Xeno-transplantation. New opportunities, new ethical questions?

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1 Background

1.1 Shortage of human organs for transplantation

Developments in transplant medicine over recent decades have also led to an increase in demand for organs. A transplant involves the transfer of living organs, tissues and cells between individuals. Such a transfer between members of the same species is known as allotransplantation or allogeneic transplantation.

There is a shortage of human organs not only in Switzerland and Europe but worldwide, and solutions are being sought to counter this. At the end of 2022, just under 1500 people in Switzerland were waiting for an organ transplant.[1] That year, 570 people received an organ from another person, and another 83 died while waiting for a transplant. Others were removed from the waiting list because their health had since deteriorated to such an extent that a transplant was no longer medically feasible.

Transplants may be necessary if a vital organ fails, for example due to an accident, poisoning, the consequences of an infection or as a result of genetic or chronic non-infectious diseases, such as autoimmune diseases, cancer or chronic kidney disease. A transplant is the last resort when all other treatment options have been exhausted. The aim is to prolong patients' lives and improve their quality of life.

A transplant entails various restrictions for the organ recipient. As the transplanted organ comes from a genetically different individual with a different immune system, the recipient has to take medication for the rest of their lives to suppress their immune system in order to prevent the acute rejection of the foreign organ. This immunosuppression makes them more susceptible to infections. Their likelihood of developing cancer is also increased and they live with the risk of chronic rejection of the organ or even complete failure of the transplant.

Despite government efforts to increase the willingness of the population to donate organs, organ shortage remains a constant problem.[2] Furthermore, developments in medical procedures and technologies, for example to increase the immunological compatibility of donor organs with recipients, as well as demographic trends and a possible expansion of indications, suggest that the demand for organs is set to grow. This situation could also exacerbate the international problem of illegal trade in human organs. Switzerland has signed the Council of Europe Convention against Trafficking in Human Organs and supports international efforts to combat organ trafficking. But despite measures to tackle it, the problem of illegal organ trafficking will persist as long as there is a shortage of organs.[3]

1.2 The search for alternatives to allotransplantation

To counteract the shortage of organs, various alternatives to allotransplantation are being pursued. *Firstly*, attempts are being made to avoid serious organ damage through prevention, early detection and the development of new treatments. *Secondly*, work is being carried out on organ regeneration, autotransplantation and temporary mechanical support to preserve the body's own organ and improve its functionality. *Thirdly*, in order to completely replace failed organs, research is being conducted into organoids (organ-like cell structures cultivated in the laboratory) and bioartificial organs (tissue structures made from cellular and mechanical elements), with the aim of one day partially or fully replacing organ functions. *Fourthly*, work is under way on using animal organs, tissues

1 For the latest figures, see: Swisstransplant (www.swisstransplant.org/de), Deutsche Stiftung Organtransplantation (dso.de), Eurotransplant (https://www.eurotransplant.org).

2 In May 2022, the Swiss electorate voted in favour of moving to a soft presumed consent (or soft opt-out) system. This will come into force in 2025 at the earliest. Unlike the current explicit consent (or opt-in) system, presumed consent assumes that people consent to the removal of organs unless they explicitly state otherwise. However, the soft presumed consent system gives the next of kin the right to refuse organ removal, although they must take into account the presumed wishes of the deceased person. If there are no relatives or the relatives cannot be contacted, or in the event of language or socio-cultural barriers, organ removal is not legally permissible. It is hoped that switching to an opt-out system, accompanied by further information and awareness-raising campaigns, will result in more people being willing to donate organs. For more information (in German), see: https://www.bag.admin.ch/bag/de/home/medizin-und-forschung/transplantationsmedizin/willensaeusserung-zur-spende-von-organen-geweben-zellen/zustimmungsmodelle-in-der-transplantationsmedizin.html#:~:text=Von%20der%20erweiterten%20Widerspruchsl%C3%B6sung%20spricht,Willen%20der%20verstorbenen%20Person%20ber%C3%BCcksichtigen.

3 https://www.bag.admin.ch/bag/de/home/medizin-und-forschung/transplantationsmedizin/internationale-zusammenarbeit-transplantationsmedizin/organhandelskonvention.html.

and cells for transplantation into humans. This type of organ transplantation, which unlike allotransplantation occurs across the species barrier, is known as xenotransplantation or xenogeneic transplantation.

A key prerequisite for xenotransplantation is that animals can be genetically modified in such a way that their organs can be used for transplantation into humans. The animals are genetically modified on the one hand to physiologically adapt their organs so that they can perform their function in humans, and on the other hand to overcome immunological rejection in the organ recipient and to reduce the risk of infection. For medical reasons, pigs have proven to be particularly suitable for xenotransplantation. Their organs can be physiologically adapted and their metabolism is similar to that of humans. However, there are also economic reasons for the current focus on pigs as a source of organs for xenotransplantation.[4, 5]

Both in specialist literature and in media reporting, xenogeneic source animals are widely referred to as 'donor animals' or 'organ donor animals'. The term 'donation' refers to something given voluntarily. Describing xenogeneic source animals as 'donor animals' is misleading. Unlike humans, who give their prior consent to organ donation, animals cannot give consent. The connotation of voluntary action also conceals the fact that these animals are genetically modified, bred, kept and killed solely for the purpose of xenotransplantation. The present report therefore avoids the use of this term.

1.3 Focus of the report

The ECNH is legally mandated to evaluate developments in and applications of biotechnology and gene technology in animals and other organisms, including their impacts on humans and the environment. It advises the Swiss Federal Council and federal authorities on the preparation of legislation and submits proposals for future legislation and recommendations on enforcement.[6] The expert debate on new developments in xenotransplantation is currently dominated by the medical and technical opportunities and risks. The ethical issues in relation to humans, and still more in relation to animals, remain in the background. It falls within the ECNH's remit to shine a light on the animal ethics aspects of xenotransplantation. This is the focus of the present report.

New genetic engineering techniques known as genome editing play a key role in the development of xenotransplantation. These techniques have given new impetus to xenotransplantation within a short period of time. They enable new and accelerated genetic modifications of animals to improve the suitability of their organs, tissues and cells for transplantation into humans and increase the chances of a successful transplant. Research into aspects of xenotransplantation is being conducted at several locations in Switzerland. Preclinical trials on apes are already being carried out in other countries, along with therapeutic trials on humans in the United States in particular. With regard to the use of animals, the ECNH investigates the extent to which technological and medical developments and the possible establishment of xenotransplantation raise new ethical questions or require new answers to familiar ethical questions. It examines the action required from an ethical perspective and, where it deems appropriate, formulates recommendations with regard to legislation and enforcement.

4 Although primates are genetically more closely related to humans, rearing monkeys is very complicated and expensive and their organs are often too small for humans. Pig organs are therefore proving a more suitable substitute for human organs.

5 For religious and cultural attitudes towards the use of pigs, see section 3.2.2.

6 See Article 23 of the Federal Act on Non-Human Gene Technology (Gene Technology Act), SR 814.91.

1.4 Bases for discussion

This is not the first time that the ECNH has dealt with the issue of xenotransplantation, although the discussion dates back some time. In early 2000, the Committee issued a statement on the subject as part of the consultation on the Federal Act on the Transplantation of Organs, Tissues and Cells, which came into force in 2007.[7] At that time, a clear majority of the Committee was in favour of a moratorium on the use of xenotransplantation. The members justified this position on the grounds of an insufficient scientific basis for evaluating its risks. They also criticised the fact that animal ethics aspects were almost entirely absent from the proposed legislation. This made it impossible to weigh the interests of humans in xenotransplantation against the associated strain imposed on animals. The smaller the chances of successful xenotransplantation, the higher the strain placed on the animals is weighted. Without a scientific basis for evaluating not only the opportunities but also the risks of xenotransplantation, or for ensuring that animal ethics aspects are also adequately taken into account, the ECNH considered it irresponsible to carry out either clinical trials on humans or preclinical trials on apes.[8]

In order to familiarise itself with the latest developments in xenotransplantation, the ECNH, among other things, commissioned two expert reports as new bases for discussion. One of these, authored by Samuel Camenzind, analyses animal ethics issues surrounding xenotransplantation in the wake of the introduction of genome editing.[9] An ethical weighing up of interests in relation strain on animals in the context of xenotransplantation involves assessing the alternatives to xenotransplantation alongside the risks and opportunities of xenotransplantation for human medicine. With a view to gaining an overview of the potential and prospects offered by such alternatives, the ECNH commissioned Anne Eckhardt to conduct a literature study.[10] It also heard from two further experts in order to learn about the current situation from a research perspective: Leo Hans Bühler, Professor of Surgery at University Hospital Geneva and Hôpital Cantonal de Fribourg, informed the ECNH about research projects and challenges linked to xenotransplantation, and Professor Nicolas Müller, Head of the Transplantation Centre and responsible for immunology at University Hospital Zurich, highlighted the immunological aspects and the risks of zoonoses in particular. While preparing its report, the ECNH was also in close contact with veterinarian Otto Maissen, Head of the Animal Experimentation Sector at the Federal Food Safety and Veterinary Office (FSVO). The ECNH would like to thank these experts for their informative and helpful insights and open communication.

The ECNH is solely responsible for the considerations that follow.

7 Transplantation Act, SR 810.21.

8 ECNH, Statement on the Transplantation Act (draft bill), February 2000.

9 Samuel Camenzind, Xenotransplantation, 2023, in: Beiträge zur Ethik und Biotechnologie, Band 16.

10 Anne Eckhardt, Alternativen zur Xenotransplantation. Grundlage für tierethische Abwägungen, 2023.

2 Developments in xenotransplantation

Developments in xenotransplantation and the medical hopes and expectations associated with it have undergone various phases. Euphoric moments, when a breakthrough seemed imminent, were followed by periods of uncertainty as to whether the technical and medical hurdles could ever be overcome and the envisaged goals of xenotransplantation could realistically be achieved.

In the early days of xenotransplantation, from the 1960s to the 1980s, it was assumed that the anatomical adaptation of animal organs to humans and the risk of infection for organ recipients were the biggest obstacles to a successful transplant. However, all attempts at xenotransplantation met with failure. It was only when rejection reactions were understood as an immunological response of the body and after the development of the immunosuppressant ciclosporin in the 1970s that both xenotransplantation and transplant medicine as a whole took a decisive step forward. With further advances in pharmacology and, in particular, the development of genetic engineering techniques in the 1990s, it became possible to produce xenogeneic source animals lacking a particular enzyme that triggers a hyperacute rejection reaction in the organ recipient. However, even this proved inadequate, as further immunological problems arose. Despite all the setbacks, confidence remained high. It was hoped that further genetic adaptations of xenogeneic source animals could overcome these critical immunological barriers, or even bypass them altogether one day. Meanwhile, however, concerns about zoonotic risks were increasingly coming to the fore – not only risks to organ recipients but also the risks posed by xenotransplantation to society as a whole.

After a spell of near euphoria around the turn of the millennium, interest in xenotransplantation within society and research institutes dropped off and remains relatively low today. Over the intervening years, only a few research centres, including two private companies in the United States and a public institute in Germany, have continued their work on the production of suitable genetically modified animals for the purposes of xenotransplantation.

Now, the development of genome editing techniques is raising new hopes and expectations that the medical and technical challenges can be overcome to the extent that xenotransplantation could be tested in clinical trials, including in Switzerland. Thanks to genome editing, it has been possible to remove more immune response triggers in multiple genetically modified animals and to better adapt xenografts to organ recipients. Another important step has been to use these genetic engineering methods to remove endogenous viruses, which can be dangerous for immunosuppressed patients, from the pig's genome.

Until recently, the literature indicated that a realistic medium-term goal for xenotransplantation was a gain in lifespan for organ recipients of one to two, possibly three, years. For this reason, discussions centred on niche applications of xenotransplantation, where the aim is to bridge the gap until a suitable human organ becomes available. One example would be kidney patients receiving a temporary xenogeneic kidney until an appropriate human organ is found. Another would be newborn babies with severe heart failure being given a xenotransplant until the child is large enough to be considered for a suitable human heart transplant. For such bridging applications, the animal organ would only have to perform its function for a limited period of one to two years.

However, a compassionate use treatment, for which the relevant US authority granted emergency authorisation for the first time, fuelled greater expectations in early 2022. In a world first, a team of doctors in the United States implanted a pig's heart into a human. Several genes in the genetically modified pig were knocked out and six human genes were inserted so that the pig's heart immunologically matched the body of the organ recipient. The xenograft was successfully connected to the patient's blood circulatory system, performed the heart's pumping function and was not rejected. However, the patient was never able to leave the hospital. After two months, his condition rapidly deteriorated and he died. In a scientific publication, the researchers point out that the transplanted organ came from a pig infected with a porcine virus.[11] Some experts claimed that the co-transmission of the swine virus could have been avoided if the xenogeneic pig had been pretested for the virus using adequate methods. However, the researchers conclude that the organ failure that led to the patient's death was not due to an infection, but to the patient's other significant pre-existing conditions. Given that there was no acute organ rejection after the transplant, the two-month survival time and the transplant itself were judged to be a medical success, not only by the scientists who carried out the experiment but also by the medical community at large.[12] Further experiments with pig heart transplants on brain-dead persons were carried out in the summer of 2023, and in September of that year the same research team implanted a xenogeneic pig heart into a 58-year-old patient.[13] A month later he was breathing on his own and the transplanted heart was functioning, but after a further two weeks the heart showed signs of rejection and the person died.[14]

In Europe, the first xenotransplantation of a pig heart is expected to take place by 2025 at the latest. Around eight years ago, heart surgeons and veterinarians in Munich began experiments on baboons. The transplants were successful during the scheduled trial period of three to six months. The tests were then discontinued, as planned, and the baboons were euthanised. The researchers said they wanted to show that a primate with a xenograft could survive for a year, before a human trial was launched.[15]

In 2021, prior to the transplantation of pig hearts, experimental transplants of xenogeneic kidneys into brain-dead people also took place. Following tests in primates, these short-term experiments were mainly used to investigate medical and technical issues.[16] In mid-July 2023, US doctors once again implanted a pig kidney into a brain-dead person[17] connected to a ventilator. Both kidneys had been removed from the body, and so the xenograft had to take over the entire function of the kidneys. A gene had previously been knocked out in the genome of the pig from which the kidney originated. As a result, the pig kidney lacked a molecule that would trigger acute immune response in humans and the rejection of the xenograft. According to the researchers, new data suggests that, for xenogeneic kidney transplants at least, unlike xenogeneic pig hearts, only a single gene needs to be modified. For the two-month duration of the experiment, the xenogeneic kidney performed its function in the brain-dead person without mechanical support, without medical complications and without any signs of rejection. What's more, only the usual immunosuppressants, also used in allotransplants, were administered. Based on these experiments with pig kidneys, which are deemed to have been successful, researchers assume that clinical applications on

11 For details of the pre-existing conditions, see Griffith, Bartley P. et al (2022): Genetically Modified Porcine-to-Human Cardiac Xenotransplantation. In: N Engl J Med 387 (1), 35–44.

12 Kögel, Johannes/Marckmann, Georg (2023), First-of-its-kind Xenotransplantation: Bedarf an ethischer Reflexion in Wissenschaft und Gesellschaft. In:Ethik in der Medizin, 35 (1), 137–143.

13 https://www.letemps.ch/sciences/sante/un-coeur-de-cochon-transplante-chez-un-patient-aux-etats-unis-pour-la-deuxieme-fois; https://www.aerztezeitung.de/Medizin/Zweitem-Patienten-in-den-USA-Schweineherz-eingepflanzt-443164.html.

14 https://www.umms.org/ummc/news/2023/announcing-the-passing-of-lawrence-faucette.

15 https://www.aerztezeitung.de/Wirtschaft/2025-erste-Schweineherz-Transplantation-in-Muenchen-435824.html.

16 Samuel Camenzind, Xenotransplantation, 2023, p. 15.

17 Research on brain-dead people opens up another separate debate on human ethics, which the ECNH will not enter into.

living patients will also take place in the near future. Indeed, the pigs genetically modified and bred for xenotransplantation have already been authorised for such use by the US Food and Drug Administration (FDA).[18]

In the meantime, another group of researchers in the United States has developed a pig line carrying a total of 69 genomic edits – in particular, all endogenous retroviruses have been removed from the genome. They have published the results of successful trials involving kidney transplants in baboons, some of which lived for more than two years with the xenogeneic kidneys.[19] The same research group is also reviving the idea of xenotransplants as a bridging measure and as early as 2024 plans to transplant xenogeneic hearts into babies with severe congenital heart defects until a suitable human heart becomes available.[20]

A research group from China is taking a slightly different approach. A paper published in early September 2023[21] describes an experiment in which pig embryos were genetically modified so as not to develop kidneys themselves. Human stem cells were then introduced, which caused the embryos to develop the rudiments of human kidneys. The experiment did not go any further than the formation of rudiments. Unlike the examples cited above, a further development of this approach would involve genetically modifying animals in such a way that they develop human organs that could be used as transplants. Among the matters requiring further investigation, including from an ethical perspective, is the fact that human cells were subsequently found not only in the rudimentary organs but also in the brains of the pig embryos.

18 https://www.scinexx.de/news/medizin/mensch-erhaelt-niere-vom-schwein; https://nyulangone.org/news/pig-kidney-xenotransplantation-performing-optimally-after-32-days-human-body.

19 Anand Ranjith P et al., Design and testing of a humanized porcine donor for xenotransplantation, Nature, Vol. 622, 11 October 2023, p. 393ff. (https://doi.org/10.1038/s41586-023-06594-4). Reference: Anand, R.P., et al. (2023). Design and testing of a humanized porcine donor for xenotransplantation. Nature 622, 393–401.

20 https://www.technologyreview.com/2023/07/17/1076392/this-company-plans-to-transplant-pig-hearts-into-babies-next-year.

21 https://pubmed.ncbi.nlm.nih.gov/37683604.

3 Ethical considerations

In a statement issued in 2000, the ECNH criticised what it considered at the time to be an inadequate scientific basis for evaluating the risks of xenotransplantation. The chances of success were also deemed to be low. The following ethical discussions will now examine the extent to which the new genetic engineering techniques and the associated developments in xenotransplantation have changed this initial situation in a way that is ethically relevant.

The development of the new techniques does not alter the fact that the ethical weighing up of xenotransplantation involves, first and foremost, dealing with conflicting moral obligations. On the one hand, there is the obligation to help patients suffering from irreversible organ damage. In xenotransplantation, a technology is being developed that could help patients whom we know will exist, even if we cannot (yet) identify them all. Moreover, the technology is now sufficiently advanced for us to consider the specific conditions in which it could potentially be applied. On the other hand, there are obligations relating to animal ethics that must be taken into account when performing interventions on animals in connection with xenotransplantation. In the first part of this section, the ECNH examines this conflict of obligations and discusses how it should be dealt with today in view of the new possibilities and opportunities offered by xenotransplantation. In the second part, further implications of xenotransplantation are presented and evaluated from an ethical perspective.

3.1 Conflicting moral obligations

Patients suffering from irreversible organ damage may be given an organ transplant as a last resort, provided they meet the relevant medical criteria. That we have an obligation to help suffering beings – in this case human beings – who are in need of, and want, help is beyond dispute. What is open to dispute is how far the entitlement to such help extends. Clearly, in life-and-death situations, help must be given insofar as possible. In the following, the ECNH assumes that, for all cases in which people currently meet the criteria for an allotransplant, such an obligation to help also exists with regard to possible applications of xenotransplantation. Where the boundaries of this obligation would lie if xenotransplants were to enable treatments going beyond the current indications for allotransplantation, for example the treatment of infertility, would need to be discussed separately.

The obligation to help patients conflicts with moral obligations towards animals. In several respects, xenotransplantation involves interventions on animals that need to be morally justified. *Firstly*, experiments imposing a strain on animals are carried out on different species for various aspects of xenotransplantation research. *Secondly*, pigs considered suitable for xenotransplantation on various grounds also undergo genetic modification in the course of animal experiments involving strain, in order to obtain the xenogeneic transplants suitable for transplantation to humans. *Thirdly*, xenogeneic transplants are tested in advance on other animals, including primates. This also involves experimentation placing strain on the animals concerned. *Fourthly*, in a further step, the xenogeneic source animals are bred under sterile conditions that impose strain on the animals.[22] *Fifthly*, they are killed so that their organs can be transplanted into humans. And sixthly, keeping xenogeneic source animal populations under sterile conditions also entails strain for the animals.[23]

Morally speaking, it is prima facie impermissible to inflict suffering, pain

22 Recipients of xenogeneic transplants are immunosuppressed. It must therefore be ensured that the animals are as free as possible from pathogens. Some of these pathogens are acquired by the animals during their lifetimes, sometimes very soon after birth. To prevent the xenogeneic source animals, and hence the subsequent organ recipients, from becoming infected, the animals are separated from their mothers after birth and the population is kept under sterile and strictly controlled rearing conditions.

23 Factors cited as particularly strain-inducing are individual housing and the low-stimulus environment. In the literature, pathogen-free rearing is described as follows (see S. Camenzind, Xenotransplantation, 2023, p. 82f.): The piglets are born by caesarean section or by removing the uterus of the mother sow. Contact between the piglet and the mother sow and the mother sow's milk is prevented and the piglet is reared in a germ-free isolator where it receives sterilised feed for two weeks. Only then is it integrated into group housing, still receiving sterilised feed and water as well as filtered air. The regular health checks involve taking blood and tissue samples.

and harm on sentient beings. However, according to the rules of the ethical weighing up of interests, this may be justified insofar as more important interests can be cited – in the present context, insofar as there is an obligation to help patients and this obligation morally outweighs the strain caused to the animals as a result of fulfilling the said obligation.

This requirement for moral justification is also enshrined in the Animal Welfare Act (AniWA. SR 455). Furthermore, since 1992, Article 120 paragraph 2 of the Swiss Federal Constitution has required that the dignity of living beings be taken into account. This moral requirement too is reflected in the AniWA. Article 3 defines the constitutional concept of the dignity of living beings in relation to animals as the inherent worth of the animal that must be respected when dealing with it. According to this provision, if any strain imposed on the animal cannot be justified by overriding interests, this constitutes a disregard for the animal's dignity. Strain is deemed to be present not only if pain, suffering or harm is inflicted on the animal or if it is exposed to anxiety. The animal must also be protected from humiliation, from major interference with its appearance or abilities and from excessive instrumentalisation. The moral concept of the dignity of living beings thus departs from the pathocentric position, based on the criterion of animal sentience, and instead adopts a biocentric position according to which a living being is to be considered morally for its own sake because it has a good of its own and something can therefore be 'in its interest'.

Violations of the dignity of living beings are not prohibited per se.[24] However, if the way an animal is dealt with affects its 'dignity as a living being', it is imperative to weigh up the interests of the animal against the interests of the human users. Only if it can be shown that the obligations to help patients outweigh the associated strain on the animals has the animals' dignity been taken into account.

For an intervention on animals to be justified, the means for which the animals are used must be suitable for achieving the objective, namely fulfilling the obligation to help patients. Even then, not every intervention is morally justified. If there are alternatives that allow the said obligation to be fulfilled, the one that impinges least on the animals' interests must be chosen. From an ethical perspective, therefore, both animal experiments and the use of animals for xenotransplantation may only be considered if they are *suitable*, *indispensable* and *proportionate* ('in the narrower sense') with a view to fulfilling the obligation to help patients.

3.1.1 The criterion of suitability

The objective of xenotransplantation is to counteract the ongoing organ shortage so that patients no longer die while waiting for a transplant. The aim of the transplant is to enable them to continue living their lives with as few limitations as possible.

Expectations regarding the success of xenotransplantation have risen sharply with the development of genome editing techniques and, since early 2022 at the latest, with the therapeutic trials taking place in the United States. Some now even expect that xenotransplantation could become the greatest lever for eliminating the ongoing organ shortage. If the medical hurdles are overcome, it could not only replace allotransplantation but would also have some significant advantages over that procedure: the number of organs available would in principle be unlimited, transplants would be easier to plan as

24 Therein lies a crucial constitutional difference between human dignity and the dignity of living beings. Violations of human dignity are prohibited. Violations of the dignity of living beings are not prohibited. However, they must be justified based on a weighing up of interests.

there would be less time pressure,[25] and the quality of the xenogeneic organs could be adapted to the specific requirements of individual recipients and thus better controlled.

As a future scenario, there is also talk of xenotransplantation making it possible to expand the indications for transplants. Animal organs, tissues or cells could also be transplanted for purposes that are currently precluded in the context of allotransplantation, such as organ transplants for the treatment of infertility.

Following the latest developments in xenotransplantation, researchers are optimistic that the hurdles that still exist, particularly linked to immunological rejection, can be overcome in the future. Even if this appraisal is based on a small number of preclinical and clinical trials and compassionate use treatments with pig hearts and kidneys, while other organs are not yet in the test phase, it can be expected that xenogeneic transplants, at least where certain organs are concerned, could become a *suitable means* of fulfilling moral obligations to help future patients in need of a new organ.

It should be noted that developments in xenotransplantation could also enable applications aimed solely at improving quality of life rather than saving lives. Whether an obligation to help also exists in such cases would need to be examined. If this was deemed not to be the case, moral obligations towards animals would render this kind of application impermissible. In the remainder of its assessment, the ECNH will focus on xenotransplantation as a life-saving measure.

The current evaluation of the suitability of xenotransplantation for fulfilling obligations to help patients is largely dependent on the quality of the research results. The world's first transplantation of a pig heart into a human in the United States in early 2022, referred to above, raises questions in this regard. The patient had been offered xenotransplantation as a compassionate use treatment of last resort. Without going into the exact circumstances of the transplant in detail here,[26] it must be ensured that the data obtained from experiments involving patients whose bodies have already been subjected to very high levels of stress has the necessary validity when evaluating the suitability of xenotransplantation as a means of fulfilling the obligation to help.

3.1.2 The criterion of indispensability

Insofar as xenotransplantation is a suitable means of fulfilling moral obligations to help patients, the next step is to examine the criterion of indispensability. Interventions on animals for the purposes of xenotransplantation are ethically justifiable only if they are also indispensable. In other words, the obligation to help people who are suffering cannot be fulfilled in any other way. In addition to research into xenotransplantation, various alternatives are being pursued to counteract the constant shortage of organs, a shortage that will presumably only become more acute in the future.[27]

One alternative would be to forestall organ transplants by means of prevention, early detection and the development of new treatments. For example, almost all transplants due to cystic fibrosis and hepatitis C can now be avoided thanks to new diagnostic options and treatments. Research into other diseases leading to organ failure, and the development of treatments for these conditions, could help to further reduce organ transplants. According to experts, a large proportion of heart

25 This could also reduce the time pressure for allotransplantation if xenogeneic organs could be used to bridge the gap until a suitable human organ became available.

26 For a critique, see: Kögel, Johannes/Marckmann, Georg (2023): First-of-its-kind Xenotransplantation: Bedarf an ethischer Reflexion in Wissenschaft und Gesellschaft. In: Ethik in der Medizin, 35 (1), pp. 137–143, especially p. 141.

27 For an overview, see Anne Eckhardt's report: Alternativen zur Xenotransplantation. Grundlage für tierethische Abwägungen, 2023.

and liver transplants could be avoided or at least delayed if concerted efforts were made to prevent cardiomuscular diseases and fatty liver disease in particular. This would reduce the gap between demand and availability of organs and relieve waiting lists.[28]

Work is also being carried out on organ regeneration, autotransplantation and temporary mechanical support. This is another way of preserving the body's own organ and improving its functionality. Ex vivo regeneration strategies in particular are currently on the rise. In this approach, an organ is removed from the patient and mechanically tested and treated outside the patient's body before being reimplanted in the same patient. The same techniques are used to test and improve the quality of an organ with a view to allotransplantation and to extend the time span within which an organ can be transplanted.

According to experts, however, other alternatives are currently still a long way from clinical application. This also applies to the use of organoids and bioartificial organs. Organoids are groups of cells that are cultivated in the laboratory and organise themselves into cell structures that resemble those of organs. In many cases, they have similar capabilities to organs. Bioartificial organs are tissue structures made from cellular and engineered elements. The goal would be to create entire organs such as hearts, kidneys and livers in the laboratory using this method, but this is still a long way off. With both organoids and bioartificial organs, research is currently not focused on their full functionality with a view to replacing organs. Rather, they are used as models, including as a substitute for animal models, in order to test substances. It is currently difficult to assess what further prospects these approaches will have.

It is assumed that, as a result of societal ageing and medical developments, there will continue to be a gap between demand and availability for organ transplants in the future. It remains to be seen whether developments in xenotransplantation will increase demand in parallel with organ availability. This would likely be conditional on xenotransplants guaranteeing at least a quality of life comparable to allotransplantation. The extent to which there would also be an obligation to help patients for indications beyond those applying to allotransplantation would need to be examined on a case-by-case basis.

In some cases, there exist alternative approaches enabling fulfilment of the obligation to help patients which do not involve interventions on animals, or not to the same extent as xenotransplantation. From an ethical perspective, preventive and therapeutic approaches that prevent people from needing a new organ take priority. If social conditions can be changed so as to render fewer organ transplants necessary, then there is a moral obligation to undertake all public health endeavours in this regard. The next step would be to ramp up research approaches aimed at restoring the body's own damaged organs. The use of stem cells could prove an ideal solution in this regard. However, the potential of this approach is difficult to assess, at least for the time being. Since it is currently not possible to prevent or treat organ damage or regenerate or support damaged organs in all cases, it is also justified to promote techniques that enhance the functionality of available human organs and the efficacy of allotransplantation.

On the one hand, how much attention an alternative approach attracts and thus how much research funding it generates has to do with financial interests and possibly also with path

28 If the majority of transplants were necessary due to social circumstances, such as poor diet and living conditions, and if it was not possible for those affected to avoid these conditions, xenotransplantation as an option would possibly be suitable and also indispensable to help the suffering individual. However, this option would be a 'technological fix', i.e. it would tackle the symptoms rather than eliminating the cause. From an ethical point of view, alongside the obligation to help the individual, there is also a general obligation to combat root causes in order to give people the opportunity to live in conditions that minimise the risk of organ transplantation.

dependencies. On the other hand, the various research approaches are all highly competitive. However, if it is shown that certain research approaches involve less strain on animals than others, but have at least comparable prospects of success, then from an ethical point of view these approaches should be prioritised, given the conflicting obligations associated with this issue.

Another issue to bear in mind is how the willingness to donate organs for allotransplantation could be increased. The federal government's campaigns to date have failed to remedy the structural shortage. It remains to be seen what impact the introduction of the soft presumed consent system will have.[29] In the context of efforts to increase the willingness to donate, ethically relevant cultural and religious influences must also be taken into account, as these factors can influence how willing people are to donate organs. The question arises as to what view the state should take of reservations based on such factors and how it can and should contribute to overcoming unfounded fears around organ donation.

3.1.3 The assessment of proportionality

If it is concluded that the criteria of suitability or indispensability (or both at once) are not met, interventions on animals for the purpose of xenotransplantation are ethically unjustifiable.

However, if the considerations lead to the conclusion that both criteria are met, the interests involved when interventions on animals are conducted must be weighed against the obligations to help patients or any other morally relevant interests. Only if the obligations to help and/or the morally relevant interests prevail are they proportionate and hence the associated strain on the animals is reasonable.

To be able to assess the animal interventions, the various levels at which animals are subject to strain in the context of xenotransplantation must be taken into account. Strain differs from phase to phase and encompasses all degrees of constraint: light, moderate and severe.[30] To start with, experiments imposing strain on animals are carried out on various species, most notably rodents, in order to investigate different aspects of xenotransplantation. In addition, animals – primarily pigs – are genetically modified so that their organs are physiologically and immunologically suitable for xenotransplantation. The xenogenic organs are then tested on other animals in preclinical trials before the first clinical trials take place on humans. This involves causing strain to and killing the animals from which the organs are taken. Furthermore, the animals – primarily primates – on which the xenogeneic transplants are tested are subjected to animal experimentation. Once produced, xenogeneic source animals are also placed under strain in the breeding process and by the special conditions in which they are reared, which must meet stringent sterility requirements.

Under current animal welfare legislation, killing an animal, for example in animal experimentation or to remove its organs for xenotransplantation, is not considered as imposing strain if the killing is carried out without causing pain to the animal using legally permitted methods applied professionally. This position makes strain solely dependent on the criteria of pain and suffering. This is both morally and legally controversial. As well as the pathocentric concept, Swiss animal welfare law also recognises the non-sentientist concept of the dignity of living beings or the dignity of animals. This leads

29 See footnote 2.

30 On the various degrees of strain/constraint, see Federal Food Safety and Veterinary Office (FSVO) (2018): Technical information on animal experimentation. Severity degrees 1.04. Online at: https://www.blv.admin.ch/blv/en/home/tiere/tierversuche/forschende.html (24.11.2022).

to the contradictory legal situation where eliminating only one function is considered as imposing strain, but eliminating all functions by killing is not. If the concept of the dignity of living beings or the dignity of animals were to be applied, even painless killing would have to be justified. Given that prolonging life can also induce severe strain, this does not mean that death must necessarily be viewed as the greatest possible strain. The need for a general debate on the moral status of animals and other more fundamental questions concerning the assessment of strain in animal experimentation[31] is not disputed. However, the argument here will focus specifically on xenotransplantation.

As far as human interests are concerned, the justification for the strain imposed on animals is that existing and future human suffering can be alleviated by xenotransplantation, allowing people to live for longer and enjoy a good quality of life. This justification applies not only to people who sign up for initial therapeutic trials and can perhaps expect to live for a few extra months, or to those subsequent patients who require long-term monitoring and whose quality of life may be impaired in other ways. It principally concerns future patients who will gain many months, or possibly even years, of good quality of life as a result of xenotransplantation. These individuals may not have fallen sick yet – indeed, they may not even have been born yet. Even if effective public health measures can reduce the need for organ donations, there will always be some people who need organs. Even if we do not yet know who they are, we know that they will exist. There is a moral obligation to help these people. The argument goes that efforts and investments made today in the development of xenotransplantation will serve to improve organ transplantation practice. This is cited to justify current animal experiments and therapeutic trials.

This justification is therefore not primarily based on the fact that people are already receiving xenotransplants in compassionate use treatments, hoping that the treatment will be successful, but rather that future patients will be helped. Animal experiments and experimental xenotransplants carried out today pave the way for these patients to receive an animal organ in the future.

If all preventive and other clinical measures currently available have been exhausted, xenotransplantation may be the last resort for fulfilling the obligation to help these people in specific cases. Xenotransplantation is still under development, but it is already being used in human therapeutic trials. The researchers are optimistic that the technology will be developed to such an extent that the medical hurdles that still exist today, particularly with regard to kidney and heart transplants, will soon be overcome. The question under discussion in the context of the ECNH's mandate is therefore the extent to which the abovementioned strain imposed on animals can be justified for the development and application of the technology in Switzerland in order to fulfil obligations to help patients.

In order to justify animal experiments imposing strain, one must be able to assume that a gain in knowledge in the sense of a positive or negative answer to a proposed hypothesis is possible with at least minimal probability. A gain in knowledge is rarely the only reason taken into consideration. As a rule, reference is made to the practical clinical application.

For both basic research and preclinical research, the strain caused to different species must be factored in. The pigs produced in order to create xenografts

31 One such question that affects all animal experiments is, for example, which animals in the experimental phase should be included in the weighing of interests. Current animal welfare legislation requires a weighing of interests in which the strain caused to animals in animal experimentation must be justified. At present, this legal weighing of interests takes into account the total number of laboratory animals per experimental unit. Animals bred 'on reserve' and those produced specifically for an experiment but which cannot be used for that experiment due to their genetic characteristics or sex are not counted. There is also no legal weighing of interests for the breeding of animals that are not subjected to strain. Such animals only have to be reported if it subsequently transpires that they undergo strain. Moreover, only if the strain is confirmed as a trait does the breeding require authorisation and is it subject to a weighing of interests. These 'surplus' breeding animals and laboratory animals not subjected to strain currently fall under the radar.
Another question concerns the relationship between strain and animal numbers. Currently, the legally required evaluation of interests in animal experiments focuses on strain, and less on the number of animals. The relationship between strain and number is considered in lexical terms, i.e. an animal subject to strain of severity degree 3 cannot be offset by a larger number of animals subject to strain of severity degree 2. A discussion should be had as to whether the interests of 100 laboratory animals subject to strain of severity degree 2 should be weighted less heavily than those of 10 laboratory animals subject to strain of severity degree 3.

and, to an even greater extent, the primates used in preclinical research have cognitive abilities that must be taken into account when evaluating the strain involved in animal experimentation.

One argument often put forward in the debate is that xenotransplantation is just another form of established animal use. The implication is that this form of animal use is equivalent to other existing forms of use. Before considering whether this can be equated with other commercial forms of animal use, it is first necessary to clarify at what point the production of animals for xenotransplantation is no longer considered experimental. This presupposes that the process will move beyond the realm of experimentation. The question then arises as to the scenarios in which xenogeneic source animals are produced. Will each animal be produced specifically for one recipient or, more likely, for a group of recipients? Will there be established breeding lines for the production of xenografts? If there are to be breeding lines, will xenotransplantation simply be another form of established animal use, alongside those in other areas of society? If animals can be killed for food, so the argument goes, then they can also be used for the purpose of organ transplants – all the more so, in fact, since this will save lives and thus fulfil an obligation to help those who benefit in this way. The objection to this, however, is that just because a practice is socially established and accepted does not necessarily mean that it is morally acceptable. Hence, a general debate about the moral status of animals cannot be avoided here either. An ethical debate is necessary, the outcome of which could be that all or some forms of animal use are morally unacceptable. The objection shows that it is not possible to defend xenotransplantation simply by reference to other animal use practices, but that embedding xenotransplantation as another form of animal use[32] touches on fundamental issues that may also have an impact on other areas of animal use.

3.2 Further considerations on ethically relevant implications of xenotransplantation

Even if the strain imposed on animals in the context of xenotransplantation can be justified, there are other implications that need to be taken into account in an ethical assessment of the use of xenotransplantation.

3.2.1 Risks to third parties

Potential organ recipients must be informed of the risks of xenotransplantation in advance and must give their prior consent to them. This involves them weighing up the opportunities and risks of a transplant for themselves. The risks include infections and rejection of the xenograft, which can lead to death. The risks may reduce or jeopardise the suitability of xenotransplantation to prolong life, reduce suffering and improve quality of life, and must be clarified from this perspective.

Third parties[33], on the other hand, cannot consent to risks arising from xenotransplants; they are exposed to the risks without being asked. Therefore, from an ethical point of view, it must be reasonably be expected that they can accept these risks. Likewise, people involved in the transplantation, including healthcare staff and people close to xenogeneic transplant recipients, can only consent to the risk to a limited extent. For them too, it must be ensured that the risks are reasonable.

The debate around risks to third parties centres on zoonoses. Zoonoses are infectious diseases that can spread from

32 Differences should also be taken into account, such as the fact that animal losses for breeding in the established live-stock sector are much lower than for the production of xenografts. Similar to animal testing, such production requires the creation and killing of many animals that cannot subsequently be used for xenotransplantation.

33 In the discussion on risks, the term 'third parties' refers to persons who are not involved in decision-making but are nonetheless indirectly affected by the decisions made.

animals to humans. They can be transmitted through direct contact with infected animals, via contaminated food or via vectors such as insects. The use of xenogeneic organs also carries the risk of animal pathogens being transferred to the organ recipient during transplantation, which could result in further transmission to other people. A zoonotic pandemic triggered by xenotransplantation could have devastating consequences. In the worst-case scenario, a global pandemic with high rates of severe illness and death could be triggered.

The specialist literature[34] divides pathogens, as risks for immunosuppressed patients and those around them and as potential candidates for zoonoses, into three categories:

1. pathogens that absolutely must be excluded ('disqualifying pathogens');
2. pathogens that must be excluded as far as possible ('non-disqualifying pathogens');
3. pathogens not currently found in pigs (in the United States) or for which it is not known whether they can infect pigs (pathogens in the 'alert/watch' group).

Pathogens that may be hazardous to immunosuppressed patients must also be eliminated in allotransplantation, but this is not always possible under allotransplantation conditions due to time constraints. Some diseases caused by such pathogens can also be treated after transplantation. Unlike allotransplantation, which has to take place under high time pressure, xenograft production is not bound by time constraints. Pathogens can be eliminated through controlled breeding measures. However, suitable microbiological test methods do not (yet) exist for all swine-specific pathogens. Swine-specific pathogens such as porcine endogenous retrovirus (PERV) are integrated in the genome of all pigs. PERVs do not normally cause disease in either pigs or humans. However, the risks of disease for immunosuppressed organ recipients are not known. PERVs can only be removed from the genome by means of genetic engineering. This has already been done successfully. However, not all xenografts used in the US trials were free of PERVs.

Experts consider the risk of PERVs developing into a zoonosis to be very low. Indeed, for a PERV to trigger a pandemic, the virus would have to overcome several hurdles. Firstly, the animal whose organs are transferred to the recipient would need to be infected with the virus and the virus would have to be transmitted together with the xenogeneic organ. The recipient would then have to contract the virus, which would need to replicate in the recipient's body over an extended period and mutate in such a way that it could easily be transmitted to other people. The possibility of a replicative infection that is also capable of being easily transmitted via the respiratory tract cannot be entirely ruled out, but is deemed very unlikely from an infectiological point of view. In comparison, the risk of a viral disease comparable to HIV, for example, which is not transmitted through the air, is considered more plausible. Moreover, experts consider the scenario of a zoonotic pandemic arising from other direct contacts between humans and animals to be much more likely. According to experts, there are more obvious candidates within the animal kingdom for such zoonoses and the resulting pandemics than PERVs.

In its assessment of the risks, the ECNH firstly states that, from an ethical point of view, it is not relevant that the risks of a zoonotic pandemic arising through other contacts between humans and animals are comparatively higher than those arising through

34 Groenendaal, H., et al. (2023). Expert opinion on the identification, risk assessment, and mitigation of microorganisms and parasites relevant to xenotransplantation products from pigs. Xenotransplantation 30, e12815. – An earlier publication (Fishman, J. A. (2018). Infectious disease risks in xenotransplantation. Am J Transplant 18, 1857–1864) is based on a division into five categories: (1) pathogens that can cause disease in both humans and pigs, such as influenza viruses or tuberculosis bacteria; (2) pathogens that can cause disease in immunosuppressed patients, such as the parasite Toxoplasma gondii; (3) swine-specific pathogens that are related to human pathogens; (4) swine-specific pathogens that are integrated in the genome of all pigs, such as porcine endogenous retrovirus (PERV). (5) In addition, currently unknown pathogens are to be expected.

xenotransplantation. What is relevant is the absolute risk. To justify xenotransplantation as a means of improving a patient's condition, there must be no (or almost no) likelihood of a zoonotic pandemic being caused by the organ transfer, given the devastating damage that such a scenario would entail. Only then could the risk to third parties be considered reasonable.

Ensuring that a zoonotic pandemic caused in this way remains very unlikely requires the monitoring and control of xenogenic animals and xenografts. Key to this is compliance with the breeding protocols for xenogeneic source animals. However, organ recipients and those around them also need to be monitored. Infections in animal organ recipients as well as associated research, medical and healthcare personnel and relatives must be subject to more than just routine medical investigations. If an illness within this group has no other obvious explanation, the diagnostic investigation must be extended, in view of the xenotransplantation that has taken place, and additional examinations must be performed. It must also be ensured that these controls can be carried out and maintained not only in individual cases, but also on a large scale worldwide if and when xenotransplantation becomes established. In practice, this will entail the meticulous setup and flawless operation of an alert system as well as the introduction of rules whereby infected contact persons can be isolated in an ethically acceptable way.

The risks of inadequate control practices should not be underestimated. Against this background, the private interests of companies and individuals involved in xenotransplantation procedures and products must not be a decisive factor in procedural and product decisions. The welfare of organ recipients and the protection of healthcare staff, patients' relatives and the general public from zoonoses must be guaranteed. The case of the transplantation of a xenograft infected with swine pathogens in the United States in early 2022 demonstrates the importance of regulation and its application. The use of an infected xenograft could have been avoided by adequate controls. Regulatory efforts must always consider the fact that avoidable mistakes also happen. This must be borne in mind given the devastating damage scenarios that could ensue from a zoonotic pandemic, even if these are considered highly unlikely. It is important not to wait until something serious has already happened before taking action.

In order to control and minimise zoonotic risks, it is also necessary to guarantee access to research data and to xenotransplantation products and procedures. Furthermore, the current parallel discourses on the issue of zoonoses caused by animal use in general and on the zoonotic risks of xenotransplantation in particular should be joined up and every form of exchange that serves to reduce zoonotic risks should be utilised.

3.2.2 Health economic and health policy implications

Assuming the medical barriers can be overcome, xenotransplantation would be superior to allotransplantation in some respects. Unlike allotransplantation, xenotransplantation could be planned in advance and personalised, and xenografts would, in principle, be available in unlimited quantities. This could have implications for transplant medicine as a whole.

On the one hand, those involved in xenotransplantation argue that it will have positive impacts on public health. They say that the xenotransplantation of pig kidneys, for example, will deliver an overall saving of financial resources in the healthcare system, even taking into account the administration of necessary immunosuppressants and close monitoring of organ recipients and those around them, since cost-intensive dialysis is avoided.

On the other hand, such positive expectations regarding the healthcare system are countered by concerns. It is argued, conversely, that the development and introduction of new technologies such as xenotransplantation can lead to new, more numerous or more cost-intensive treatments, potentially exacerbating the problem of healthcare funding. This fundamental discussion, while meriting a mention here, relates to the healthcare system as a whole. Going into further detail would lead away from the specific issues of xenotransplantation, which are the focus of this report.

The developments in xenotransplantation could also entail risks of commercialisation and privatisation of transplant medicine. The availability of animal organs gives them advantages over human organs that make them not only medically but also financially attractive. If the success of xenotransplantation comes anywhere near to what can be achieved with allotransplantation, it could become so financially attractive as to have a disruptive impact on allotransplantation. As a first step, allotransplantation could be pushed out of the market by monopolists charging dumping prices for xenogeneic transplants, and the associated structures dissolved in order to subsequently drive up the costs of xenografts. Thus, for example, institutionalised human organ donation – which is based on altruistic motives – could be nullified by the commercialisation of xenotransplantation. Alternatively, xenotransplantation could generate its own market and the availability

and accessibility of organs could be limited in this way. In both cases, the consequences for society of privatising transplant medicine would need to be examined and assessed. To be able to gauge the plausibility and likelihood of such scenarios, the players and their financial interests would need to be known.

Studies into the health economic and health policy implications of xenotransplantation should also take into account the motives of potential organ recipients for favouring human organs, whether for religious, cultural or ideological reasons. In a pluralistic society, these types of reasons cannot determine ethical judgement and legal regulation as a whole. However, they raise the question of whether, for example, the almost exclusive focus on pigs as the organism of origin for organ transplants may entail an implicit discrimination against certain patients. This would be ethically relevant. It would therefore need to be clarified whether an irreconcilability, on religious or other grounds, exists.

The general availability of xenogeneic organs could have the desirable effect of weakening the illegal trade in human organs. Xenografts would have to be available in such a way that the demand for human organs on the black market dried up, which in turn would require that access to xenografts could not be restricted by private actors. Also, xenografts would have to be cheaper than human organs. However, assuming that breeding lines are created for the production of customised xenografts, this does not mean that animal organs will reduce the cost of a transplant, even taking into account that xenogeneic transplants may one day eliminate the need for the life-long use of immunosuppressants. A human organ on the black market would probably still be cheaper because black market prices are also governed by the laws of the market economy.

3.2.3 Research policy implications

Against the backdrop of a possible trend towards the privatisation of transplant medicine amid developments in xenotransplantation, the impacts of patenting techniques and breeding lines for xenogeneic source animals must also be considered. The fact that animal experiments imposing strain are involved in the research, development and application of xenotransplantation calls for maximum openness in the exchange of knowledge between researchers in order to minimise the number of animal experiments. However, the drive to acquire patents has the opposite effect, as researchers are also competing with each other.

This strengthens the argument in favour of public research in the field of xenotransplantation and against leaving such research in the hands of private research institutions.

4 Conclusion and recommendations

The debate around new developments in xenotransplantation is currently focused on medical and technical aspects, in particular the adaptation of xenogeneic organs and overcoming immunological hurdles. The ethical issues in relation to humans, and still more in relation to animals, remain in the background. The ECNH's mission is to bring the ethical issues of non-human biotechnology into the debate. The animal ethics aspects of xenotransplantation are therefore central to its considerations.

On the one hand, there is the obligation to help people suffering from irreversible organ damage for whom, in the face of a shortage of human organs, xenogeneic transplants may offer a last resort. On the other hand, this obligation to help patients conflicts with moral obligations towards animals. In several respects, xenotransplantation involves interventions on animals that impose strain. According to the rules governing the ethical weighing up of interests, such interventions may be justified if the moral obligation to help people is weighted higher.

It is possible that the current hurdles, particularly the immunological rejection of xenografts, could be overcome in the future and that xenogeneic transplants could become a suitable substitute for at least some human organs. If a compassionate use treatment or clinical trial involving xenogeneic transplants were to be debated in Switzerland today, the following ethical considerations would have to be taken into account with regard to the necessary weighing up of interests:

- **Is there an obligation to help?** The ECNH *unanimously* believes that there is an obligation to save lives.[35]
- **Is the means suitable?** Whether xenotransplantation is a suitable means is – as in all cases – subject to a case-by-case assessment. The assessment of suitability depends in part on the quality of the research results. Clinical trials and compassionate use treatments are carried out on seriously ill individuals, who often have other underlying health conditions. The validity of data obtained in this way for assessing the suitability of xenotransplantation must therefore be carefully and critically examined.
- **Are there alternatives?** It must be ensured that xenotransplantation is an indispensable means, i.e. the obligation to help cannot be fulfilled in any other way. The alternatives must therefore be examined in advance.
  - If social conditions can be changed so as to render fewer organ transplants necessary, then there is a moral obligation to undertake all public health endeavours in this regard.
  - All research approaches that involve fewer animals and less strain for the animals must be prioritised if there are at least comparable prospects of success. For example, all approaches and techniques aimed at restoring the body's own damaged organs and increasing the efficiency of organs available for allotransplantation must be promoted.
  - Technological and financial path dependencies that hinder the development of such research approaches must be avoided.
  - In the context of efforts to increase the willingness to donate, ethically relevant cultural, religious and ideological influences must also be taken into account.

35 Should the development of xenotransplantation enable applications that do not serve to save lives, it must be clarified how far the obligation to help extends. The discussion of the suitability criterion (section 3.1.1) excluded these possible applications and focused solely on life-saving applications. If an obligation to help was deemed not to exist in certain cases not involving the saving of lives, xenotransplantation would not be permissible in these cases owing to moral obligations towards animals.

- **Is the intervention on animals proportionate?** If an obligation to help is deemed to exist and the criteria of suitability and indispensability are fulfilled, the strain imposed on animals must be weighed against the obligations to help people. Only if the obligations to help in the individual case prevail are they proportionate and hence associated strain on the animals is reasonable.

What does this mean for the evaluation of current animal experiments in which transgenic animals are produced for the purposes of xenotransplantation or interventions imposing strain are carried out on animals? *Half of the ECNH members* consider the chances of xenogeneic organ transplantation fulfilling obligations to help people to be so high that the current strain-inducing animal experiments for the production of xenogeneic organs are proportionate and can be justified. The *other half of the members*, taking all aspects into account, consider the severe strain on primates associated with the development and preclinical research of xenotransplantation to be too high to justify the current application of xenotransplantation.

Assuming that the animal strain linked to xenotransplantation can be justified when interests are weighed up, in the next step, the possible negative effects on society must also be factored into the overall assessment:

- **Risks to third parties.** The welfare of organ recipients and the protection of healthcare staff and relatives as well as the general public from zoonoses must be the primary consideration. Potential organ recipients must agree to the risks of xenotransplantation in advance. Third parties, on the other hand, are exposed to the risks without being consulted. These include the general public as well as the healthcare staff involved in the transplant and people close to the patient. It must therefore be reasonably be expected that they can accept these risks. The risks of zoonoses take centre stage here, in particular the risks of a global zoonotic pandemic. To ensure that such a devastating scenario remains unlikely, the following measures must be taken:
  - The xenografts must be tested for pathogens based on the latest available knowledge. Regulatory efforts must consider the fact that avoidable mistakes happen and provide for appropriate safety measures.
  - There must be tight controls and long-term monitoring of organ recipients and those around them. This means that, once the technology is established, large-scale controls must be maintained on a long-term and global basis.
  - Access to research data as well as to xenotransplantation products and procedures must be guaranteed.
  - The discourses on zoonotic risks from animal use in general and on xenotransplantation in particular should be joined up and exchange on reducing zoonotic risks promoted.
  - Compliance with these points must not be left to companies under their own responsibility, but requires state regulation.

- **Health economic and health policy implications.**
  - Particular attention must be paid to the risks of commercialisation and privatisation of transplant medicine so that possible negative impacts can be assessed.
  - Privatisation must not restrict the availability of and access to organs.
  - Steps must be taken to prevent human organ donation based on altruism from being displaced, the costs of xenografts being driven up and existing structures being lost.
  - Studies into health economic and health policy implications should also take into account the motives of potential organ recipients for favouring human organs, whether of a religious, cultural or ideological nature.

- **Research policy implications.** The patenting of procedures and xenogeneic animal breeding lines by private actors may impair the open exchange of knowledge. However, such exchange is essential in order to minimise the number of animal experiments. Relevant implications for research policy must be kept in mind so that countermeasures can be taken in good time if necessary.

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