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Human genome surgery – towards a responsible evaluation of a new technology

Analysis by the Interdisciplinary Research Group *Gene Technology Report*

Berlin: Berlin-Brandenburg Academy of Sciences and Humanities, 2015
ISBN: 978-3-939818-58-8

Persistent Identifier: urn:nbn:de:kobv:b4-opus4-24861

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BERLIN-BRANDENBURG ACADEMY OF SCIENCES AND HUMANITIES



Berlin-Brandenburg Academy of Sciences and Humanities (BBAW)

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GROUP *GENE TECHNOLOGY REPORT*

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This booklet is a translation of "Genomchirurgie beim Menschen – Zur verantwortlichen Bewertung einer neuen Technologie" of the Interdisciplinary Research Group *Gene Technology Report*, published in July 2015 (ISBN: 978-3-939818-57-1)

Published by: Berlin-Brandenburg Academy of Sciences and Humanities
Interdisciplinary Research Group *Gene Technology Report*

Editing: Jens Reich, Lilian Marx-Stöltzing

Design: angenehme gestaltung/Thorsten Probst

Cover photo: Stock photo © JackyLeung

Translation: Aileen Sharpe, Sharpe Translations

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This publication was funded by the Senatsverwaltung für Wirtschaft, Technologie und Forschung des Landes Berlin and the Ministerium für Wissenschaft, Forschung und Kultur des Landes Brandenburg.

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ISBN: 978-3-939818-58-8

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Human genome surgery – towards a responsible evaluation of a new technology

Analysis by the Interdisciplinary Research Group *Gene Technology Report* of the Berlin-Brandenburg Academy of Sciences and Humanities

SUMMARY

New, precise genetic engineering methods for genome alteration in living cells, which can be classed together under the generic heading “genome surgery”, are currently sparking a revolution in biomedical research. The Interdisciplinary Research Group *Gene Technology Report*¹ is, in principle, in favour of research on these promising new methods for the medical sector. However, for the time being, it has clearly spoken out against gene surgery experiments on the human germ line, which could also enter the realm of possibility thanks to these methods. The research group, therefore, supports the call, which has already been discussed at length in scientific and public circles, for a moratorium for germ line experiments. The period of the moratorium should be used to debate the experimental, ethical and legal aspects of germ line therapy in an open, transparent and critical manner with a view to more clearly defining the opportunities and risks of these technologies for man and nature, and to elaborating recommendations for future regulations. The goal of this analysis is to promote a discourse of this kind.

The legal issues of germ line therapy have to do, for instance, with the scale of the statutory ban imposed by the German Embryo Protection Act (EschG) (Section 5) and the issues surrounding the justification for and the interpretation of this Act in the light of these new opportunities. The ethical issues include ones that look at the consequences for the respective individual but also ones that address the potential repercussions for society as a whole. Against this backdrop the ethical issues, which have already been discussed in the past in conjunction with different methods (for instance in the context of cloning, pre-implantation and prenatal diagnosis), are once again attracting attention. In some cases,

¹ The Interdisciplinary Research Group *Gene Technology Report* is a monitoring project of the Berlin-Brandenburg Academy of Sciences and Humanities which addresses current developments in genetic engineering in Germany.

controversy still surrounds them today. This analysis is restricted to outlining in a list the main arguments behind the pros and cons of medically and non-medically motivated germ line alteration in humans.

These arguments can be formulated from very different ethical positions and need to be presented in more detail and then discussed. This raises the question whether germ line therapy constitutes an advance infringement of the right to self-determination and physical integrity of the individual in question or could be seen as a violation of dignity resulting from instrumentalisation of the future individual. There is likewise a need for discussion of the fear that embarking on medically induced germ line interventions could open the door to applications beyond medicine on a larger scale (for example for eugenic purposes). This could have incalculable consequences in the social sector. Given the complex, problematic nature of these issues and their many compounding factors, any action recommendations derived from ethical arguments could indeed contradict each other. Hence, there should be a call for a carefully moderated, responsible and differentiated ethical discussion about germ line alterations in humans prior to any practical applications and any preparations for their use.

ACTION RECOMMENDATIONS

- The Interdisciplinary Research Group *Gene Technology Report* stresses that the new genome surgery methods are not to be considered in isolation. Their ethical defensibility depends far more on the context in which they are applied and the goals they pursue. Any general evaluation of these methods would, therefore, be inappropriate. Clarification of the question about the risks and applications – and here too and above all of the issue of unintended effects on the genome – should be the subject of thorough research that looks at the safety and risk aspects, in addition to the open basic research in the field of genome surgery. This is the only way of ensuring an expert assessment of the risks.
- The research group supports, in this context, the accompanying research on new genome surgery methods for the medical sector by means of an intensive discourse on the potential risks.

- A distinction should be made between:
 1. Research on human somatic cells *in vitro*, which is already ongoing and does not, in principle, pose any ethical problems,
 2. applications in humans for somatic-genetic therapy and prevention purposes. The precondition for this is that the new method is fully developed, can be justified ethically and is sufficiently technically safe in line with the provisions that apply in general to medical research in humans, and
 3. applications of germ line therapy for which the technology is definitely not mature at the present time and its use is, in principle, up for discussion. Here the research group supports the call for a moratorium for germ line experiments in humans, which has already been discussed at length by science and the public at large.²
- The period of the moratorium should be used for further research on the opportunities and risks of the method and for a social debate on the ethical and legal questions of germ line therapy.

² See also the calls by Lanphier et al. (2015) and Baltimore et al. (2015) which triggered the current discussions.

1. INTRODUCTION

In this analysis the term “genome surgery” encompasses the latest genetic engineering methods that are currently being developed. These methods aim to facilitate the targeted and permanent alteration of hereditary factors encoded in the DNA of the genome in human cells, tissue or the entire human organism³ with up to now unprecedented accuracy and precision. This includes methods which are described in scientific terms as “gene editing”. One method, which is currently the subject of intensive research, is the CRISPR/Cas technique⁴. CRISPR is the acronym for “Clustered Regularly Interspaced Short Palindromic Repeats” and Cas stands for “CRISPR-associated” proteins. These and other methods are currently being used mainly in basic research. However, there are already some preliminary clinical trials on disease prevention or treatment.

The refinement and increased precision of these methods are currently being tested in animal experiments and in human cell cultures in numerous research laboratories around the globe. Building on this, a clear increase in the clinical use of these methods to “repair” mutations in medically relevant “gene loci”⁵ is to be expected over the next few years within the framework of somatic gene therapy⁶. This could be an effective therapy for monogenic disease predispositions (e.g. a genetic defect transmitted within a family with severe health consequences for the persons affected). It could likewise facilitate the desired engineering of gene-embedded resistance to infections (for instance to the human immunodeficiency virus, HIV).

At the same time, the optimisation of “gene editing” methods also opens up new opportunities for targeted germ line alteration. However, it is these very applications that throw up ethical, legal and socio-political questions. We advocate the staging of a responsible and transparent ethical discussion about the use of fundamentally new methods in human medicine before they reach application

3 This analysis does not look at the use of these methods in plant or animal genetics. Genome surgery is, however, used in these areas, too.

4 For an overview of CRISPR/Cas9 see for instance Doudna/Charpentier (2014) or Hsu et al. (2014).

5 Here genomic loci stand for specific sections in the DNA building block sequence. A mutation often affects only one single DNA building block (point mutation) or several building blocks or even alters entire sections.

6 “Somatic” gene therapy targets cells or tissue in the developed organism. The result cannot be passed on to progeny. Genetic alterations to the “germ line” affect the germ cells (egg cells, sperm cells) or their precursors in the gonads (ovaries, testicles) of an organism or analogous cells treated outside the body (ex vivo). They are passed on to all progeny.

maturity and any political regulations are pending. For that reason we present, in this analysis, what we see as the most important social issues surrounding targeted germ line alteration

2. CHARACTERISATION OF GENOME SURGERY WHEN USED IN HUMANS

Technologies used for targeted DNA modification in the genome of living beings have been the subject of experimental development and successful application for around three decades. However, most of the customary methods used have not achieved a high degree of fit, precision or specificity. When applied to micro-organisms, plants and animals this shortcoming was not as important because a larger number of experiments could be conducted. The alteration obtained in some of the set-ups could then be validated by screening and replicated in selection or breeding methods. In this way, for example, transgenic murine breeding lines could be successfully engineered through genetic modifications. In addition, genetic modifications were also made where the investigated gene modification only intervened at a certain stage of development or only in specific organs.

Elaborate strategies of this kind are used in experimental medical research. They can also prove successful in conjunction with somatic gene therapy by treating isolated cell populations (*ex vivo*). However, if there is a desire in future to carry out gene therapy or prevent a severe genetic disorder *in vivo* (e.g. “repair” genetically defective cardiac muscle cells in the intact heart), then exact fit (i.e. adjustment to the alteration in the DNA double-strand molecule at the desired locus), precision (i.e. the success of the intended alterations to the targeted cells) and specificity (i.e. the exclusion of genetic modifications at loci other than the intended ones) are the decisive preconditions. What’s also important is the stability of the genetic alteration in the further fate of the cell line or treated organism.

For some years now methods have been developed which could move closer to these ideal requirements as a result of further technical perfection. In the case of the CRISPR/Cas methods which are currently to the fore of research interest, special enzymes were examined which can help bacteria (e.g. specific streptococci) to detect invasive phage DNA (virus DNA), to cut it at a precise location using DNA nuclease (“DNA scissors”) thereby destroying it, and to then initiate its

degradation. A defined RNA sequence guides the nuclease enzyme to the right (complementary) DNA locus in such a way that only the phage DNA and not the bacterial genome structure is cut. In this genetic engineering application the RNA sequence is constructed in such a way in the CRISPR/Cas system that it is directed to the desired genomic locus and triggers a strand break in the DNA there. The DNA repair mechanisms in each cell then swing into action and “sew” the cut. An additional DNA sequence introduced externally can serve as the template. With its help the repairs can be made in such a way that the DNA section concerned ends up with the precise desired sequence.

A “scissor tool” geared in evolution in a targeted manner solely to the “acquired immune defence” of bacterial cells against phage infection can be reconstructed biochemically in so many different ways that, as soon as it is introduced via a suitable vector (a “gene shuttle”)⁷ into a viable cell of any biological origin, it can initiate mutations in a targeted manner or inactivate entire genes. With the help of a sequence template the genome can, in addition, be “edited” at the desired location. The scientific name for this process is gene editing. It fits very well with the analogy of the editing of a text before it goes to print.

Genome surgery can be used not only for the specific alteration of a single genome locus but also as a multiplex variant for the modification of several genome loci in one step. The risks of side-effects like chromosomal abnormalities do, however, increase significantly. This means that its use in the clinic (in contrast to research in isolated cells and use in micro-organisms, animals and plants) is unlikely in the near future. In contrast, many of the previous methods available up to now for modifying several genomic loci could only be used in a highly complex and consecutive manner.

When it comes to ethically, legally or socially controversial applications of this new technology, a key element could be that “editing” of the gene can lead to a result where it is no longer possible to prove that it was achieved through natural mutation (and selection) or through targeted genetic engineering. A targeted

⁷ Vectors (in popular science “gene shuttles”) are natural or artificially engineered constructs that penetrate the barrier of the cell membrane and can deliver DNA or RNA molecules into the cell interior. In gene therapy viruses are frequently used as vectors which have been modified in such a way that they are still “infectious” but are no longer able to trigger the related disease (see Fehse/Domasch 2011 and 2015 for the principles of somatic gene therapy and current developments). In recent years there have been major advances in the development of cell- or organ-specific gene shuttles (see Fehse/Domasch 2015, pp. 213–232). By limiting gene editing to selected target cells or organs, the risk of undesirable germ line alterations could be considerably minimised.

alteration of this kind had always been detectable up to now as the artificial product of intervention in all gene constructs.

3. APPLICATION PROSPECTS OF GENOME SURGERY IN HUMAN MEDICINE

Aside from its use in research on the foundations of such diseases in which alterations to genetic make-up could be an important cause, it is likely that gene editing will also be increasingly used for therapeutic purposes after corresponding fine-tuning of the method's effectiveness and specificity.

Promising applications for gene therapy of this kind are firstly diseases, primarily monogenic or oligogenic diseases (i.e. diseases which can be accurately attributed to the alteration of one or a few genomic loci). Other possible applications include the engineering of desirable traits like for instance:

- targeted, acquired immunity against specific infections (for instance against the human immunodeficiency virus, HIV),⁸ for which some individuals have a naturally mutated entry receptor;
- activation of the autologous immune system against infections, systemic diseases or types of tumours where mutated genes play an important role;
- prevention of cancer onset in individuals who have a marked genetic predisposition (e.g. carriers of a breast cancer gene or individuals with a genetic alteration that carries an elevated risk of colorectal cancer).

Because of the potential risks of off-target effects and the insufficient specificity and efficiency of these methods up to now, they are currently only suitable for the treatment of severe diseases and clinical trials. Furthermore, the cells are modified outside the body (*ex vivo*) in the first trials in such a way that the risk of adverse side effects is restricted to the removed cells that are returned after the alteration. It is likely that molecular biomedical research will make important contributions to "somatic" gene therapy in Germany, too. Preliminary studies on these customised genome surgery methods are already being conducted abroad or are about to be translated into clinical use.

8 Tebas et al. (2014).

4. GERM LINE ALTERATIONS

With every use of gene modification methods *in vivo* there is a risk that the germ line of the individual concerned will be altered, as an undesirable side-effect, along with the actual target tissue. This means that the genetic modification can be passed on unintentionally to the later progeny of a treated person.

The unintended germ line alteration is set against the intended one. This intended effect could be, for instance, to free all the progeny of a certain person from a specific genetic risk or endow them with specific genetic traits. In between there is the conscious acceptance of a germ line alteration through a planned somatic modification (f.i. in the case of somatic gene therapy in an embryo or foetus) prior to differentiation of the various cell types. In future, germ line therapy in combination with artificial fertilisation will probably be a simpler technological method than somatic gene therapy because it only has to be undertaken in one or just a few cells *in vitro* whereas an alteration targeting a specific cell type in the organism (e.g. liver cells) would possibly have to reach several billion cells.

As many genetic defects already manifest during the organism's early developmental stage, there is a medical indication for gene therapy already in the foetal or even in the embryonic stage. The impact on later germ cells would then have to be consciously accepted. The precondition of independent informed consent from an individual capable of giving this consent cannot be met in this case either but must be restricted to the objectively informed decision of the future parents taken on behalf of their child with its well-being in mind.

5. SCALE OF THE STATUTORY BAN ON GERM LINE INTERVENTION IN GERMANY

The German Embryo Protection Act prohibits, subject to punishment for any infringements, in Section 5(1) ESchG any artificial alteration of genetic information of a human germ line and in Section 5(2) the use of a human germ cell with artificially altered genetic information for fertilisation. Hence, the Act likewise prohibits any attempt at germ line therapy, i.e. any attempt to heal genetic diseases and alleviate suffering by altering or replacing the defect DNA sequence through intervening in the gametes, pronuclei or germ line cells. If its use for

fertilisation has been ruled out, artificial alteration of the genetic information of a germ cell situated outside the body is exempt from the ban (Section 5(4)(1) ESchG). The artificial alteration of the genetic information of another autologous germ cell line, that has been removed from a dead embryo, individual or deceased person, is not banned if it has been ruled out that it will be transferred to an embryo, foetus or human being or that a germ cell will originate from it (Section 5(4)(2) ESchG). A germ line alteration, which is an unintended side-effect of inoculation, chemotherapy or radiation, is likewise exempt from the ban (Section 5(4)(3) ESchG). What is not explicitly covered by the last-mentioned exemption is a germ line alteration which is the unintended consequence of somatic gene therapy. According to the *ratio legis* it must go unpunished, too.

For the term "germ line cell" the Act gives a definition⁹ which refers to a direct lineage chain from the individual cells ("one cell line") of the egg cell, sperm cell, fertilised egg cell down to the germ cells of the progeny. There is a loophole in this legal definition as the early embryo does not contain any cells after the first cell division that could be identified as germ cells. Up to around the third week of development it is not clear which of the existing cells will become the direct "progenitors" of the later primordial germ cells. This means that it is not possible to differentiate between "somatic cells" and germ line cells. The totipotent cells in the earliest stage of embryonic development could be deemed to be "germ line cells".¹⁰ However, in the case of cells after the 8-cell stage it is still unclear whether gene therapy *in vitro* is prohibited in individual representatives of these cells.¹¹ To correct certain genetic defects (e.g. the capacity for implantation or the correct formation of the organ anlage) one would, however, have to resort to therapy particularly in this early embryonic phase.

Furthermore, it is unclear whether the germ line alteration would be exempt from punishment when it is undertaken in an embryo which – as was the case in a recently published study¹² – was not viable. Arrested embryos, in which cell division

9 Section 8(3) ESchG: "Germ line cells, for the purpose of this Act, are all cells that lead in one cell line from the fertilised egg cell to the egg and sperm cells of the resultant human being and, further, the egg cell from insertion or penetration of the sperm up to completion of fertilisation by fusion of the nuclei."

10 Günther (2014), Section 5 marginal number 9.

11 Concerning the lack of clarity whether the germ line in mammals, i. e. also in humans, is interrupted by the pluripotency of embryonic blastomers, see Taupitz (2014), Section 8 marginal number 65.

12 In China the CRISPR/Cas9 method was used in non-viable embryos for research purposes (Liang et al. 2015).

does not take place (any more), are not protected by the Embryo Protection Act.¹³ Section 5 ESchG with its ban on germ line alteration does not focus on the embryo and only exempts those germ cells from the blanket ban, which are not used for fertilisation.¹⁴ Fertilisation or attempted fertilisation has already been carried out in arrested embryos. Moreover, it is unclear and disputed whether the inability to develop is to be assumed only when there is no cell division or whether this also applies to embryos which cannot achieve nidation or cannot continue to develop up to birth for genetic reasons.¹⁵

Finally, the Act does not contain any statements about whether the term “germ cell” encompasses only naturally formed egg and sperm cells or also artificially engineered egg and sperm cells (e. g. from induced pluripotent stem cells (iPS cells)).¹⁶ Given the lack of any contrary provisions in the Act, artificially engineered germ cells are probably meant to the extent that they are functionally equivalent to germ cells that have formed naturally.¹⁷ When germ cells are engineered from iPS cells and no germ line cell was used to engineer the iPS cell, there is no artificial alteration of the genetic information of a human germ cell as defined in Section 5(1) ESchG.¹⁸ Hence, this kind of method is not prohibited by the Embryo Protection Act.

What is clearly not covered by the ban on germ line alterations is any alteration to the genetic information of a somatic cell. Nor is the transfer of the cell nucleus of an altered cell to an enucleated egg cell banned by Section 5 ESchG.¹⁹ Furthermore, the transfer of a genetically modified cell nucleus to an enucleated egg cell does not constitute an infringement of the ban on cloning as defined in Section 6 ESchG as no embryo is created with the “same” genetic information as another embryo, foetus or human.²⁰

Overall, the bans in Section 5 ESchG are not very clear or very consistent.

13 Taupitz (2014), Section 8 marginal number 20 f.

14 Moreover, also the actions mentioned in Section 5(4)(2) too.

15 On this point see Taupitz (2014), Section 8 marginal number 14 ff.

16 According to unanimous opinion in the literature Section 5 ESchG only encompasses human germ and germ line cells, i.e. cells which stem solely or were manufactured from human material, see Günther (2014), Section 5 marginal number 10.

17 German Ethics Council (2014), p. 5; see also Günther (2014), Section 5 marginal number 10.

18 German Ethics Council (2014), p. 5.

19 Federal Government (1998), p. 17; Günther (2014), Section 5 marginal number 15.

20 Taupitz (2001).

6. THE LEGISLATIVE JUSTIFICATION FOR THE BAN ON GERM LINE INTERVENTION

The legislator's main intention when introducing Section 5 ESchG was protection from germ line therapy because of the related technical problems. Any experiments where the results could not be predicted with sufficient reliability were to be prevented. Section 5 ESchG is not, therefore, a provision to prevent "positive" eugenics, i.e. individual "enhancement", to protect human dignity without any concrete existing bearer or to push through other general moral demands. Instead Section 5 ESchG contains a concrete strict liability tort as protection against irresponsible human experiments at the cost of human life and the physical integrity of future individuals affected in a concrete manner by a germ line alteration.²¹ Hence, more hypothetical objections ("If... then...") were taken into account in conjunction with the technical opportunities and less categorical objections with a view to specific standards or principles. If safe germ line therapy were to be possible one day, then the legislative justification for the ban would cease to be valid. If one interprets the wording of the Embryo Protection Act contrary to this understanding as meaning that it bans any therapy which impacts the individual germ line and, by extension, the hereditary disposition (gene) of future progeny irrespective of the safety of the method, then this would mean that the Act likewise bans gene therapy prior to the transfer of an *in vitro* embryo to the mother. A ban of this nature would, however, conflict with the intention likewise anchored in the Embryo Protection Act of helping an embryo to implant and thus to survive instead of classifying it as unsuitable because of its undesirable traits, and "discarding it". Hence, there is a need for a more in-depth weighing up of the arguments that back or decry the reliability of germ line therapy.

In terms of definitions germ line protection is not the same as embryo protection either and alterations to the germ line may be authorised or banned without protecting or harming a concrete embryo. When it comes to protection oriented towards the germ line, Section 5 ESchG is an alien element in the "Act for the Protection of Embryos".

21 More precisely Günther (2014), Section 5 marginal numbers 3 ff.

7. ETHICAL CONTROVERSIES AND PROBLEMS OF EFFECTIVE GERM LINE THERAPY IN HUMANS

For the discussions of genome surgery a number of ethical arguments are of importance. They address, on the one hand, the consequences for the respective individuals and, on the other, the possible repercussions for society as a whole. The most serious ethical problem, which attracts attention because of the highly effective methods of genome surgery, results from alteration to the germ line or the precise targeting of the genome of the germ line cells.²² This is where ethical issues once again appear on the agenda that have already been and are still being discussed in the context of cloning (of humans), research in embryos and embryonic germ cells, preimplantation diagnosis and prenatal diagnosis because of the possible discarding or abortion of embryos and fetuses used in these methods. There is already extensive bioethical and biopolitical literature on these issues. Its relevance for the context of genome surgery must be examined and, if appropriate, specified. From today's perspective it must be borne in mind that our understanding of the function and individual make-up of the human genome has changed *inter alia* because of new findings in genome and epigenome research.

This analysis cannot look at every aspect of these issues but restricts itself to outlining in a list the most important arguments for and against medically or non-medically motivated germ line alteration in humans.

Some arguments in favour of germ line therapy merit consideration. They may be formulated from very different ethical positions.²³ The intended correction of a mutation in order to re-establish a severely disrupted gene function would be a medical motive. Any objection to the "artificiality" of this method doesn't hold up in this variant as otherwise every single therapy involving human intervention would have to be rejected. From the angle of the identical factual situation of natural mutations compared with "artificial" mutations that leave no trace and are possible with the new methods, this distinction may also lose any practical meaning. However, natural mutations can only indirectly introduce the ethical aspect into the debate about the proposed or prohibited actions of a

22 So far very effective interventions in the human germ line have only involved untargeted mutagenesis, e.g. radiation- or chemically induced.

23 Interventions of this kind could be justified by the therapeutic benefits they offer or on the grounds of fairness. For an opinion in favour see, for instance, Miller (2015).

“responsible party” whereas every artificial alteration engendered by humans must face this question from the angle of individual responsibility, too.

One day with genome surgery it may be possible to protect an individual from a severe hereditary disease. If a modification of germ line cells were to be banned definitively, this would raise the question of the moral justification for consciously failing to remove a serious risk of disease for the potential progeny.

All the same, a germ line alteration intervenes in the existence of a “future” human being and all his/her future progeny in a way that differs from any other parental or state order and from the decision about whether he/she should be born at all. The genetic alteration is undertaken without the consent of the individual who does not yet exist, and cannot be reversed by that individual. This raises the question whether this constitutes a violation of the right to physical self-determination and integrity of that individual although he/she does not yet exist as a bearer of fundamental rights. Furthermore, existential decisions of this kind without consent could violate the (future) dignity of the individual concerned. This violation of dignity could constitute inadmissible instrumentalisation involving the technical manipulation of the genetic make-up exercised through the empowerment of other people.

Other ethical arguments refer to the unwanted social consequences of germ line alteration. In this context slippery slope arguments play a major role. Even in the case of justified medical indications, germ line therapy may, under certain circumstances, constitute a step on the slide towards the deliberate design of the germ line justified by the benefit it would bring. Eugenic objectives like “optimisation of the human gene pool” would attract attention in the same way as private action in the context of family planning (“designer” offspring). The goal of alterations of this kind could be to eradicate hereditary traits which are not seen as “normal” but also to deliver desired genetic traits. In this context there is likewise the fear that the germ line therapy and the related possibility of preventing genetic handicaps would impact how society deals with handicapped people. The goal of standardising the genetic make-up of the human population would be highly problematic both on biological grounds and from the ethical angle.

In conjunction with germ line therapy there will also have to be discussion of whether and, if so, how a line can be drawn between medical therapy and mere

enhancement.²⁴ The advancing research on the (not only phenotypically visible) variability of the human genome may lead to further demarcation problems.

Other aspects look beyond the question of human dignity and the fundamental rights status of the embryo. They encompass issues about the identity and dignity of the human race if the human germ line were to become an available technological option. At the same time, consideration would have to be given in this same debate to the extent to which technological self-design is part of man's historical heritage. Against this backdrop there is a need for clarification of why targeted gene alteration in particular, which aims to prevent serious diseases, should be seen as instrumentalisation that violates dignity.

When it comes to germ line alteration it is not possible overall to clearly distinguish between a morally right and a morally wrong alternative. The moral risks are highlighted in the above-mentioned fundamental issues. Technological advance confronts us with ethical dilemmas which have to be weighed up in a social debate and this debate must be conducted in a highly differentiated manner. It is not just the various contexts of germ line therapy that are up for discussion. Another question that is raised is whether this differentiation between somatic and germ line therapy can be upheld and whether germ line effects must also be strictly ruled out in conjunction with somatic gene therapy or could be tolerated as the side-effects of a therapy. One solution that is equally valid for all applications is not to be expected.

Other questions concern unintended genetic alterations to the germ line. The problem is particularly clear in the case of therapies which have to intervene in the early embryo, for instance when the embryo can only survive thanks to the therapeutic intervention (e.g. in the case of a genetic disorder affecting implantation in the uterus). Other examples involve complex malformations which manifest very early in embryonic development and cannot be corrected at a later stage. The earlier the genetic engineering intervention takes place, the more difficult it is to rule out an unintended alteration of the germ line. Hence this raises the question whether a germ line alteration of this kind can be tolerated as a side effect which is admissible, according to the Embryo Protection Act, in the case of the inoculation, chemotherapy and radiation of a born human.

²⁴ See also Lenk (2011).

Given the complex, problematic nature of these issues with their many compounding factors, any action recommendations could indeed contradict each other. Hence, there should be a call for a carefully moderated, responsible and differentiated ethical discussion of germ line alterations in humans prior to any practical application and any preparations for their use.

The aim of this analysis is to call for a debate of these experimental, ethical and legal issues which will lead, in the foreseeable future, to broader social discussion of these methods.

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The current status of the series and individual texts can be accessed *inter alia* on the Internet on www.gentechnologiebericht.de. On the same website there is also information about the current lectures, workshops and meetings of the research group.

ISBN 978-3-939818-58-8