molecular food research), Inno Regio, Ernährung – moderne Verfahren der Lebensmittelerzeugung (food – modern processes of food production), Biologische Sicherheitsforschung (biological safety research), GABI, GABI-Future, Plant Genomics ERA-NET, Bioindustrie 2021.

Source: Zweiter Gentechnologiebericht, 2009:309.

Figure 10: Percentages of cultivated GM crops referred to separate crops hectares

Corn	2006	2007	2008
	Percentage of GM maize cultivated on overall maize hectareage	Percentage of GM maize cultivated on overall maize hectareage	Percentage of GM maize cultivated on overall maize hectareage
Germany	<0,1	0,143	0,152
Baden-Württemberg	<0,1	<0,1	<0,1
Bavaria	<0,1	<0,1	<0,1
Berlin	0	0	0
Brandenburg	0,370	0,978	0,792
Bremen	0	0	0
Hamburg	0	0	0
Hesse	0	<0,1	0
Mecklenburg-Western Pomerania	0,264	0,601	0,639
Lower Saxony	<0,1	<0,1	<0,1
Nordrhein-Westfalen	0	0	0
Rheinland-Pfalz	<0,1	<0,1	<0,1
Saarland	0	0	0
Saxony	0,310	0,730	1,145
Saxony-Anhalt	<0,1	0,128	0,195
Schleswig-Holstein	0	0	<0,1
Thuringia	0	<0,1	<0,1

Source: Zweiter Gentechnologiebericht, 2009:321.

Each individual case is intensively tested for potential health risks as part of its compulsory authorisation process. After being in use for longer than a decade, there is no evidence that authorised transgenic plants have any particular negative health effects. Public reports that claim otherwise would not bear up to scientific examination.

Possible ecological effects will continue to be tested, for each individual case, as part of the authorisation for GM plants. On the one hand, this must ensure that cultivating them does not exacerbate the ecological problems associated with conventional present-day agricultural practices. On the other hand, it would be a mistake to ignore the potential positive effects GM plants could demonstrably have in improving the environmental impact of agricultural cultivation as compared with conventional methods of cultivation (e.g., by reducing insecticide).

As long as the policy decision within the European Union is to allow GM plants to be cultivated after testing, national laws of neighbourly coexistence between countries that use gene technology in agriculture, and countries that do not, should not result in making their cultivation de facto impossible.

The comprehensive scientific tests for possible risks carried out by the European Food Safety Authority (EFSA) have stood the test of time, and cannot be reproached for any tangible shortcomings in the scientific quality of their expertise. The precautionary principle valid within the EU should not be misused to restrict the use of GM plants without any concrete scientific evidence that they present a danger to nature or humans.

It remains open as to whether gene technology in the food industry will falter due to a lack of consumer acceptance. Widespread public scepticism and organised pressure from society mean that at present food manufacturers and traders supply hardly any food that clearly displays the use of GMO. Moreover, GM plants authorised so far have no directly identifiable benefits for consumers.

In Germany, GM plant varieties will not constitute a noteworthy proportion of crops in the next few years (figure 10). The reasons for this are independent of the recent ban on cultivating MON810. At the same time, gene technology in the food industry has also clearly found its uses in Germany, for example, in the form of food additives made of GM microorganisms or animal feed made from GM plants. According to EU law, neither of these forms of usage requires labelling. The label "ohne Gentechnik" (GM-free) introduced in Germany is a reasonable extension of EU-labelling, but it also allows for exceptions, which must be excluded in any thorough labelling system that does not depend on detectability.

Internationally – in contrast to Germany – GM plants are gaining importance in the cultivation both of food and animal feed. Although the price of seeds is higher, even small farmers in emerging countries can benefit from cultivating GM varieties, because of the reduced losses through pest attacks. At present, the farmers do not depend exclusively on a single seed supplier. Likewise, patents that impose licence fees for saving seed from one year's harvest for replanting do not mean greater dependency, compared to the much used hybrid varieties.

Also in the future, farmers must continue to have a fair choice to cultivate varieties produced without gene technology. In addition, it must be ensured that in future, patents can only be taken out for inventions, but not on the gene sequence alone, which is also found in traditional heirloom plants.

6. Cross-sectional survey of basic research: current developments in science and technology (Core statements and recommended action)

From the field of basic research, the report carried out closer analyses of four areas as examples. Firstly, the development of systems biological approaches in interaction with (human) genome research, secondly, the development of new sequencing technologies and their impact on pathogenetic diagnosis and therapy, thirdly, the development potential of RNA-technologies, and fourthly, the development of epigenetics.

Genome research and systems biology

Genome research and systems biology are the key to solving many of the medical and economic problems faced by contemporary societies. Therefore, there must be targeted funding in this field. This funding should concentrate on (1) integrating genome research and systems biology, (2) corresponding development in technology and bioinformatics, and (3) risky, but innovative projects.

Precisely in order to develop approaches that are easily applicable, it is essential to expand existing centres of genome research and systems biology into centres of systems genomics and to create centres that can compete on an international level.

It is also important to preserve the existing tradition of funding programs of the Federal Ministry of Education and Research (BMBF) (e.g., QuantPro – quantitative analysis for the description of dynamic processes in living systems) and to continue to support the field of technological development, in particular that of bioinformatics, through targeted funding programs. Without the BMBF playing a central role in the fields of genome research and systems genomics, it is inconceivable that Germany will be able to participate in these key developments in medical-biological research.

In addition, innovative research without any preconceived outcome must also be funded. A proportion of the funding should therefore be earmarked for “blue sky research”, i.e., for innovative high-risk research that pursues important general goals.

Genome sequencing

It must be ensured that Germany contributes appropriately to the further development of sequencing technologies. In research into human genetic variability, made possible by new technologies, the emphasis should be on pathogenetically relevant modifications. Clinical genetics should be concentrated at large university centres. We recommend appointing a committee to identify particularly important disease patterns, involving human genetics/genome research, epidemiology, clinical research, infection biology, and pharmaceutical research.

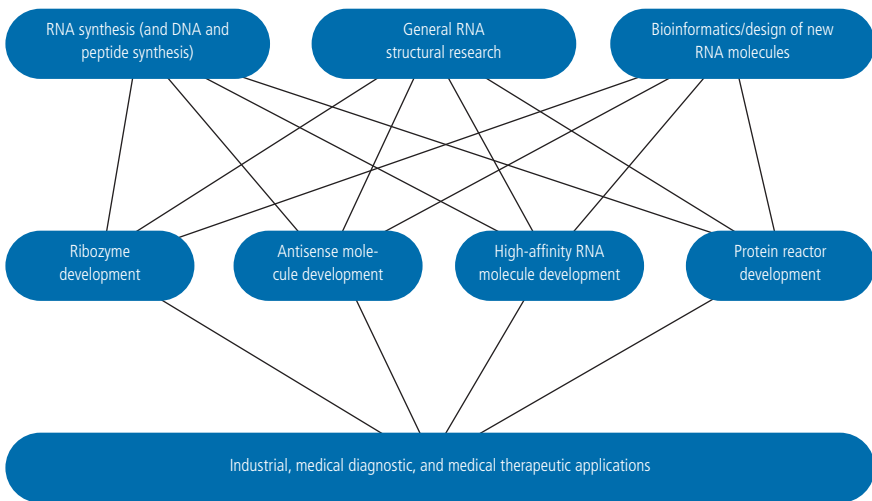
We further recommend that policy makers and the funding organisations in Germany thoroughly concern themselves with the consequences from developments in the field of genome sequencing for

health research and medical care. Furthermore, suitable measures must be adopted to ensure German participation at a level commensurate with the economic power and research potential of the country.

RNA technologies

RNA technologies are molecular technologies of the present and the future, which are worthy of particular funding. They have versatile applications, ranging from basic research in the stricter sense, the advancement of nucleic acid chips, the industrial manufacture of protein products, through to cancer therapy and nucleic acid pharmacology (figure 11).

Figure 11: Scientific preconditions and aims for establishing RNA technologies



Source: Erdmann et al., 2006:49; Zweiter Gentechnologiebericht, 2009:355.

Epigenetics

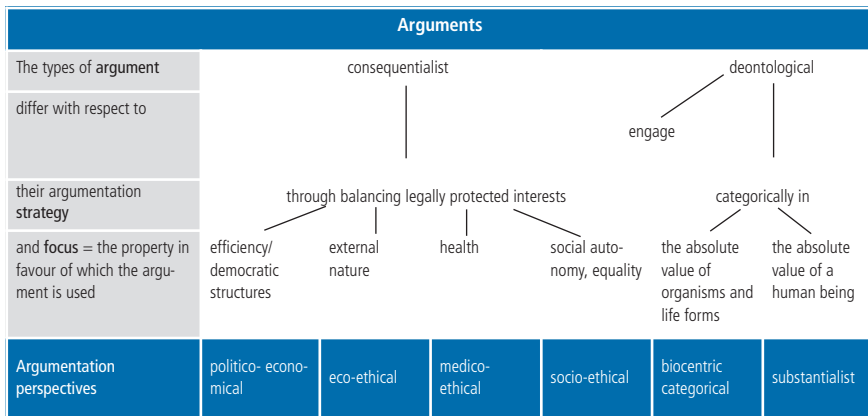
Epigenetics offers conceptually new approaches for understanding genetically-regulated molecular processes, both in normal development as well as during the course of disease. Epigenetics is at present one of the central fields of basic research requiring intensified support. Epigenetic research opens the horizon to a broad range of applications in the areas of the production of anti-bodies, epigenetic approaches to therapy, as well as in the generation and use of stem cells.

7. Cross-sectional survey of ethics: argumentative dimensions in the ethical evaluation of gene technology (Extracts from the introduction)

In its function of taking a stance vis-à-vis the developments in gene technology and their implications, the Gene Technology Report resorts to a specific tool to rationalise the mass of available information and data: the selection of indicator sets (Hucho et al., 2005:17 et sqq.). The aim here is to represent the phenomena "gene technology" as a complex and confusing problem area as distinctly as possible by using measurable and representative indicators, thereby helping to clarify problems and controversies, or to register emerging developmental trends. With the great need for conceptually tangible differentiation in the varying uses of the term at present in different specialist disciplines (ibid.), the definitive characteristic that makes the use of such indicator sets appropriate in the Gene Technology Report is that they are ultimately observable, quantitative parameters.

Being able to measure and quantify indicators, however, becomes all the more difficult, the "softer" the areas of phenomena are that they are trying to describe. In particular, given that the field of focus in the Gene Technology Report is essentially very broad (as it would have to be to genuinely appreciate the phenomena "gene technology"), in that it considers scientific, technical, and economic aspects, as well as ethical, political, and social aspects, and therefore, it is not always possible to do adequate justice to the claim of establishing meaningful indicators. With respect to the ethical cross-sectional dimension of certain branches of research and fields of technology, the Gene Technology Report has responded so far to the general framework of its studies by describing the

Figure 12: Differentiation of the ethical arguments regarding gene technology



Source: Runtenberg, 2001:122; Zweiter Gentechnologiebericht, 2009:394.

ethical problem areas that are pertinent to concrete forms of application – mainly in the form of an ethical discussion of a circumscribed question.

This report chose a different path: the pivotal question is that of which fundamental positions and opinions form the structure of the diverse ethical discourse about the multifarious options for action associated with gene technology. In other words, the aim is to grasp the types and lines of argument that determine the numerous individual ethical questions. When we refer below to a “philosophical-ethical system of categories” what we mean is the attempt, using a very few polarisations, to bring some order into the mass of opposing positions, arguments, and complex lines of debate in the ethical debate about gene technology.

In the chapter of the report dealing with ethics we attempt, through a grid of opposing categories, to highlight the key terms and viewpoints of the rival assessments and judgements of possible actions in gene technology (figure 12). We created four pairs of opposites to designate these types of arguments: deontological versus teleological forms of argument, human dignity versus animal dignity, bioconservative versus bioliberal, natural versus artificial. The diversity of these descriptions alone illustrates that the pairs of opposites are very different in terms of logical or categorical status. What they all have in common, however, is that when applied to problem areas in gene technology they result in the adoption of contradictory ethical positions. In that sense, they interact against clear answers to the question of whether certain developments in gene technology should be permitted or forbidden out of ethical considerations.

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