A molecular scalpel for intervention in the genome: Opportunities and risks associated with genome editing

Abridged version of the study «Genome Editing»

TA-SWISS, Foundation for Technology Assessment and a centre for excellence of the Swiss Academies of Arts and Sciences, deals with the opportunities and risks of new technologies.

Genome Editing – Interdisziplinäre Technikfolgenabschätzung

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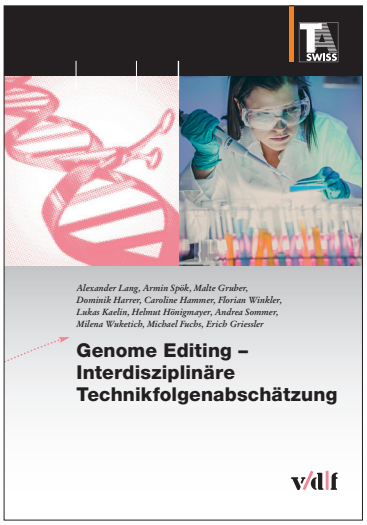
This condensed report is based on a scientific study that was carried out on behalf of TA-SWISS by an interdisciplinary project team under the leadership of Dr Erich Griessler and Alexander Lang from the Institute for Advanced Studies, Vienna. The Graz University of Technology, the Catholic Private University Linz and the University of Lucerne also participated in the study. This version of the report is addressed to a broad public and presents the main findings and conclusions in condensed form. It also reflects the outcome of the intensive debate on the study by the TA-SWISS Steering Committee. Based on this debate, the Steering Committee formulated its own recommendations concerning genome editing, which are presented in this condensed version.



Genome editing in a nutshell

Genome editing (sometimes also referred to as «genome surgery») uses the cell's own repair mechanisms in order to modify the genome. In this way it enables more precise intervention in the genetic material than conventional genetic engineering. With genome editing, applications in the fields of medicine, animal and crop breeding that were once scarcely thought possible may be rendered feasible in the near future, and it may even be possible to genetically modify entire populations of insects or rodents.

Opportunities …

In the field of medicine, genome editing could facilitate therapies for severe hereditary diseases for which there is currently no prospect of a cure. Through genome editing, other ailments that until now have only been held in check through the lifelong ingestion of medicaments may be permanently cured.

Furthermore, genome editing has the potential to alleviate the shortage of donor organs. It can be used to align the genetic make-up of pigs and human beings and eliminate viruses that are embedded in the genetic material of these biungulates and are regarded as a potential threat for human recipients of transplanted organs.

In the field of agriculture, genome editing could significantly accelerate the development of new crop varieties with beneficial properties. In the field of animal breeding, the use of genome editing for producing livestock immune to certain animal diseases would be beneficial.

Finally, genome editing could be used to provide certain species with «turbo genes», which are passed on rapidly in the wild. Through the use of these «gene drives», the species concerned could be given the desired traits so that, depending on the objective, they could be decimated or their level of resistance to diseases enhanced.

Risks …

In the same way as conventional genetic engineering, the still young technique of genome editing harbours risks that in some cases remain difficult to assess. In view of the high expectations that are being placed on genome editing both in the economy and in the field of medicine, there is a risk that uncertainties and lack of knowledge could be ignored.

Gene therapies are expensive and strengthen the trend towards massive increases in the costs of the healthcare system. If new gene therapies were to be

widely applied, this could not only exert additional pressure on the shared financing of Switzerland's healthcare system, but could also foster two-tier healthcare if the new therapies should only be available to the wealthy.

It is often not possible to distinguish plants and animals produced with the aid of genome editing from those produced using conventional breeding methods. This makes both regulation and labelling more difficult, and thus could reduce transparency and freedom of choice for consumers.

Gene drives give rise to potentially irreversible interventions in nature. Once organisms that have been equipped with «turbo genes» have been released into the environment, it is no longer possible to control them. Gene drive constructs could cross over to other species that were not the intended target. The ecological consequences are therefore very difficult to assess.

… plus a few recommendations

Given the broad variety of potential uses of genome editing, the associated risks and opportunities cannot be assessed globally, and thus have to be determined for each specific application.

A public debate on this new and controversial science is therefore imperative. For a constructive social debate it is essential that the information available is as unbiased as possible. The exchange should be open and permit a variety of perspectives, and does not necessarily have to culminate in consensus.

Switzerland should also actively voice its negative stance towards germ line interventions in human beings at the international level.

> The recommendations of the TA-SWISS Steering Committee, which are based on its discussion of the findings of the study, are presented in full in the final chapter of this report.

Genome editing: revising the composition of life

The diversity of life forms is attributable to genetic mutability: modifications in the genome give rise to changes in external appearance and ultimately to new species of flora and fauna. Scientists use their knowledge about the processes that result in the repair, activation and immobilisation of genes in order to bring about targeted mutations in the genetic material.

At first glance, brewer's yeast and the South African clawed frog *(Xenopus laevis)* have little in common, but both these organisms serve as models in the field of biological research aimed at discovering the complex processes that take place in the interior of cells.

At the end of the 1980s, a research group at the Louis Pasteur Institute in Paris discovered that there are certain genes in brewer's yeast that have no other function than to disseminate themselves in the genetic material. They do this by providing the assembly instructions for a protein (called «homing endonuclease») that cuts the spiral-shaped intertwined DNA double strand. The resulting damage triggers a repair mechanism that reassembles the DNA and uses the «self-serving» gene as a template for the repair. This then integrates itself at other loci in the genome. Later on, researchers discovered how the recognition sequence of the protein can be modified so that it cuts the DNA at other selected loci.

Laboratories getting ready for action

At around the same time, in the course of a study of the South African clawed frog, a group of scientists at Cambridge University discovered finger-shaped, folded proteins held together by zinc ions. These attach themselves to specific loci in the genetic material and switch the gene in question on or off. These structures, which are referred to as zinc fingers, are equipped with a kind of read head that shows them the DNA segment to which they should attach themselves. Zinc fingers occur in most life forms. Around

one percent of human DNA contains rules for their formation. Later research set out to determine how to equip zinc finger proteins with customised read heads in order to activate or deactivate selected gene segments. However, the production of designed zinc fingers proved to be complex and expensive.

Once researchers had identified many of the mechanisms that activate or deactivate genes, scientists began to anticipate the possibility of intervening in the genome in a targeted manner. The prerequisite for this was genome sequencing, which had been widely practised since the 1990s. In order to carry out therapeutic interventions in the DNA, it is necessary to know which gene segments are responsible for which biological processes.

Bacterial immune system as a tool

The breakthrough for precise modification of the genome occurred in 2012. Here, researchers Emmanuelle Charpentier and Jennifer Doudna made use of the bacterial immune system memory: if a bacterium survives an attack by a virus, it integrates short pieces of the viral DNA into its genome so that it can use this «molecular memory» in order to defend itself more quickly against a renewed attack. To do this the bacterium inserts the viral DNA snippets into short, repeating gene sequences called CRISPRs (Clustered Regularly Interspaced Short Palindromic Repeats).

A protein called Cas9 plays a significant role in the bacterial immune system. Following initial infection it is responsible for cutting the viral DNA so that the snippets can be inserted into the CRISPR segments of the bacterium. In the event of a renewed virus attack, the CRISPR sequences are converted into ribonucleic acid (RNA). These RNA molecules attach themselves to Cas9, for which they act as a «probe» for identifying the invading virus sequences. Cas9 then cuts up the virus sequence and renders it harmless. In scientific circles, the term «gene scissors» is now also widely used when referring to Cas9. The term «genome surgery», a common way of referring to «genome editing», is deliberately not used in this publication, because it is too directly associated with the field of medicine.

Just one year later (in 2013), scientists discovered that CRISPR/Cas9 can be applied not only to bacteria, but also to significantly more complex plant and animal cells. It also turned out that gene scissors can be carried out at practically any desired locus of the genetic material with the aid of specifically produced guide RNA. Cas9 cuts the DNA double strand at the desired locus and different objectives – ranging from deactivation of the involved gene through to the exchange of individual DNA building blocks or the insertion of additional gene sequences – can be attained depending on how the subsequent repair takes place.

Microscopic means of transport

A CRISPR/Cas9 construct can only be effective in immediate contact with the DNA. In both plant and animals, this is located in the cell nucleus, which means the gene scissors has to be inserted there. To accomplish this, fat droplets, small protein molecules or nanomaterials can be used which penetrate the cell wall by means of various mechanisms. In this way they function as a transport medium for the attached or enclosed CRISPR/Cas9 gene scissors.

Agrobacterium tumefaciens, which is widely found in nature, is now used in particular for the genome editing of plants. This bacterium can infect numerous plants and as a rule causes tumorous growths. To ensure that it can act as a transport medium for the CRISPR/Cas9 construct without undesirable side effects, the genes that cause the tumorous growth are removed from it.

Transport with the aid of viruses, which essentially infect the cell with the CRISPR/Cas9 structure, is regarded as a particularly efficient solution. Although their disease-causing properties are eliminated in advance, viral carriers are nonetheless potentially risky.

The CRISPR gene scissors can also be injected with a microscopic glass pipette, or «shot» into the cell by means of gold particles. Another method involves rendering the cell walls temporarily permeable by means of electrical impulses so that the CRISPR/Cas9 structure can penetrate them.

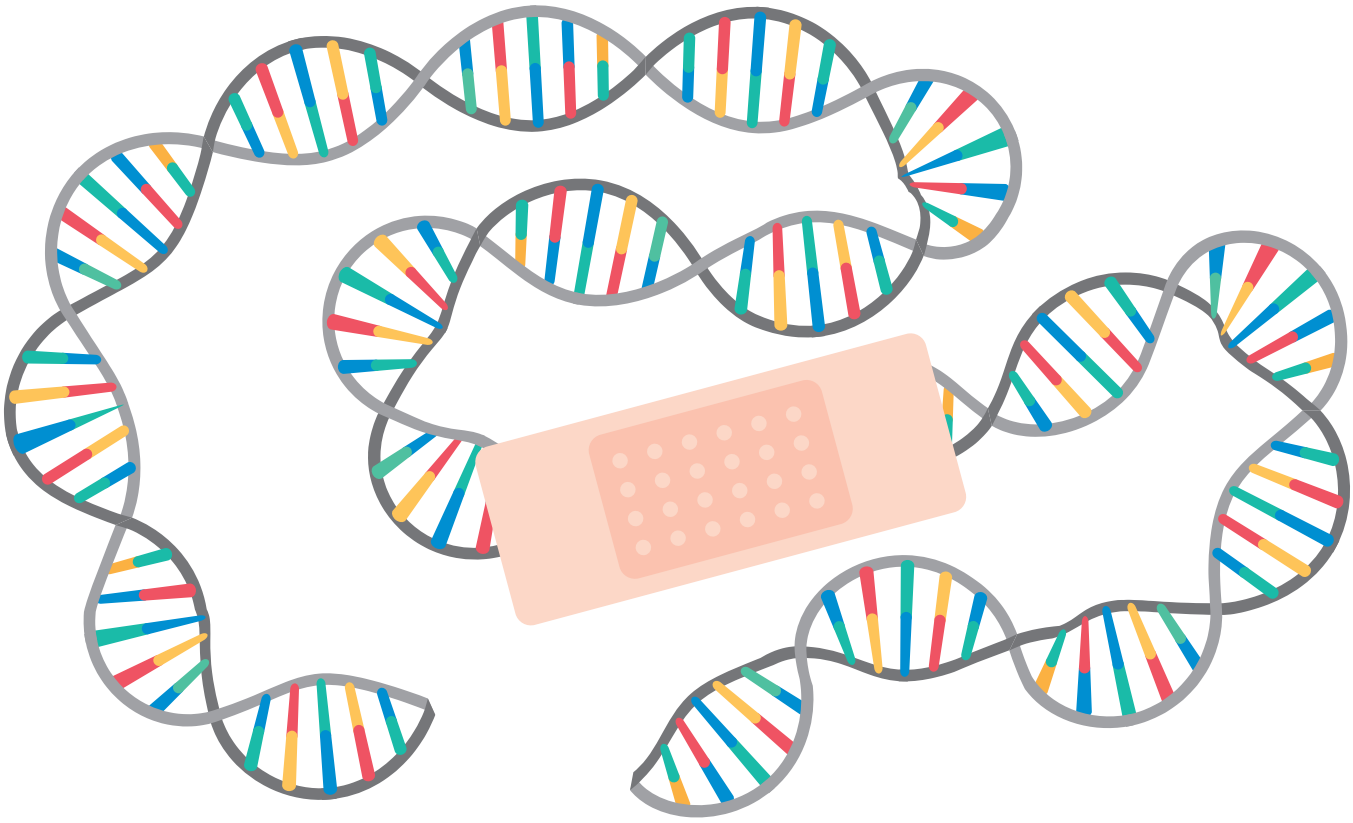
Mistakes can never be entirely ruled out

Although genome editing with CRISPR/Cas9 is considered to be relatively precise, malfunctions can nonetheless occur. For example, it has to only cut the DNA at the desired locus, but since certain gene sequences with minor variations occur repeatedly in the DNA and the CRISPR/Cas9 structure overlooks minor deviations, the risk exists that gene segments could be modified that were not targeted. Here we speak of «off-target» effects, which under certain circumstances can have grave consequences.

Even if the double-strand break occurs at the correct locus, it is by no means certain that the intervention will be successful. If, for example, a disease-causing gene variant is to be corrected, the repair of the DNA break has to be made in accordance with a precise model. However, the cell's own repair mechanism does not always function as planned, and the deviations prevent the attainment of the targeted outcome. In the worst case, the effects can be harmful («on-target» effects).

Ultimately, the genetic modification has to take place in the same way in all treated cells. If it only takes effect in a certain segment of the targeted cells or treated organism, this results in what is referred to as a mosaic. The DNA and, consequently, the metabolism of various cells then deviates so greatly from one location to the next that the desired effect is only achieved in a reduced form or unfavourable reactions even occur.

Off- and on-target effects and mosaicism are the focus of numerous research projects, not least because they represent risks that have to be ruled out so that the CRISPR/Cas9 method will be able to meet the high expectations that have been placed on it.



Somatic gene therapy: Correcting genetic dysfunctions

Changes in the genome can result in serious disorders. Genome editing opens up possibilities for new therapies for these disorders, especially those attributable to mutations on a single gene.

Chronic coughing, shortness of breath and frequent infections of the airways, risk of malnutrition due to a malfunctioning pancreas, a tendency to suffer from cirrhosis of the liver, gall stones and osteoporosis – these are some of the symptoms that people who are afflicted by a serious form of cystic fibrosis have to battle with. Cystic fibrosis is caused by mutations on one particular gene. Monogenic diseases like this, where only a single gene is involved, are the best candidates for successful treatment through gene therapy. The chances of finding a cure are now even better thanks to CRISPR/Cas9.

Not a resounding success at first

Interest in somatic gene therapy began growing in the 1970s. Somatic gene therapy was first used in 1990 in the USA on a young girl born with a serious congenital immune deficiency syndrome. Genetically modified white blood cells (T cells), which are responsible for fighting off pathogens in the body, were introduced into the child by means of a viral vector. However, the modified T cells only had a limited life span in the body. Thus, the treatment did not result in a definitive cure but had to be repeated periodically.

Another application of gene therapy carried out in 2001 in France on children suffering from an immunodeficiency disorder similar to that of the American

girl who had undergone gene therapy ten years earlier initially seemed to be more successful. Nine of the ten patients developed functioning immune systems. In the following year, however, four of them developed leukaemia that was brought about by a malignant change in their blood stem cells caused by the therapy itself.

A series of failures quashed the hopes that had initially been placed in somatic gene therapy. The method came to be largely regarded as risky and disproportionately complex and costly given the limited prospects of success. Since CRISPR/Cas9 has become available, however, significant interest in this treatment approach has been rekindled.

Two approaches tested in numerous clinical studies

By the end of 2018, around 3,000 clinical studies on somatic gene therapy had been approved worldwide, focusing on treatments for a variety of problems, from monogenic disorders to infectious diseases, cardiovascular diseases and a range of different types of cancer. These studies generally rely on two fundamentally different approaches.

In the one case, the gene scissors construct is introduced into the organ or organism being treated (*in vivo* approach). Whether viruses deliver the molecular scalpel into the body or other kinds of vectors are used (see p. 6), transporting the genome editing system into the cells in question is difficult. Not all approaches are equally suited for all diseases. With some viruses the effects of the gene therapy dissipate over time, making them only suitable for short-term treatment goals, such as immunotherapy of cancer. Other viruses build the modified genetic information into the genome, making the effect of the treatment permanent. The use of vectors is tricky, and the side-effects may be formidable – excessive immune reactions, cancers and even poisoning due to toxicity of non-viral vectors.

In contrast, the *ex vivo* approach takes cells from the patient's own body, multiplies them in the laboratory, modifies them by genome editing and subsequently places the genetically modified cells back into the patient's body. The *ex vivo* approach has the advantage that it allows the success of the genetic modification in the cells to be verified in the laboratory. Also, because with this approach cells can be introduced into the body that have already been genetically modified, there is no need to expose patients to the vectors otherwise required for the gene transfer.

Treatments for various conditions now in sight

In recent years, somatic gene therapy has begun showing treatment success for a range of different diseases. Medications have already been approved for some monogenic disorders, including several serious immunodeficiency disorders. Effective treatments are on the horizon for congenital retinal diseases, various forms of muscular weakness, serious motor disorders and cystic fibrosis.

Promising advances in the treatment of conditions caused by multiple genes – such as rheumatoid arthritis, which affects the skeleton, and certain forms of cardiac insufficiency – are also being facilitated by somatic gene therapy. Major research efforts are directed at finding treatments for cancer; two thirds of the gene therapy trials on humans approved in 2017 targeted tumours. Several gene therapy drugs for treating different kinds of cancer have already been launched on the market.

The European Union has approved nine different drugs for somatic gene therapy since 2015.

How much is the cure allowed to cost?

Gene therapy has garnered a lot of attention and strong criticism because of its high cost. One drug, Glybera, which was approved in 2012, was withdrawn from the market after being used to treat only one patient – at a cost of nearly one million euros.

The general public is shocked by the excessive cost of the new therapies, which comes on top of the already alarmingly high expense of the healthcare system. The suppliers of these new drug treatments attribute the high price to their expenditure for research and development – and they point out that an expensive therapy that may only have to be used a single time may still be cheaper than the life-long treatment and care the patient would otherwise require.

Several pharmaceutical companies are working together with health insurers to come up with payment models so that patients who require expen-

sive gene therapies can afford them. One idea on the table is to create social funds supported by private companies and insurances that would serve to relieve the burden on social health insurance schemes. Under another payment model being considered, the costs of the treatment would only become payable if the treatment was actually successful.

Risks comparable with established treatment regimes

Preventing diseases and the associated suffering is a paramount ethical standard. In Switzerland, gene therapy for the treatment and prevention of disease is fundamentally permitted, although subject to official approval.

Politically the key questions surrounding gene therapy concern how to finance the costly treatments. Broad access to these therapies could make the entire healthcare system massively more expensive and undermine the principle of solidarity as the basis of the health insurance system under law. On the other hand, the notion that certain drugs can only be afforded by the wealthy contravenes equal opportunity and the sense of justice of many people who are against a «two-tier» healthcare system.

The medical risks associated with somatic gene therapy are comparable to those of a bone marrow or organ transplant. In deciding for or against an intervention, the pros and cons of continuing to live with a serious health impairment or accepting the uncertainties associated with a new form of treatment have to be weighed up for each individual patient in their own particular circumstances. For diseases for which conventional therapies already exist, the question arises of whether the benefits of somatic gene therapy outweigh the possibly still unknown, negative, long-term consequences.

Interventions in the germ line: Inherited consequences of therapies

If diseases that have already developed are treated with a somatic gene therapy, the consequences of the therapy and any possible side effects remain limited to the patient. This is not the case with germ line therapy: here, modifications of the genome carried out on the embryo or germ cells are passed on to offspring.

Diseases attributable to mutations of one or a number of genes can be inherited by offspring. The likelihood that a child will suffer from the same disease as its progenitors depends on the nature of the genetic modification and the means of inheritance. For example, haemophilia – which was responsible for eliminating several dynasties in the European aristocracy – is a sex-linked hereditary disease. In the vast majority of cases it is only males who develop the symptoms, but the disease is passed on by the mother because it is associated with an X chromosome defect. Whereas in the past, haemophiliacs tended to die at a young age, thanks to modern treatments and medicaments they can now expect to live as long as anyone else.

There are also dreaded diseases such as Huntington's chorea, which only manifest themselves during adulthood and result in severe movement impairments and premature death, and for which no therapy is available. It would be possible, at least in theory, to prevent a disease of this type by «repairing» the faulty gene at the prenatal stage, i.e. in the germ line of the embryo. If it involves a mutation that is passed on by the mother, it is also conceivable that the therapy could be carried out in the ovum, thus avoiding the need for a genetic intervention in the embryo.

In any case, even if germ line therapy were to be authorised, it would require state-of-the-art reproduction methods. The treatment of ovules and in some cases sperm cells, as well as of the embryo, would be carried out in a laboratory, i.e. outside the

future mother's body. It is highly likely that preimplantation diagnosis would also be carried out in order to ensure that an embryo that does not bear the faulty gene is planted in the woman's body. This justifiably raises the question as to why preimplantation diagnosis is not used in the first place.

Experiments in the USA and China

Interventions in the germ line are prohibited in the EU as well as in Switzerland. The few such interventions that have been scientifically addressed to date were carried out in China and the USA. With one exception, these interventions took the form of experiments in which the embryos were only allowed to develop for a maximum of 14 days and were not used for inducing a pregnancy.

One experiment focused on options for treating sickle cell anaemia – a hereditary disease that primarily occurs in the Mediterranean region, Africa and India. The success rate was only moderate: CRISPR/Cas9 only had an effect at all on around one-third of the 86 embryos that were used, and the proportion of the targeted modifications was very low. Unintended and undesirable transformations probably ultimately outweighed the targeted corrections.

Another experiment that involved an inherited cardiac insufficiency showed that the effectiveness of genome editing varies according to the developmental status of the embryo. Other experiments have indicated that better results can be achieved if, instead of setting out to repair a double strand break, certain base pairs are exchanged. The findings point to the fundamental feasibility of germ line therapies, but they also reveal that the approach is still a long way away from a reliable application – not to mention the issues relating to ethical desirability.

Breach of research guidelines in the Far East

At the end of November 2018, it was reported to widespread astonishment that twin girls had been born in China whose germ line had been altered by a researcher in order to render the babies immune to AIDS by modifying their CCR5 gene. This gene produces a protein that is used by the HI virus for penetrating human cells. In one of the twins the gene was successfully knocked out, while in the other baby the correction did not take place in all cells, as a result of which mosaicism will have occurred.

This experiment was sharply criticised throughout the world, including in China itself, where the scientist in question was suspended. Apart from the fundamental criticism of the performance of a germ line intervention on human beings, critics also pointed out that it is not necessary to resort to risky interventions in the germ line of healthy human beings in order to induce resistance to a disease when various preventive measures and effective therapies already exist. Furthermore, it could not be ruled out that the deactivation of CCR5 could have a negative effect on other cells. In any case, a new study has found that knocking out this gene shortens the life of the person concerned.

Trailblazer for «perfecting» human beings?

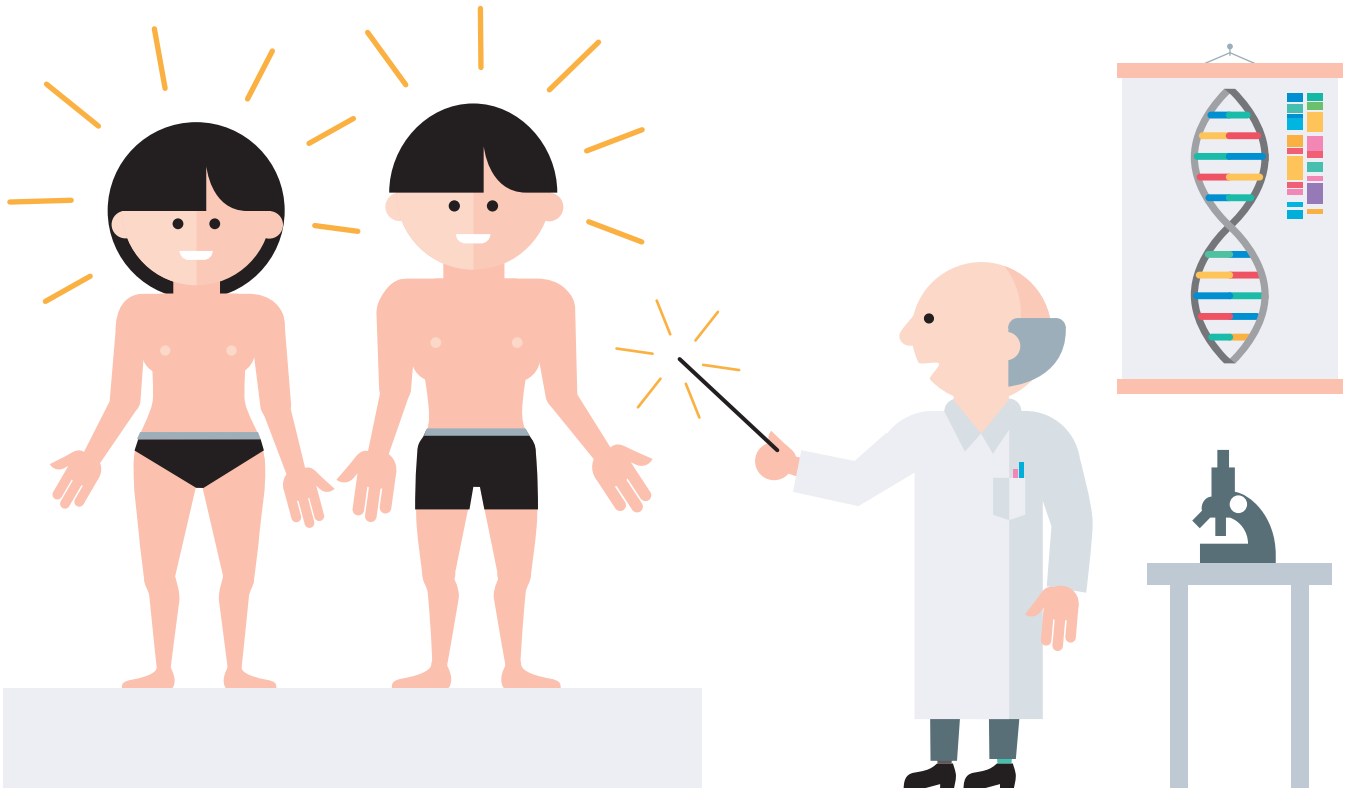
While the consequences of somatic gene therapy are limited to the treated individual, modifications of the germ line are transferred to the next generation. Also, germ line therapy is carried out even before the symptoms appear. Consequently, citing the prevention of suffering as an argument in favour of performing such interventions is not valid, especially in view of the fact that there are now other methods for detecting embryos with pathological genetic mutations at an early stage and thus not allowing them to grow to maturity.

In the scientific community there is broad agreement that currently too little is known about the interactions between the various genes and the long-term consequences of germ line modifications to permit such interventions on human beings for therapeutic purposes. Furthermore, the procedures involved are not yet sufficiently developed.

Some voices also express concern that interventions in the germ line will ultimately exacerbate social imbalances and could lead to the stigmatisation of individuals with certain genetic features. Others also warn of a reduction of diversity in humans if certain genetic expressions were to be systematically eliminated – here, Down syndrome is frequently cited as an example.

From discussions concerning modifications of the germ line through genome editing it is clear that the boundaries between sickness and health or between normality and deviation are often difficult to define, as are the boundaries between prevention, therapy and optimisation.

While any social consequences arising from germ line interventions will only become apparent over the longer term, it is important to already pay attention today to the protection of embryos. In the view of many experts, the instrumentalisation of the embryo conflicts with respect for human dignity and it is necessary to carefully weigh up the risks of using human germ cells against freedom of research. In addition, some scientists have pointed out that trade with embryos for research purposes could result in the exploitation of women in distress. In Switzerland, stem cells may be derived from surplus embryos for research purposes, but research on embryos may only be carried out if the results of the scientific work could directly benefit the embryos.



Xenotransplantation: Transplantation of organs from pigs

Genome editing could be used in order to genetically align certain domestic animals, in particular pigs, to human beings. These animals would then no longer solely provide us with meat, but would also produce organs suitable for transplantation.

In 2018, the waiting list of Swisstransplant, the national foundation for organ donation and transplantation, included 148 patients hoping to receive a new heart. Twelve of them did not survive the waiting time, while fifty received a heart from an organ donor. Livers and kidneys are scarce too. If domestic animals whose meat we consume could also supply us with new organs, this would reduce the bottleneck in the field of transplantation medicine.

The pig is the domestic animal closest to human beings, at least in terms of the size and structure of organs. However, in xenotransplantation (i.e. the transfer of an animal organ to a human body) the risk of rejection, which is already a problem in human-to-human transplantation, is even higher.

In the mid-1990s it was discovered which pig gene needs to be knocked out so that the antibodies that induce a particularly strong immune reaction in human beings are no longer produced. CRISPR/Cas9 has made it possible for genetically modified pigs to be more closely aligned with the human immune system in that up to seven genetic modifications can be carried out simultaneously. One of these is designed to shut out pathogens that in the course of evolution have become established in the genetic material of pigs. While pigs pass on the viruses to their offspring, they remain free of the disease themselves. But when an organ from a pig is transplanted to a human being, these pathogens can be passed on and harm the organ recipient's health.

Animal donor organs: faster production, lengthier functionality

With the CRISPR/Cas9 method it is possible to genetically modify pigs so that when their organs are transplanted into human beings they induce weaker levels of rejection and offer various other advantages such as better blood circulation properties. The new CRISPR/Cas9 method speeds up the production of animals with multiple genetic modifications.

Of all transplanted animal organs, the hearts of pigs with multiple genetic modifications have attained the longest survival times. In some cases, pigs' hearts that were introduced into the abdomen of baboons for test purposes kept functioning for around two and a half years. The average survival time was approximately one year. The purpose of these experiments was solely to test the survival of the heart in the body of another species without it having to perform as a pump. For this purpose the immune system of the baboons had to be weakened with the aid of medicaments, and the use of inflammation inhibitors, coagulants and antibiotics was also required. In more recent experiments in which the purpose was to provide a replacement organ, the pigs' hearts transplanted in baboons continued to function for up to 195 days.

Experiments with transplanted kidneys also proved to be successful. Kidneys of genetically modified pigs that were transplanted to baboons functioned for up to 300 days. Liver transplantation is more problematic than the transplantation of hearts and kidneys: baboons with a transplanted pig's liver only survived for a maximum of 29 days. And the transplantation of lungs is even more problematic: here, the maximum survival time was just ten days.

Islet cells, i.e. certain portions of the pancreas that are required for sugar metabolism, appear to be the most suitable for xenotransplantation. These cells can be transferred in encapsulated form and are therefore insulated from the recipient organism, which diminishes the rejection mechanism. Diabetic primates have already been successfully treated by

transplanting islet cells from pigs that had not been genetically modified. CRISPR/Cas9 could be used to more closely align the production of insulin in pigs' islet cells to the production of insulin in humans.

Animal organs in humans

We have always consumed animal products as part of our diet, but with xenotransplantation the boundaries between humans and animals will be more radically crossed, as cells, tissues or entire organs of animals are incorporated into our own bodies. Revulsion and social and cultural rejection could thus be consequences of xenotransplantation. In addition, changes in self-perception and perception by others could also have negative impacts.

If animal transplants were to be used as an interim solution until a human organ were to become available, or if an animal organ were to remain functional for a shorter time than that of a human being, xenotransplantation could even intensify the shortage of human donor organs. It is also important to clarify at an early stage the economic issues that would arise if major for-profit businesses were to gain a monopoly on the production of animal transplants.

Consideration of alternatives

Research on transplanting animal organs into human beings is being carried out above all because there is a shortage of human organ donors. Thus, for an assessment of xenotransplantation it is important to examine alternatives that could help solve this fundamental problem.

Preventing organ-damaging diseases – for example by encouraging changes in lifestyle or through early detection of the diseases – could help reduce the number of transplants that would be required. Furthermore, in the future it will likely be possible to cultivate tissue or even entire organs from cells, thus reducing the need for donor organs.

Crop and animal breeding: On the threshold of a new agricultural revolution?

In the 1960s, new and very high-yield plant species gave rise to a green revolution in agriculture. Today, in the view of many experts genome editing could give rise to a similar surge in development in the direction of more resistant and even higher-yield cultures, as well as more profitable and lower-maintenance livestock.

The red-fleshed ruby star grapefruit is available from various major Swiss retailers today and is described as «mildly sweet and aromatic». It was first brought onto the market in the 1970s when it was developed in the USA by radioactive irradiation of the original Hudson variety, which was unpopular because of its large number of seeds.

In the 1950s, mutation breeding underwent a veritable boom: researchers exposed numerous crop plants to radiation in so-called atomic gardens. The International Atomic Energy Agency (IEA) was founded in Vienna in 1957, and since that time all irradiated plants have had to be registered with this body. Today, the database contains around 3,300 plants that have been produced through radiation-induced mutagenesis.

While thousands of plants die from nuclear exposure, those that survive possess properties that are beneficial in the fields of agriculture and horticulture. In most cases, genes that should have remained unchanged also mutate during exposure to radiation, and this means that backcrossing is necessary in order to obtain a utilisable product.

Targeted instead of randomised

Mutation breeding is still used today. It is regarded as a classical breeding method and a special permit is not required for cultivating the resulting products.

But the same objective, i.e. faster mutation, can be achieved more precisely today with the aid of genome editing.

In the field of crop breeding, genome editing permits various levels of intervention. For example, it is possible to apply the gene scissors construct in order to produce relatively targeted double-strand breaks without the need for a repair template. The repair mechanism itself then gives rise to the mutation. However, it is also possible to use the CRISPR/Cas9 method to deactivate (knock out) the function of a given gene.

Furthermore, the cell's internal repair mechanism can also be used to insert gene segments of the same species into the plant on the basis of a template. This results in the production of what are referred to as cisgenic plants. Such plants can also be produced with the aid of traditional cross-breeding methods, though these require much more time than genome editing. Finally, gene segments from an foreign species can be introduced into a plant with the aid of genome editing to produce a transgenic plant.

Predominant in the field of crop cultivation

Genome editing has become firmly established within a very short time in the field of plant research and development. Since 2014, CRISPR has been the most frequently applied method. Here, the most common experiments are those in which no repair template is used and thus no external genes – of either the same or a foreign species – are introduced into the plant.

In terms of the number of published studies, China and the USA lead the field by a considerable margin. Rice is the focus of particularly intensive research, followed by maize, soya and tomatoes.

Genome-edited crops are not only grown in laboratories, but are also tested in the field. In the USA, genome-edited crops are not subject to the regulations governing genetic engineering, and this means it is difficult to find out how many field trials are being carried out throughout the world. In the European Union, several field trials have already been carried out, mainly involving potatoes, rapeseed and barley. In Switzerland, field trials with cisgenic apples attracted a great deal of attention among scientific circles.

Hopes of higher yields with less use of pesticides

While the main objective associated with previous generations of genetically engineered plants was to render them resistant to herbicides and diseases, the focus of genome-edited plants is on improving their quality in terms of provision of foodstuffs and animal feeds and bringing about modified agronomic traits such as earlier flowering or larger grain size.

In Switzerland, activities that could lead to the reduced use of pesticides are also of particular interest. Here, for example, research is being carried out on wheat that is resistant to mildew. In heavily infected fields, mildew can destroy up to a third of the harvest and is combated with antifungal agents, while sulphur-based preparations are used in organic farming. Whereas in Switzerland, laboratory experiments are based on traditional genetic engineering methods, the USA and China are also experimenting with the CRISPR/Cas9 method. One American company is currently conducting field trials with genome-edited mildew-resistant wheat types.

Genome editing significantly accelerates the development of new species. It can be used simultaneously for carrying out both targeted interventions and various modifications. The rapid development of new crops is likely to have consequences for agricultural practice; for example, if the harvest time has to be changed because the crop ripens sooner. Foodstuff producers would also have to adapt their processes if, for example, potatoes with changed processing characteristics or wheat with a higher nutritional value should be brought onto the market.

Complex regulation

In July 2018, the European Court of Justice handed down a ruling according to which genome-edited plants are to be made subject to the same regulations that apply to plants modified through genetic engineering. This ruling was made regardless of the fact that the plants created through the use of genome editing could in many cases also have been produced using traditional breeding methods. Norway then put forward the proposal to exempt genetic modifications that can be achieved using conventional breeding methods from an approval requirement.

The question remains open as to how genome-edited plants are to be controlled if they cannot be distinguished from conventionally bred types. This question needs to be dealt with urgently, especially because, like the USA, other countries do not plan to introduce a special approval requirement for genome-edited plants, and seeds and other products from such cultures could also find their way into Europe, including Switzerland, via global goods trade.

As a non-member of the European Union, Switzerland would have the option of choosing a different regulation. In view of this, the Federal Council intends to clarify whether and how the existing legislation could be adapted so that it incorporates the risks associated with the new developments. The relevant authorities are currently examining how genome editing and its products can be categorised on the basis of the associated risks.

The focus of the risk assessment is on genetic modifications that do not occur at the target location. The likelihood that imprecise and unintended genetic modifications could occur depends on the level of the intervention: for example, with mutation through radioactive irradiation, 500 times as many erroneous modifications occur as the number that occur spontaneously in nature. With modifications induced by CRISPR/Cas9, the probability of errors is significantly lower than it is with mutagenesis induced by radiation or chemicals. The intensity of a molecular intervention could therefore serve as an indicator in risk assessment. There is broad support within the scientific community for the proposal to define the maximum number of nucleotides that may be modified while still allowing a plant to be classified as genetically unmodified.

Fertile pigs, hornless cattle and muscular carp

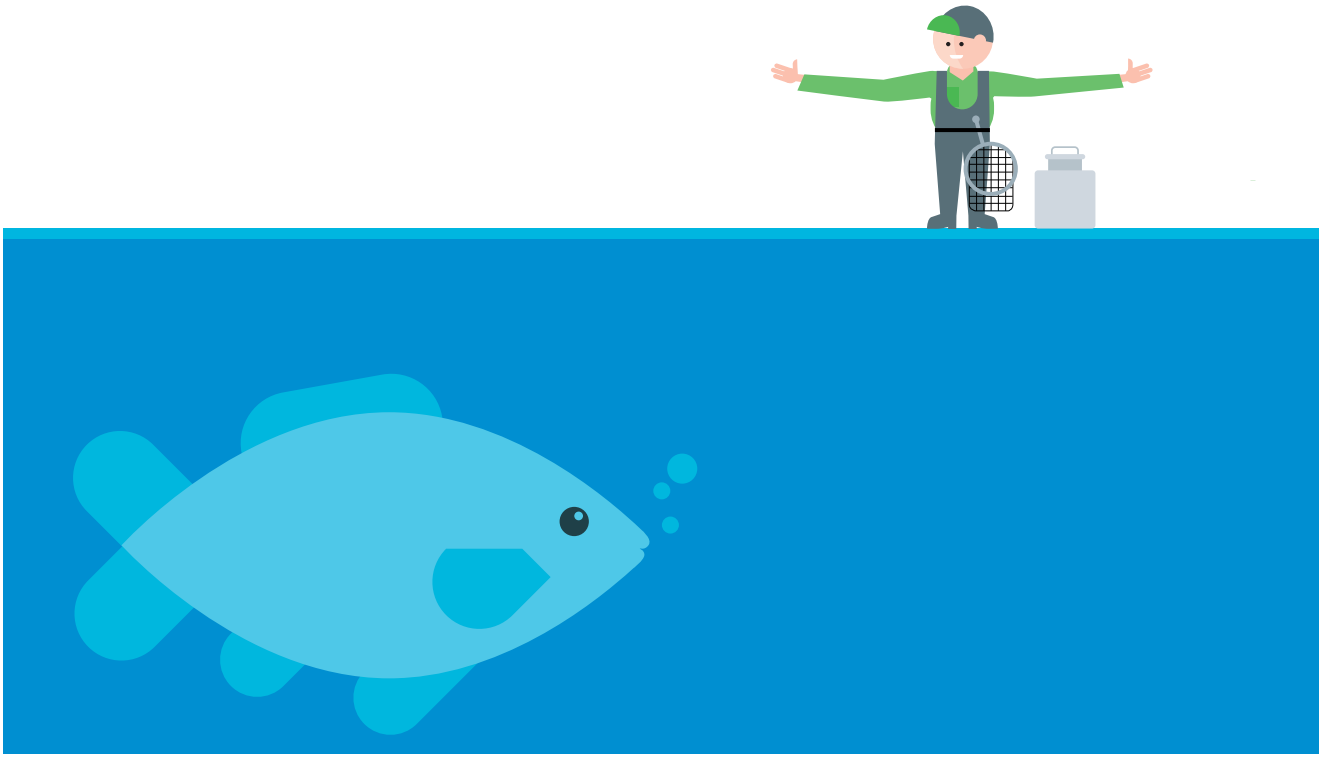
If chickens, cattle or pigs are kept in large numbers and in a confined space, there is a high risk that diseases will spread. In view of this, in the fields of animal breeding and agriculture there is a great deal of interest in the potential of genome editing to render animals more resistant to certain pathogens.

In pig sties, PRRS (porcine reproductive and respiratory syndrome) is a particularly feared viral disease that is harmless to humans but reduces the fertility of mature pigs and causes fever, coughing and sneezing among piglets. Switzerland has been declared free of PRRS. In 2016, with the aid of CRISPR/Cas9, a gene was deactivated that plays a major role in the onset of a PRRS infection. Infected pigs in which the gene concerned had been deactivated did not subsequently develop any symptoms.

In the interests of animal welfare, an increasing number of farmers are distancing themselves from the practice of tethering their cattle. In order to reduce the risk of injuries, they tend to prefer keeping only dehorned cattle in enclosures. For this purpose, they burn out or cauterise the horn buds of calves. Swiss animal protection legislation stipulates that dehorning may only be performed under anaesthetic. Although genetically hornless cattle exist (for example, Angus cows), their milk yield is low. In 2016, the gene in Angus cattle that determines hornlessness was identified and was successfully introduced into Holstein cattle with the aid of genome editing. With this method it would be possible to breed hornless dairy cows within a single generation.

An American company has developed genetically modified salmon that grow twice as quickly as salmon living in the wild. Two genes from other fish that promote growth and strengthen resistance to cold temperatures were introduced into these fast-growing salmon. The transgenic salmon that are kept in extensive fish basins were approved as a foodstuff for the Canadian market in 2017. CRISPR/Cas9 is to be used to enlarge the muscle tissue (and thus the yield) of carp and in an effort to increase the resistance of the brown bullhead (a North American fish) to intestinal infections.

Furthermore, various research projects are looking for ways to genetically modify livestock so that the animals produce active medical substances for human beings. Research is being carried out on genome-edited pigs that produce human insulin and on cattle that form human serum albumin – an important blood plasma component. Genome editing is also useful in the production of model animals that are used in the field of medical science for researching human diseases.



Consideration of the dignity of living beings

With crops that are planted in open fields there is a risk of outcrossing with relatives in the wild, whereas livestock are normally easier to control because they are kept in stalls or monitored enclosures. At fish farms, flooding or damage to the facility may enable genetically modified fish to enter open bodies of water where they can cause ecological problems.

Certain major issues relating to animal welfare need to be resolved. For example, a pig that has to be kept sterile because it is later to serve as an organ «donor» cannot be allowed to roam freely outdoors. Furthermore, in accordance with the provisions of Swiss legislation governing genetic engineering, genetically modified animals that are to be used for the production of active medical substances or as model organisms must be kept in closed facilities. These animals have to be denied exercise, grazing and surroundings that are as natural as possible (contrary to the provisions of Swiss legislation governing the protection of animals). Whether genome editing can be reconciled with the requirements of animal protection depends on whether genome-edited animals are governed by genetic engineering legislation. It is foreseeable that conflicts could arise between the provisions governing genetically modified animals and animal protection legislation.

Sceptics view genetic modifications in a critical light even if they are justified on the grounds of animal welfare: appropriate stall management allowing horned cattle sufficient space to move around in could reduce the risk of injuries just as easily as breeding hornless cattle could.

The issue of respecting the dignity of living beings also sets limits on genome editing. In the assessment of ethicists, the principle of respecting the dignity of the living being is more gravely violated if the genetic modification alters the outward appearance of the animal than if the milk produced by the animal is altered in composition, for instance. The principle of the dignity of living beings is anchored in the Swiss Federal Constitution. In view of this, genome editing of animals will have to be practised with restraint here in the near future.

Gene drives: Faster evolution

Gene drive constructs represent a special case in the practice of genome editing. Gene drives are genetic modifications that are linked to a mechanism that assures their rapid distribution among a given population. They could cause entire species to disappear, or by contrast could help them make a breakthrough in the wild.

Every year around half a million people (including many children) die of malaria. Quite apart from the associated human suffering, this periodically recurring swamp fever also causes enormous economic costs. In 2016 alone, countries and non-governmental organisations invested around 2.7 billion euros in the fight against this disease. Three out of a total of around 800 species of mosquito that are found in the affected countries serve as hosts for the *Plasmodium falciparum* parasite that causes malaria. If it were possible to decimate these three types of mosquito, new infections could be prevented and the disease could ultimately be eliminated. This is the view of the scientists who are carrying out research for the «Target Malaria Programme» financed by the Melinda and Bill Gates Foundation.

When gene transmission goes «turbo»

The instrument deployed for this purpose is called a «gene drive». It facilitates the distribution of a gene by means of genome editing throughout entire populations. It is especially suitable for use in animal populations that reproduce quickly, such as insects or rodents.

In comparison with unmodified genes, a «turbo gene» can be distinguished by the fact that it establishes itself in a given population within a very short time. If, for example, a given gene is introduced into a mosquito, it is only present as a single copy, i.e. only half the sperm or egg cells contain it. If the mosquito mates with an unmodified member of a wild population, only half the offspring will inherit the introduced gene. The process of genetic inheritance proceeds in the normal manner and the introduced gene remains within the population at a low level or disappears again. With a gene drive construct, the modified gene also initially only resides in the somatic cells of the modified mosquito as a single copy, but in the germ line it copies itself from one chromosome to the other so that all spermatozoa and ovules contain the gene, which is then passed on to all the offspring. In this way it is continually distributed until all the mosquitoes in a given population possess it.

In the fight against malaria the aim is to introduce a defect into the fertility gene of female mosquitoes. In combination with a gene drive construct, the defect will spread throughout the entire population within one to two years. During this period, although an ever increasing number of mosquitoes are produced that carry the infertility gene, they remain capable of reproducing because they carry a second version of the gene that is still intact. The desired effect of the intervention occurs as soon as two modified mosquitoes mate. All their offspring then carry a second defective reproduction gene. Ultimately, all the females will be infertile and the population will die out.

Although the concept of the gene drive is in theory promising, in practice there are still some obstacles to be overcome, because it is not always the case that the break caused by the gene scissors is repaired as intended. This means that a «turbo gene» accelerates the mutation rate at precisely the locus at which it is intended to be active.

The pitfalls associated with the release of gene drives into the environment

The main reservations concerning gene drives, however, relate to their potential consequences for the environment rather than to methodological shortcomings.

A gene drive is an instrument that can only be optimally effective in organisms that reproduce sexually, can be bred in large quantities in the laboratory and reproduce rapidly. In view of this, insects and rodents are the focus of the use of the «turbo gene». However, an unintended release of gene drive organisms into the environment is regarded as a considerable risk due to the high rate of distribution among populations in the wild. If they were to be released into the environment, insects and other creatures modified with «turbo genes» would be practically impossible to control, and it would be

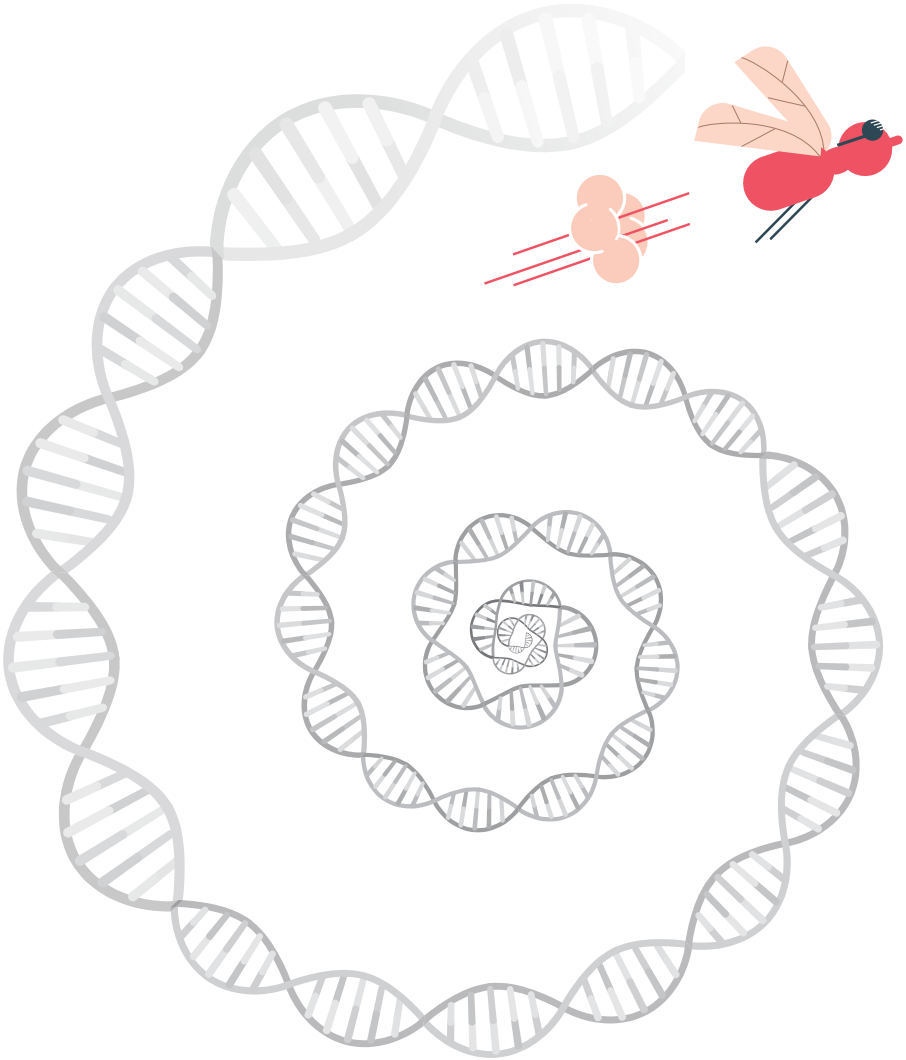
extremely difficult to reverse the consequences for the ecosystem. Furthermore, the danger exists that the gene drive construct could be transmitted to closely related species that had not been targeted.

Critics also claim that under certain circumstances gene drives could merely shift the problem. They feel it is conceivable that if malaria mosquitoes were to be decimated, the parasite they carry which causes the disease would be forced to seek an alternative host. The hoped-for eradication of malaria would thus be deceptive and short-lived.

Potential benefits for the environment

When we intervene in the ecosystem for our own benefit, the concerns with respect to the environmental consequences of our actions are even greater. But gene drives can also have impacts that are beneficial for the protection of nature and the environment. Their use is being considered, for example, as a means of combating populations of rats, opossums and stoats which pose a threat to bird life in Australia and New Zealand. Through the use of gene drives it would be possible to reduce the fertility of these creatures, which are currently often combated through the use of poisons that pollute the environment.

Another option would be to render endangered species resistant to those diseases that pose a threat to their existence. Here, for example, the Tasmanian devil is being plagued by a facial tumour disease that is transmitted via bites. Many of them die because they are no longer able to feed due to the painful tumours on their mouth and throat. There are only a few of these scavengers left in the wild, but it would be possible to save the species if it could be rendered resistant to this disease.



In addition, gene drives could be used as an instrument for increasing the genetic diversity of small animal populations that are thus susceptible to inbreeding.

Out of the question in Europe

According to the relevant legislation, animals possessing a gene drive construct are classified as genetically engineered organisms. Their release into the environment is prohibited in Europe. In view of the potential benefits of the «turbo gene», however, both the scientific community and the relevant regulatory authorities consider further research into this science to be appropriate. At present the focus is primarily on identifying the risks that could arise following the unintended release of gene drive organisms from enclosed systems, and how this could be avoided.

It is also widely agreed that the regulation of gene drive organisms must be internationally harmonised, since it would be virtually impossible to prevent organisms that possess «turbo genes» from crossing national borders.

With respect to further research into gene drives and, in particular, future experiments involving the release of gene drive organisms into the environment, scientific organisations explicitly call for a step-by-step approach – only after the originally specified safety criteria have been met may the next phase with a higher risk level be initiated. Everyone also agrees that potential risks have to be clarified individually for every single issue and every single case.

The agreed step-by-step procedure could also mean that experiments involving the release of gene drive organisms into the environment would initially be carried out on islands in order to restrict their distribution. Initial projects of this nature are currently in preparation: on two islands north of New York, a research group at the Massachusetts Institute of Technology plans to combat the rampant spread of Lyme disease (Borreliosis), which is affecting the local population and many tourists. The scientists are considering releasing mice that have been immunised to the disease with the aid of a gene drive. This means the rodents would not transmit the pathogen to the ticks that pass it on to human beings, and thus the infection cycle would be interrupted. The researchers and their backers were not alone in organising this project – right from the start, the inhabitants of the islands were included in the decisions about whether the mice should be modified with «turbo genes» and released into the environment and, if so, how to go about it.

High expectations among Swiss companies, low acceptance by clients

In an online survey, Swiss companies were asked to assess the economic potential of genome editing. From the point of view of entrepreneurial practice, their assessment is less optimistic than that expressed by scientific laboratories.

Genome editing is awakening major economic expectations. In the past six years, private entities in the USA alone have invested more than a billion US dollars in startups focusing on the new science, and primarily on CRISPR/Cas9. In Europe, the company founded by Emmanuelle Charpentier, one of the discoverers of CRISPR/Cas9, has attracted investments amounting to 124 million euros since 2017.

Projects in the business sector have so far remained speculative in nature because assessments of the economic potential of genome editing have barely been made to date. The online survey of Swiss companies that was carried out within the framework of the TA-SWISS study has yielded some initial indicators. Although many of the contacted companies chose not to complete the questionnaire, the responses that were received permit some conclusions to be drawn as to whether genome editing could establish itself on the Swiss market and what the greatest obstacles are that would have to be overcome.

Acceptance and legal framework as key factors

Relatively few respondents declared an intention to refrain from using genome editing in the future. Most would consider using it at some later date. Where respondents declared they did not intend to use genome editing at present, the reasons they gave were the uncertain legal situation and the lack of acceptance by their clients. The latter is all the more significant in that it was not included in the questionnaire and was addressed by the respondents themselves in various blank comment fields. One respondent stated that the company would only use genome editing for applications that could be expected to meet with widespread approval in society. Otherwise the method would only be used if the declared objectives could not be achieved through alternative methods at acceptable cost.

None of the respondents felt that the legal framework in Switzerland is favourable for the use of CRISPR/Cas9. In the responses, neutral assessments judging the existing legislation as neither conducive nor obstructive held the scales even with assessments that found the existing legislation has a prohibitive effect, in particular in the field of crop breeding, or that its effects cannot be calculated.

No clear views regarding the consequences for the labour market

The respondents' assessments of the consequences of CRISPR/Cas9 for the labour market are varied: some companies anticipate job growth because the new gene scissors will make it possible to operate multiple projects at the same time, while others expect a reduction in the number of jobs because, in their view, it will be possible to implement research projects more quickly and efficiently and thus with fewer personnel.

On the other hand, there is general consensus concerning the assessment of the economic environment: most of the respondents expect CRISPR/Cas9 to fuel competition. Companies in the USA in particular could extend their lead because they could use CRISPR/Cas9 sooner than their competitors in Europe and without restrictive conditions.

Overall, the responses received from the online survey reflect many issues that are still open due to the current lack of practicality and the ongoing debates on legal aspects.

Recommendations of the Steering Committee of TA-SWISS

Genome editing methods are applied for a broad variety of purposes to various cells and organisms and are undergoing constant development. Depending on the applied method, the objective and the organism concerned, different challenges arise and different impacts have to be taken into account. In addition, social implications and appraisals may vary depending on the application and objectives in question.

The Steering Committee of TA-SWISS discussed the findings of the «Genome Editing» study in depth and decided to formulate its own recommendations based on these findings. The Steering Committee makes general recommendations, but also recommendations aimed at specific areas of application.

General recommendations

Transparent structure of public debate

As is the case with other controversial technologies, the call for public debate on the challenges associated with genome editing is omnipresent. To ensure that the debate is meaningful and constructive, the players who want to initiate such discussions need to comprehensively reflect on what the conditions of such a debate should be. It is important to clarify how a constructive debate should be structured, as well as which objectives are to be pursued and what is to happen with the results.

For a constructive social debate it is essential that the information available is as unbiased as possible. The exchange should be open and permit a variety of perspectives, and it does not necessarily have to culminate in consensus.

Identifying uncertainties

With methods such as genome editing, forecasts and expectations are often formulated that do not stand up to critical analysis. These should be carefully scrutinised and their underlying fundamentals be made transparent.

Scientists, journalists and politicians should openly address the limits of existing knowledge. They should clearly communicate ambiguities and uncertainties so that it will be possible to more effectively assess the risks and opportunities, as well as the impacts associated with the use of genome editing for different purposes.

Risk limitation

As compared with the previous methods of genetic engineering, genome editing strives for a higher degree of precision with respect to interventions in the genome, but undesired effects (e.g. off- and on-target effects) can nevertheless occur that are difficult to assess.

Systematic research into off- and on-target effects is necessary in order to more accurately assess the risks and opportunities associated with genome editing in the various areas of application. In addition, the relevant federal supervisory authorities should formulate adequate scientific standards, draw up guidelines for measuring on- and off-target effects and introduce a system for monitoring genome-edited organisms.

Application-specific recommendations

Somatic gene therapy

Initial uses of somatic gene therapy were developed without genome editing methods and official approvals have been issued. In view of the extremely high costs involved, somatic gene therapy is only used for diseases for which no other therapies exist. Through the use of genome editing, research into new gene therapies is progressing more rapidly. However, in view of the complexity of clinical studies and the relatively limited numbers of patients, it is difficult to predict how genome editing will develop.

The challenges associated with the financing of somatic gene therapies need to be widely discussed and resolved at the political level, because numerous new applications have to be anticipated. Balancing the (financial) interests of producers and health insurance providers is a central issue. Furthermore, new remuneration models (e.g. payment based solely on effectiveness) have to be given consideration.

Interventions in the germ line

There is currently widespread consensus among scientists that too little knowledge is available and the practical processes are not yet sufficiently advanced to permit the clinical use of genome editing for interventions in the human germ line. Because such interventions would affect future generations, their legitimacy is also being questioned from an ethical perspective.

In Switzerland, interventions in the germ line are prohibited in accordance with Article 119 of the Federal Constitution. This prohibition is broadly supported because the method is not yet ready for clinical application and for most of the conceivable uses of genome editing, preimplantation diagnosis is available as an alternative. Nonetheless, the experiments conducted by Chinese researcher He Jiankui show that it is indeed possible to carry out interventions in the germ line, and it is to be expected that other countries will follow suit.

Switzerland should actively voice its negative stance towards germ line interventions in human beings at the international level.

Xenotransplantation

The new possibilities for genetically modifying pigs in a targeted manner with the aid of genome editing indicate that the use of these animals as potential organ «donors» is growing more realistic. However, the high expectations should be viewed with caution. Furthermore, the ethical assessment of xenotransplantation is unlikely to be made any simpler through its successful medical application. The problems that arise in the context of the various ethical implications, including adverse effects on animals, the identity of human beings and animals and the degree of social acceptance, do not depend on the status of the technology.

Further research is required in order to also facilitate a better assessment of the ethical issues and social impacts associated with xenotransplantation. As an alternative, the production of organs in the laboratory, for example through the use of stem cells or with the aid of 3D printers, should be further developed.

Crop and animal breeding

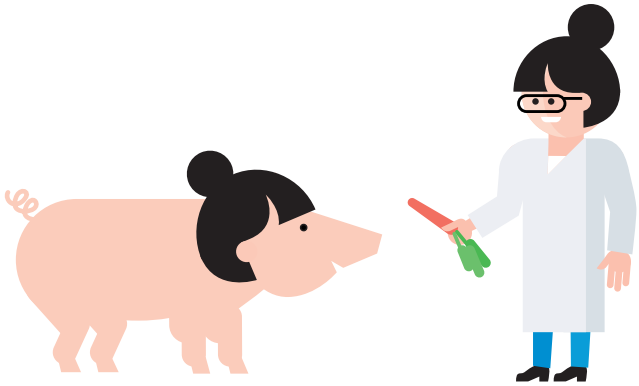
Currently, the modifications that are triggered in plants through the use of genome editing cannot always be clearly distinguished from natural mutations. Nonetheless, in 2018 the European Court of Justice ruled that such plants are to be classified as genetically modified. In the view of the court it is the production process that is decisive. This means that, in the European Union, plants that have been modified through genome editing are subject to the same legislation in terms of approval, marketing and labelling as that which applies to plants that have been modified using previous methods of genetic engineering. This regulation also applies in Switzerland.

Given the low level of acceptance for genetically modified foodstuffs, methods should be researched that make it possible to demonstrate whether a given product has been modified through genome editing methods applied to the plants and animals from which the product concerned has been derived (principle of traceability as a prerequisite for product labelling). If this form of demonstration cannot be achieved, efforts should be made to determine which measures can be implemented to prevent foodstuffs derived from genome-edited organisms from entering the production chain and being brought onto the market.

Gene drives

The objective of gene drives is to rapidly distribute desired genetic properties among specific populations. Here, insects are the main focus of research. This method could be applied with the intention of genetically modifying populations, culling them or eliminating them altogether. Conceivable applications include combating pathogens, pests or invasive species, but the possibility that the modified organisms could unintentionally be released into the environment with uncontrollable consequences remains a significant problem. This means that interventions in the food chain could potentially alter entire ecosystems. In Switzerland, gene drives are subject to genetic engineering legislation.

Scientific studies in enclosed systems should show whether field trials with gene drives and their applications can be considered in Switzerland at all. A public debate should be held in order to clarify under which conditions it might be possible to use gene drives. In addition, it is necessary to examine whether the existing genetic engineering legislation could suffice to limit the risks associated with gene drives. For this purpose the development of European legislation relating to biosecurity should be taken into account.



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New technology often leads to decisive improvements in the quality of our lives. At the same time, however, it involves new types of risks whose consequences are not always predictable. The Foundation for Technology Assessment TA-SWISS examines the potential advantages and risks of new technological developments in the fields of life sciences and medicine, information society as well as mobility, energy and climate. The studies carried out by the Foundation are aimed at the decision-making bodies in politics and the economy, as well as at the general public. In addition, TA-SWISS promotes the exchange of information and opinions between specialists in science, economics and politics and the public at large through participatory processes. Studies conducted and commissioned by the Foundation are aimed at providing objective, independent, and broad-based information on the advantages and risks of new technologies. To this purpose the studies are conducted in collaboration with groups comprised of experts in the relevant fields. The professional expertise of the supervisory groups covers a broad range of aspects of the issue under study.

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