

Human genome editing



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Summary

- › Genome editing, a new set of methods of genetic engineering, enables targeted interventions in somatic as well as in germline cells in humans.
- › Genome editing can help improve somatic gene therapies and expand their scope of application. Initial approaches are currently being tested in clinical trials.
- › Research and innovation policy impulses are needed for the development of gene- and cell-based therapies, particularly for rare diseases. The costs of the procedures likely will remain high. Accordingly, novel reimbursement models are needed.
- › Unresolved health risks and fundamental ethical issues preclude a clinical application of germline interventions.

What is involved

Genome editing refers to the latest variant of genetic engineering. These molecular biological tools can be used to target a specific site in a cell's genome and induce a DNA strand break there. This activates cellular repair mechanisms that can be used to **modify gene sequences**. Newer variants of genome editing allow the targeted conversion of individual or multiple DNA components – the bases – at the respective site.

Compared to previous techniques, genome editing enables more diverse and precise modifications in the genome of a wide variety of cell types, including fertilised eggs. Particularly with methods based on the CRISPR-Cas9 system, interventions in the genome can be made quite easily, quickly and cost-efficiently. With genome editing, targeted and heritable interventions in the human germline, i. e. modifications of germ cells and embryos, are conceivable for the first time. Most importantly, genome editing is capable of and intended for improving and expanding gene- and cell-based therapies in other (somatic) cells of the body.

The discovery of the CRISPR-Cas9 system as a genome editing technique was awarded the Nobel Prize in Chemistry in 2020. For several years already, there has been a veritable boom in

research on genome editing in plant and animal breeding as well as in human medicine. With regard to the potential application of human **germline genome editing**, an intense scientific and, to some extent, broader public controversy has developed – culminating in the reactions to the clinical experiments in China that became public in November 2018. In this context, basic biomedical and moral objections to such transgenerational genome modifications are being discussed. In contrast, the discussion on **somatic gene therapy using genome editing** focuses on the hopes of improving and expanding gene therapy options. For both somatic applications and germline interventions, there is also a need to consider the safety of application, i. e. the precision and the predictability of undesirable side effects.

Genome editing techniques

Since the mid-1990s, **zinc finger nucleases** and **transcription activator-like effector nucleases** (TALENs) have been developed. They combine functions for recognising a specific DNA sequence and cutting the double-stranded DNA molecule at that site. Genome editing tools based on the **CRISPR-Cas9** system have been under development since 2012. Their development is much easier, faster and cost-efficient due to the use of RNA molecules instead of proteins for DNA sequence recognition. Moreover, they allow cutting at multiple sites at the same time.

Despite specific targeting of DNA target sequences, the application of genome editing can result in unintended changes at sites in the genome other than the actual target sequence (off-target effects). This can lead to an inactivation of genes and their function, to changes in the amount of gene products or to rearrangement of different chromosome

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segments (translocations). Even at the targeted sites, there is only limited control over the mechanisms by which the cell repairs the double-strand break. Unplanned insertions or (sometimes very extensive) removals of genetic information might occur, so that – although an inactivation of gene functions can often be achieved – a targeted sequence modification or a targeted insertion or exchange of genes still represent challenges.

Two other tools based on the CRISPR-Cas9 system – **base editing** and **prime editing** – do not cut the entire double-stranded DNA molecule, but use a modified Cas protein that unravels only a single strand. By means of further enzymes inserted into the tools, one base is converted into another at a specific site (base editing) or RNA molecules provided are converted into the desired sequence of DNA molecules and inserted into the strand (prime editing). Both methods promise fewer undesirable side effects (fewer off-target effects) and more control over the modification of genetic information. Prime editing in particular, however, has so far only been used on an experimental basis in the laboratory.

Potential applications in humans

Genome editing tools can be used both in **basic and pre-clinical research** to investigate the role of individual genes in basal cellular and medically relevant processes on a genome-wide scale and to identify new target molecules for drugs. Moreover, models for researching diseases in animals and human cells can be created in a more differentiated way than before (e.g., through research on induced pluripotent stem cells and organoids instead of living organisms). Finally, researchers hope to gain a better understanding of the causes of infertility resulting from early embryonic arrest by performing functional analyses of genes in early human embryos. In Germany, however, research on human embryos is prohibited by the Embryo Protection Act. Particularly parts of the scientific community call for relaxing the prohibition in order to be able to achieve research goals, such as a better understanding of early embryonic development. Corresponding findings from animal experiments can only be transferred to humans to a limited extent.

In the field of **somatic gene therapy**, several therapies for monogenic diseases and cancers have been approved in Europe and the USA in recent years. These are based on the random addition of genes into body cells. Genome editing techniques allow for a more targeted insertion of genes into the genome. They are intended to reduce the risk of insertional mutagenesis, due to which intact genetic structures are unintentionally disrupted in their function (e.g. switched off or unintentionally activated), thus making therapies more efficient and safer. Moreover, for the first time, it is theoretically possible to treat diseases for which existing gene

sequences have to be altered (e.g. Huntington's disease). In principle, thanks to genome editing, even interventions in gene regulation and an inactivation of genes become possible. This potentially enables new gene therapy applications (e.g. in therapies against the blood disease β -thalassemia as well as cancer immunotherapies).

First clinical trials applying genome editing have been started. In Germany, for example, a patient with β -thalassemia is being treated. As with conventional approaches, the comparatively inefficient and only partially tissue-specific gene transfer represents a challenge. Thus, some hereditary diseases currently cannot be treated efficiently or at all with somatic gene therapy approaches. This is particularly the case for diseases that cause damage in several organs, some of which might be difficult to reach with genome editing tools (cystic fibrosis, muscular dystrophies), but also for diseases (e.g. certain metabolic diseases) in which a gene mutation leads to severe or irreversible damage at a very early stage (e.g. already in utero or at the time of birth). **Challenges** also arise for genome editing approaches due to off-target effects, unintended damage at the target site (on target), and immune responses to the editing tools (derived from bacteria).

In Germany, there are established medical laws to ensure safety of application. From an ethical and social perspective, another issue to address is equitable access to gene therapies, which are expected to remain very expensive and pose a challenge to the existing drug reimbursement system.

It is genome editing that made possible **targeted genetic modifications of germline cells** in the first place. With these modifications, all cells of a developing organism can potentially be reached at the earliest possible point in time. This would allow gene therapies to be used even in cases that cannot be treated efficiently or even at all with somatic gene therapies.

Results of corresponding **experiments on human embryos** were first published in 2015. China apparently saw the birth of at least one pair of twins with altered genomes in 2018. So far, there has been no independent confirmation of this experiment, which was conducted in violation of applicable legal regulations and ethical requirements. Due to the low editing efficiency and the risk of off-target mutations, but also due to the insufficient knowledge about the interaction of human genes, **initially only those applications of heritable genome editing appear to be technically feasible that would require the modification or correction of a single gene**. These applications include:

- › preventing the transmission of monogenic diseases in couples for whom pre-implantation genetic diagnosis (PGD) is not promising (because no embryos or too few embryos without a genetic defect would result from which to select);

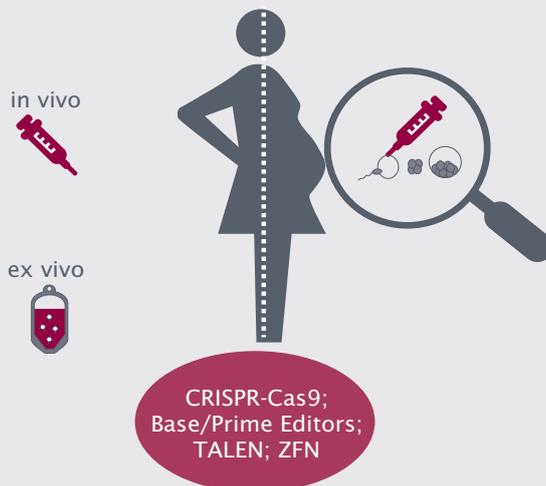
- > the preventive modification of gene variants that are associated with a very high risk of disease (e. g. mutations that can cause breast and ovarian cancer), provided that embryos without such mutations can only be obtained with a low probability or not at all;

unrealistic for the foreseeable future, because too little is known about the effect of gene variants and their interaction, especially with regard to complex traits such as cognitive abilities.

Potential applications of genome editing in humans

somatic gene therapy

germline interventions



Where does the intervention take place?

- > in cells of the body that do not develop/give rise to gametes
- > in cells of the germline (egg/sperm cells, single-cell embryo)

Who is affected?

- > only the treated person
- > also descendants

How is the intervention carried out?

- > in the body (in vivo) or in cells obtained from the body (ex vivo)
- > in single-cell embryos or during fertilisation (in vitro)

What is the purpose of the intervention?

- > improving/enabling the therapy of monogenic diseases
- > enabling intrauterine therapy of inherited diseases that manifest very early or multi-organically
- > enabling the therapy of chronic infections
- > improving/enabling immunotherapies for cancer
- enabling ...
- > therapies for monogenic diseases
- > therapies for inherited diseases that manifest very early or multi-organically
- > corrections of gene variants associated with high disease risks
- > therapies for infertility

- > approaches to eliminate early embryonic arrests (when cells fail to proliferate due to single gene defects after in vitro fertilisation) in egg precursor cells or fertilised eggs, provided the causes can be traced back to single genes.

Corresponding cases in which the less risky PGD cannot be used are still extremely rare. Genetic enhancement – i. e. using germline interventions without medical indication with the intention of improving certain traits – appears

Legal and ethical assessment of germline interventions

Regardless of their intended use, germline interventions are almost unanimously and internationally regarded as ethically unacceptable, because **safe use is not yet guaranteed**. Particularly off-target effects and mosaicism (cells of one organism having different genetic information) represent health risks to potential genome-edited children as well as to subsequent generations. In the case of germline interventions, standards of medical ethics – such as obtaining informed consent from those treated – cannot be complied with in the traditional sense, and health consequences would have to be monitored over several generations.

Health risks are also the central reason for the **ban on germline interventions in Germany**, which is based on the Embryo Protection Act. New medical procedures such as nuclear transfer and the production of germ cells from induced pluripotent stem cells, which also appears possible in humans in the future, might result in regulatory gaps in the Embryo Protection Act. So far, however, these gaps have no discernible practical relevance and could presumably be closed

quickly. At the international level, there are bans on clinical germline interventions in many countries, but these are often not based on laws or not clearly formulated. In 2018, an expert committee was established at the World Health Organization (WHO) to develop global governance mechanisms for genome editing in humans.

Fundamental ethical objections to germline interventions are justified by the interference with the right to self-deter-

mination or the personal rights of still unborn human beings. Some involved in the debate also fear that germline interventions could call into question basic preconditions of sociality, namely the autonomy that humans as social beings reciprocally assume. Moreover, the establishment of certain normative ideas regarding the genetic make-up of humans might encourage discrimination against people who deviate from these ideas. In favour of germline interventions, it is pointed out that these may be a preferable or even the only option for affected people to have genetically related children without hereditary diseases.

Options for action

In the **field of somatic gene- and cell-based therapies**, genome editing techniques have spurred a variety of research and development activities in order to improve existing approaches or to develop new ones. First clinical trials have already begun. In the years to come, there will be tangible opportunities for political action in terms of **public support for research and development**, for example through **tax benefits for R&D investments** and **mega-fund models** for financing high-risk but potentially high-profit projects. Given that costs are likely to remain high in most cases, existing **reimbursement models** could be supplemented with performance-based models and the effect of innovation incentives on drug development for rare diseases could be investigated more closely.

In comparison, the **future way of dealing with possible germline interventions** is much more the subject of political and societal debates. However, **the number of realistic application scenarios is small** and the uncertainty regarding options for their implementation is high. If research were to be initiated in Germany to obtain findings that could point the way to germline interventions, the legal ban on experiments on embryos would have to be amended first. Already for corresponding initiatives – but even more for further steps on this path – a broad societal forming of opinion and debate are likely to be an important prerequisite, the strengthening of which is called for by many stakeholders from science and civil society. However, given the lack of reliable knowledge about success rates and potential side

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effects as well as correspondingly hypothetical application scenarios, the benefits of a debate on enabling germline interventions are likely to remain limited at present. With regard to the international level, agreements could be worked towards **observing research on germline interventions by competent institutions** and to refrain from clinical trials until the requirements regarding medical safety, ethical justifiability and societal acceptance are fulfilled.

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