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Xenotransplantation in the Age of Genome Editing: Results From the Expert Report for the Federal Ethics Committee on Nonhuman Biotechnology With a Special Focus on Animal Ethics

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ABSTRACT

Background: The Federal Ethics Committee on Non-Human Biotechnology (ECNH) of Switzerland is an independent expert committee appointed by the Federal Council and mandated to advise the federal authorities from an ethical perspective in the field of nonhuman biotechnology and gene technology. Due to recent developments in the field of xenotransplantation after the introduction of genome editing technologies, the ECNH has commissioned an expert report on the ethical questions of xenotransplantation with a focus on animal ethics. The subject of the inquiry is, in particular, if current developments in the field of xenotransplantation raise new questions regarding ethics in the nonhuman realm or if existing questions have to be re-examined and answered anew.

Methods: An interdisciplinary approach was applied to answer this question. Based on the latest empirical results from medicine and biotechnology, xenotransplantation is analyzed and evaluated with reference to the dignity of the creature (*Würde der Kreatur)*—which is defined in the Swiss Federal Constitution—and the dignity of animals (*Tierwürde*) that is stipulated in the Swiss Animal Welfare Act and the Federal Act on Non-Human Gene Technology, as well as contemporary positions in the ethics of the human–animal relationship.

Results: The report concludes that genome editing for xenotransplantation does not generate any qualitatively new ethical issues concerning ethics in the nonhuman realm.

However, contemporary biotechnological developments must be taken as an opportunity to discuss existing ethical issues in an urgent and intensified manner, particularly regarding the significance of animals' moral standing. The lack of consideration of animal-related aspects and the neglect of current developments and the state of the art of animal ethics in the recent

Abbreviations: AWA, Swiss Animal Welfare Act; B4GALNT2, beta-1,4-*N*-acetyl-galactosaminyltransferase 2; CMAH, cytidine monophosphate-*N*-acetylneuraminic acid hydroxylase; CRISPR/Cas, clustered regularly interspaced short palindromic repeats; ECNH, Federal Ethics Committee on Non-Human Biotechnology; GE, genome editing; GGTA1, alpha-1,3-galactosyltransferase; GTA, Federal Act on Non-Human Gene Technology (Gene Technology Act); PERV, porcine endogenous retroviruses; SCNT, somatic cell nuclear cloning; TALEN, transcription activator-like effector nucleases; XT, xenotransplantation; ZFN, zinc finger nuclease.

The expert report *Xenotransplantation. Neue gentechnische Möglichkeiten–neue ethische Fragen?* (Beiträge zur Ethik und Biotechnologie, Bd. 16), Bern: Bundesamt für Bauten und Logistik BBL: 2023 was written on behalf of the ECNH in 2022. It is available open access at https://www.ekah.admin.ch/de/externe-gutachten/buchreihe-beitraege-zur-ethik-und-biotechnologie. This article was written during the APART-GSK fellowship (Austrian Academy of Sciences) and contains updated literature.

discussion about xenotransplantation is a scientific, ethical, and political issue because animals are most negatively affected by xenotransplantation. This is especially relevant because the contemporary state of the art in animal ethics tends to consider and protect animals more strongly than in the past.

1 | Introduction

As in other biotechnological application fields, so-called genome editing technologies (GE), notably CRISPR/Cas9, have revolutionized xenotransplantation (XT) research [1–3]. By conferring the possibility of carrying out precise and multiple interventions in the animal genome at the same time, these procedures have overcome or reduced key medical challenges, so that the transplantation of animal organs is now closer to the clinical application phase than ever before [4]. The recent achievements in the field include several transplantations of pig kidneys into brain-dead humans starting in 2021 and two successful pig heart implantations into living persons in 2022 and 2023, and the latest pig kidneys and pig liver transplantation into living humans in 2024 [5–12]. The first patient survived for 2 months postsurgery and the second for 6 weeks with a 10-fold genetically modified pig heart. Further clinical heart trials are planned for 2025 [13]. Although the history of XT has shown that concrete predictions are hard to make and although the research for various organs is at different stages of progress, the slogan of the surgeon Norman Shumway "Xenotransplantation is the future, and always will be" is no longer valid in general [3, 14].

XT is a complex field that encompasses medical and scientific aspects but also raises questions concerning the humanities and ethics. While it was pointed out at the turn of the millennium that almost all ethical contributions on XT also addressed aspects that concern animal ethics and discussed animal-related aspects [15], the current state is that the medical-technical discussion dominates the human ethical and, even more so, the animal ethical discussion. For instance, a review article by Nienke de Graeff et al. [16] revealed several ethically relevant insights, including that the debate about GE is dominated by the natural sciences, whereby the focus lies on technical feasibility. Hence, if ethical aspects are discussed, they are approached from consequentialism, and animal-related aspects are mainly absent [16], whereby the same is true for genome-edited XT. This is problematic for several reasons.

First of all, ethical permissibility is the precondition to pursuing XT as a research and treatment approach and has to be assessed independently from the realization and technical feasibility. This means that, in addition to the feasibility of the overriding objectives of XT, namely prolonging and improving the quality of life, the question of whether the transplantation of animal organs is an ethically acceptable means to achieving these ends is crucial.

Second, apart from human-related aspects, animal-related aspects must also be taken into account when examining the ethical acceptability of XT. The lack or complete absence of reflection on animal ethics was already criticized by the ECNH 20 years ago and is still highlighted in national and international reports and guidelines regarding XT or GE [17–20]. Regarding the current state of the art in the field of animal ethics, this deficiency weighs even more (see Section 4.6). Over the last 20 years, it is not only biotechnology that has developed further but also ethics in the nonhuman realm. With concepts such as the dignity of creature, the integrity approach, and the telos approach, ethical approaches have been developed that allow the ethical evaluation of genetic modification of animals that go beyond the sentientist paradigm.[1] In contrast to traditional animal welfare concepts, which focus primarily or exclusively on subjectively experienced (animal) welfare, these approaches facilitate the assessment of genetic engineering by using a nonsentient concept of harm and "harmless wrongdoing" such as excessive instrumentalization. Both are ethically relevant criteria that go beyond subjective welfare. The biotechnological developments were further accompanied by the inclusion of nonsentient animals in moral considerations. However, regarding the moral significance of animals, the majority of proponents of these concepts supported hierarchical positions and did not advocate a ban on genetic engineering.

Lastly, and most importantly, disregarding or not addressing aspects of animal ethics means ignoring those beings that are most negatively affected by XT, both now and in the future.[2] Given that the animals used in XT count morally, it is ethically imperative to take them into account in the ethical analysis and evaluation of XT.

2 | Materials and Methods: Subject and Purpose of the Report

In 1998, the Federal Ethics Committee on Non-Human Biotechnology (ECNH) of Switzerland was appointed by the Federal Council to observe new developments and applications of nonhuman biotechnology and gene technology and assess them from an ethical perspective. The committee covers the disciplines of philosophical ethics, theological ethics, environmental philosophy, law, agricultural sciences, veterinary medicine, biology, and molecular biology. As an extra-parliamentary committee, it is among other tasks concerned with ensuring that respect is given to the constitutional principle of the dignity of creatures (*Würde der Kreatur*) and informing the public on ethical issues regarding biotechnology.

Due to recent developments in the field of XT research, the ECNH has commissioned an expert report on the ethical questions of XT after the introduction of GE methods. Additionally to the ethics report and in order to gain an overview of the potential and prospects of alternatives to XT–which are relevant for the balancing of interest procedure (see below para. 4.5)–the ECNH commissioned a literature study and consulted experts from the fields of surgery, immunology, veterinary medicine and laboratory animal medicine.[3] The ethics report is intended to

provide an overview and an analysis of ethical issues in the nonhuman realm in the context of GE procedures for XT and focuses on the following questions:

- Do current developments in the field of XT raise new questions regarding ethics in the nonhuman realm?
- Do existing questions have to be re-examined and answered anew?

The study serves the ECNH as a basis for discussion of ethical issues raised by new developments in XT research. In particular, the Swiss constitutional principle of the dignity of creature (Art. 120 Const.), the dignity of animal in the Swiss Animal Welfare Act (Art. 3a AWA), and the Federal Act on Non-Human Gene Technology (Art. 8 Gene Technology Act GTA), as well as current developments in the ethics of the human–animal relationship are taken into account. As an *ethical treatise*, the report allows to adopt a critical distance from Swiss law and to reflect on it against the backdrop of current research in animal ethics. The ethical analysis and evaluation of XT, with special consideration of GE technologies in relation to the dignity of creature and current developments in the ethics of the human–animal relationship, breaks new ground, at least in part, and makes a genuine contribution to XT research from an ethical perspective.

It should be noted that XT is not a homogeneous area of transplantation medicine that allows a uniform ethical assessment as it comprises different sub-areas (cells, tissue, and organs) that are at varied stages of development. As the latest biotechnological advances particularly relate to the XT of organs, and for pragmatic reasons, this report focuses on the transplantation of organs, specifically the heart. Further ethical reflections on other organs would be desirable.

Due to the complex and multidisciplinary nature of the XT research, the inquiry encompasses medical and scientific aspects while also considering questions that concern the humanities and ethics. Therefore, an interdisciplinary approach is applied. In the first step, methodological and metaethical considerations are outlined. Second, with a focus on GE, various procedures and their role in solving medical issues are introduced. Third, an overview of ethical issues is drawn up based on previous studies, expert reports, and relevant literature, and it is examined whether—and to what extent—the ethical conclusions need to be reassessed against the background of GE procedures. For pragmatic reasons, the ethical evaluation focuses on genetically modified pigs as organ source animals and the nonhuman primates used in preclinical experiments as organ recipient animals. Animals that are used in basic research in surgery, immunology, virology, and biochemistry and are directly related to XT were only marginally considered in this study.

The report comprises a total of 191 pages. In this journal article, biotechnological principles are described briefly and only the key points that are relevant for the ethical evaluation are mentioned. Considerations about the interdisciplinarity and entanglement of descriptive and normative judgments, the relationship between human and nonhuman ethics, and reflections on justifications of XT (such as the present-usage argument, the human-priority argument, the argument of solidarity, and whether XT represents an ethical dilemma) unfortunately cannot be discussed here. Due to the dynamic nature of XT research, new literature that is ethically relevant is included and added to the report.

3 | Biotechnological and Medical Principles

The overriding aim of XT is to prolong and improve the quality of life of patients affected by irreversible organ failure. The advantages of XT over allotransplantation include the following:

- availability, number, and quality of organs;
- plannability of transplantations;
- avoidance of viral infections (e.g., hepatitis-, herpesviruses); and
- reduction of immunological rejection reactions (custom-made organs).

However, before these advantages can be utilized, three medical hurdles must be overcome [21]: first, to ensure the physiological function of the animal organs; second, to overcome the immunological defense reactions triggered by the foreign organ; and third, to control the infectious risks of so-called xenozoonoses, which could pose an individual danger to patients and society. To solve these problems, high expectations are placed on biotechnology and, recently, GE technologies.

3.1 | Biotechnological Solutions for Medical Problems

GE methods include molecular biological technologies such as zinc finger nuclease (ZFN), transcription activator-like effector nucleases (TALEN), or clustered regularly interspaced short palindromic repeats (CRISPR/Cas).

The basic principle of GE consists of identifying a specific genome sequence and inducing a site-specific double-strand break in the DNA, which triggers cellular repair mechanisms in which the affected genes can lose their function (knock-down or knock-out). CRISPR/Cas can also be used to introduce DNA sequences in a targeted manner (knock-in) or to replace endogenous sequences. In ZFN and TALEN, proteins, and in CRISPR/Cas a so-called single guide RNA (sgRNA) are used as a probe to specifically detect the desired gene segments and then separate the DNA with "nuclease scissors" [22].

Between 2011 and 2016, over 300 genome-edited cattle, sheep, and pigs were produced [23]. An overview of genetically modified swine to date and the possible modifications provided an estimation of the scientific potential of GE methods for genetically modifying animals [3, 24–26].

An analysis of recent milestones of the XT research reveals that GE was successfully applied to solve problems in all three areas (physiology, immunology, and xenozoonoses, including PERV). One reason why GE was responsible for the new impetus of XT is that the production of multiple genetically modified animals has not only become simpler and less time-consuming but GE can

also be applied highly efficiently to species that were previously far less suitable for genetic modification than classic laboratory rodents.

While the breeding of multi-modified xenogenic pigs using conventional genetic engineering methods took several years, xenogenic pigs with the same genetic modification can be produced in a few months using CRISPR/Cas, as several modifications can be made simultaneously in the animal's genome [1, 27]. In two compassionate use trials mentioned above, tenfold modified pig hearts were used, while other pigs exist with a thirty-fold modified genome [28].

The possibility of simultaneously performing multiple knockouts and knock-ins on XT-relevant genes has sparked a new debate in XT research, which centers around the question of how many genetic modifications are optimal [24, 26]. This question is also ethically relevant because certain modifications could have negative side effects on the health and welfare of GE animals (see Sections 3.2, 3.3, 4.3, and 4.4). The more the animal genome is interfered with, the higher the risk of unforeseen interactions between the various interventions [29]. Furthermore, it is currently not known whether a genetically edited standard pig is the ideal solution for all organs or whether a separate, differently genetically modified animal should be preferred for each organ.

3.2 | Genome Editing: Precision, Efficiency, and Security

So far, CRISPR/Cas9 [30], TALEN [31], and ZFN [32] have been applied successfully in pigs for the use of XT. Unfortunately, despite the prevailing notion that GE is "easier, cheaper, and more efficient," only limited data is available. As Jarrod Bailey states: "While this method [CRISPR/Cas9; S.C.] is generally considered to be much more efficient and specific compared to other approaches, any accurate, definitive, quantitative estimation of the efficiency of CRISPR is difficult to find, as estimates vary considerably and are affected by many factors, including the nature of the target site and the CRISPR molecule used" [33].

A valid analysis and evaluation of GE methods should distinguish between *on-target efficiency*, *unintended on-target effects*, and *unintended off-target effects*. Moreover, for an ethical analysis, data should be collected that relates these efficiency rates to animal health and welfare. While the lack of ethically relevant data in scientific publications on XT has already been criticized in the past, this aspect concerns biotechnology in general [34, 35].

3.3 | Genome Editing and Somatic Cell Nuclear Transfer Cloning

Interestingly (and often not clearly communicated in public media), GE technologies do not simply substitute 1st generation genetic modification technologies and somatic cell nuclear cloning (SCNT cloning), as the latter is still in use. First-generation geotechnologies are used synchronically or in conjunction with GE and it will be shown that the combination of GE with SCNT cloning is ethically relevant, as sufficient health and welfare-related data concerning this aspect are available.

The history of SCNT cloning and XT is closely linked. For instance, in the publication concerning the first successfully SCNT cloned pig, it is mentioned how cloning could be used to breed αGal-deficient pigs, whose organs would trigger weaker immunologic defense reactions in the human body [36]. The recent milestones of XT show that SCNT cloning is prominently represented in the production of genetically modified animals [37].

The problem with SCNT cloning, however, is that even today it is generally a challenging technique, which has remained unsafe and inefficient, although significant species-specific differences exist [23, 27, 38]. These differences depend on the species, as well as the type and age of the donor cell. The live birth rate (LBR: live born animals per transferred embryos) in pigs persists at a value of circa 6% and a range between 0.6% and 7%. Some of the clones born alive suffer from health-related strains, which can be lethal [39, 40]. These include diarrhea, meningitis, cardio-pulmonary functional abnormalities and cerebromeningitis, malformations, asphyxia through *respiratory distress syndrome*, or (in pigs) *adult clone sudden death syndrome* [41, 42]. If the offspring of the clones are born through conventional breeding techniques, neither of these health and welfare-related strains appear.

To summarize, the probability that SCNT cloning of pigs results in abortions at different stages of gestation, deformities, and weak young animals is high. According to the Swiss strain scale[4], the health and welfare risks for the animals involved in SCNT cloning range from no strains to mild, moderate, and severe strains (e.g., lung failure or heart insufficiency of the clone) [40].

If GE processes are combined with SCNT clones, this can have an additional negative impact on animal welfare and health [16, 20]. Even if GE methods are generally simpler, cheaper, and more efficient than traditional genetic engineering methods, and GE in combination with cloning is currently the best method for minimizing experimental animal numbers (evaluation of off-target effects), from an animal ethics perspective the question arises of whether this combination is *safe enough* for the animals.

4 | Ethical Analysis and Evaluation With Regard to the Swiss Dignity Concept

The main questions the ethical analysis follows are:

(4.1) Is a morally relevant entity E instrumentalized to generate a scientific or medical benefit?

(4.2–4.4) Does the instrumentalization of E involve harm to E?

(4.5, 4.6) How can the harmful instrumentalization be justified?

The normative relevant framework, which is relied upon in the report evaluating XT is the so-called "dignity of creature" or, in our case more specifically, the "dignity of animals" approach. Due to its incorporation into the Swiss Constitution in 1992 (Art. 120 para. 2 Const.), the Animal Welfare Act in 2005 (Art. 3 lit

a AWA), and the Federal Act on Non-Human Gene Technology (Art. 8 GTA), it became one of the most addressed and also very controversially discussed topics in the German-speaking animal ethics discourse [43]. The concept of animal dignity that is relevant in this context can be described as a *hierarchical biocentric approach* that is based on a *neo-Kantian traditional* notion of dignity, with a combination of *sentient* and *non-sentient harm concepts*. According to the Swiss Animal Welfare Act (Art. 3 lit. b AWA), dignity is defined as the "Inherent worth of the animal that has to be taken into account when handling it." The concept of "inherent worth" is well-known within animal ethics and refers to the claim that we should behave morally toward them for their own sake. Hence, moral agents would not behave morally toward animals if they only value them based on their aesthetic, culinary, social, or other instrumental values and treat them well accordingly. Every being that has an inherent worth thus has to be respected independently of its benefit to others.

Before analyzing and evaluating XT, the Swiss dignity concept and its elements (hierarchic biocentrism, neo-Kantianism, sentient, and nonsentient harm concepts) will be introduced.

4.1 | The Moral Status of the Organ Source and Recipient Animals

The dignity of creature position can be described as the hierarchic biocentrism concerning moral status and hence regarding the question of which entities are morally relevant. For the ethical assessment, the question of who will be considered morally is crucial. Entities that have a moral status belong to the moral community and can be instrumentalized and harmed in a morally relevant way. Moreover, entities that belong to the moral community may not be instrumentalized arbitrarily, because any harm must be justified on morally relevant grounds.

Biocentrism claims that all (and only) living beings count morally, and living beings are defined as entities that can flourish. Following the functional approach of Aristotle, Christine Korsgaards defines "flourishing" as follows: "A living thing just as such may also be viewed as a functional system, as Aristotle taught us: we can view its function as a kind of self-maintenance, or survival and reproduction, or as leading the life characteristic of its kind" [44]. This definition incorporates vertebrate and nonvertebrate animals, plants, and other organisms into the moral community. According to this biocentric position, all animals that are part of XT research are morally relevant from the stage at which they can develop independently.

At this point, it should be highlighted that, for practical reasons, the Swiss Animal Welfare Act only refers to sentient animals, which constitutes an impermissible restriction to the biocentric concept. According to the Federal Food Safety and Veterinary Office, and Austrian and German law, it is assumed that in mammals, including pigs and primates, sentience is present in the last third of pregnancy (cf. BLV 2010).[5] However, Switzerland's biocentrism is generally understood as a hierarchical biocentrism, whereby the hierarchy roughly follows the complexity of the organism, in addition to cultural and practical considerations for which it must be clarified to what extent they are ethically sound or even relevant.

4.2 | Are Xenogenic Pigs and Nonhuman Primates Harmed?

Because pigs and nonhuman primates have a moral status, it is morally relevant if they are harmed during XT, and if so, how the harm can be justified.

What it means to be harmed, and what kind of harm is morally relevant, is mentioned in the Swiss AWA and the GTA. Concerning the quality of harm, two different harm concepts [45] have to be distinguished, both of which are part of the AWA.

Sentientism claims that the subjective perception of an animal is the normative relevant point of reference for determining harm. According to sentientism, sentience is a necessary prerequisite for defining a morally relevant harm. In contrast, *nonsentientism* claims that it is also possible to speak of morally relevant harm that is independent of subjective experience. According to this harm concept, it is also appropriate to talk about harm if the above-mentioned species-specific features such as self-maintenance, survival, reproduction, or leading the life characteristic of its kind are prevented by human intervention. Since the death of living beings stops all these species-specific behaviors, death and the action of killing is the ultimate harm. The fact that the protection of life is not yet explicitly stipulated in Swiss law has already been criticized several times [46–48].

Although the Swiss AWA (Art. 3 lit, b AWA) speaks of "strains" and not "harms" the two ethical harm concepts are clearly present in the formulation of how the dignity of an animal can be disregarded:

> "If any strain (*Belastungen*) 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 in particular if pain, suffering or harm is inflicted on the animal, if it is exposed to anxiety or humiliation, if there is [a] major interference with its appearance or its abilities, or if it is excessively instrumentalized."

In this context, pain, suffering, and anxiety refer to sentient harms while a "major interference with its appearance or its abilities" refers to non-sentient harms. In this paragraph, two further ways in which dignity can be disregarded are mentioned, namely through humiliation and excessive instrumentalization. Although "humiliation" is critically addressed, how it fits into a biocentric approach will not be considered in more depth in this article, whereas "excessive instrumentalization" is regarded as the paradigmatic dignity violation [49]. Adapting Immanuel Kant's second formula of the categorical imperative, it claims that animals are not mere means and instruments to be used for whatever end one likes.

In the following, it will be analyzed whether and how animals are negatively affected by sentient and nonsentient harms and excessive instrumentalization in the process of XT. This process involves the following steps:

- generating genetically modified pigs,

- husbandry conditions in pathogen-free laboratories for genetically modified pigs,
- organ removal and killing of genetically modified pigs,
- transplantation of the xenogenic organs into nonhuman primates and postoperative phase, and
- the killing of the recipient animals.

It must be pointed out that a discussion of all aspects relevant to animal ethics exceeds the scope of the almost 200-page report and this article. As a result, the article focuses on paradigmatic cases.

4.3 | Sentient Harms

The pigs bred for XT are genetically modified animals that are bred specifically for XT, and both classic and new genetic engineering methods are applied for their modification. In contrast to the development of drugs and other treatments, where a disease or individual symptoms are simulated in an animal model that affects the welfare of the animals, XT aims to produce animals that are as healthy as possible. However, genetic modifications such as adding (knock-in), removing (knock-out), switching off or weakening gene expression (knock-down), or replacing individual gene sequences, can have unintended effects on the health or welfare of genetically modified pigs.

Significantly, the genetic modifications are too diverse—ranging from a single GGTA1 knock-out to over 50-fold modifications that include knockouts and humanizations—to make general statements on the health risks of xenogeneic pigs. While fewer surplus animals can be expected with the new GE technologies, if SCNT cloning is involved to generate genetically modified pigs, abortions at different stages of gestation deformities, and weak young animals are still to be expected. Low birth weight, low cloning efficiency, and health problems are not uncommon in paradigmatic GGTA1 knockout pigs [50], and the health and welfare risks for the animals range from no strains to mild, moderate, and severe strains (e.g., lung failure or heart insufficiency of the clone).

To minimize the risk of infection with pathogenic microorganisms—bacteria, parasites, fungi, and viruses—for human patients, the genetically modified pigs are bred and kept in special, pathogen-free facilities (SPF for specific pathogen-free or DPF for defined pathogen-free). These husbandry conditions include among others: the birth of piglets by cesarean section or hysterectomy (removal of the uterus of the mother sow); avoidance of contact between the piglets and the sow and the sow's milk; piglets reared in isolators, fed with sterilized feed (2 weeks); transfer to group housing with sterilized feed, water, filtered air, regular health checks, blood and tissue samples. SPF or DPF conditions include mild to moderate degrees of severity and here, too, it must be noted that the laboratories may differ in terms of equipment, husbandry, and enrichment methods (play and activity opportunities). However, contrary to the statements of Bobier et al. [51], it is doubtful whether the SPF or DPF conditions will satisfy the natural behaviors and needs of pigs, whose broad behavioral repertoire and complex cognitive and emotional abilities are comparable to those of dogs and chimpanzees [52].

Although it is not possible to determine the exact number of nonhuman primates that were used for XT in the last 20 years, the number of organ recipient primates—particularly baboons and cynomolgus monkeys—for transplanted pig hearts, kidneys, livers, and lungs in North America, Europe, and Russia alone exceeded 1800 animals between 1998 and 2013 [53]. For example, 760 baboons and cynomolgus monkeys were used to test xenogenic hearts.

With an adequate anesthetic and postoperative analgesia regiment, the sentient harm of the postoperative phase of the XT can be minimized for the organ recipient [54]. Nevertheless, according to the exposure categories of the Swiss Federal Food Safety and Veterinary Office (FSVO), orthotopic XT is classified as a severe constraint and therefore falls under the highest severity degree (severity grade 3), whereas heterotopic XT is classified as a moderate strain (severity grade 2). This assessment is shared by the severity categorization of Directive 2010/63/EU of the European Union, where XT counts as procedures "where organ rejection is likely to lead to severe distress or impairment of the general condition of the animals" [55]. This is due to the fact that the following unforeseeable causes of death can occur: dysfunction of organs, kidney failure, liver failure, brain damage, (superior vena cava) thrombosis, lung failure, pancreatitis, or sepsis. In addition, the application of immunosuppressive drugs can have such serious side effects that the monkeys have to be euthanized, and prolonged isolation or individual housing after the surgery cause also severe strains.

4.4 | Nonsentient Harms and Excessive Instrumentalization

The nonsentient harms are described as "major interference with its appearance or its abilities" (Art. 3 lit a AWA) or, formulated slightly differently in the GTA, as a substantial change of an animal's "species-specific characteristics, functions or ways of life" (Art. 8 para. 1 GTA). In contrast to the sentient harms, the nonsentient harms do not have to be subjectively experienced, but they can be objectively observed. While interferences with the appearance of a genetically modified animal are not intended in XT, the various modifications such as humanization and knock-out of growth hormone receptor genes are paradigmatic cases of changing species-specific characteristics or interference with an animal's abilities. However, whether these modifications are major or substantial is questionable. Further, it is not clear if other genetic modifications such as the knock-out of GGTA1, CMAH, B4GALNT2, or the inactivation of PERV-C violate the species-specific characteristic. In this regard, the dignity of creature position (and other biocentric approaches) falls short in identifying a species-specific norm that serves the purpose of ethically assessing genetic modifications.

The "excessive instrumentalization" strain is a complex category and it exceeds the scope of this article to discuss it in depth. Fundamentally, it builds on the idea that every animal that has an inherent moral worth has to be respected independently of its benefit to others. Hence, if the value of an animal is

TABLE 1 | Animal's dignity and the balancing of interest procedure stated in the Swiss Animal Welfare Act.

Definition:	**Animal's dignity = inherent worth that has to be taken into account when handling it**	
	Handling	
	Strains	**No strains** = dignity is regarded
Level 1	Sentient strains: pain, suffering, harm, anxiety Non-sentient strains: major interference with its appearance or species-specific characteristics Harmless wrongdoing: Humiliation, excessive instrumentalization	
	Balancing of interests between animal's strains and humaninterests	
Level 2	animal's strains outweigh human interest = dignity is disregarded	Human interests outweigh animal's strain = dignity is regarded

merely or mainly given because of its instrumental value—for example, to serve as an organ source—it is a form of unpermitted instrumentalization. Indicators for excessive instrumentalization are breeding for external purposes, manipulation of the genome that involves health and welfare risks, a strongly heteronomously controlled life, and killing for external purposes. Since the transgenic pigs are bred for the sole purpose of providing organs for humans, which is associated with health and welfare risks and finally ends in an unnatural, premature death for the pigs, the indicators are unambiguous, namely that the instrumental value is weighted more heavily than the inherent worth of animals and nonhuman primates.

To summarize, it is evident that, given the deliberations outlined up to this point, all animals involved in XT are negatively affected by sentient harm and partially by nonsentient harm. These harms range from minimal to severe. Further, the animals are excessively instrumentalized. Since the Swiss dignity concept does not provide absolute protection, the next step is to evaluate whether these violations of dignity can be justified.

4.5 | Balancing of Interests

As stated in the Swiss AWA, the imposition of strains or harms on the animal can be justified by overriding interests within a procedure of balancing interests (*Güterabwägung*). The Swiss concept can be described as a two-level concept (see Table 1).

Level 1: After clarifying, if the criteria of instrumental suitability and indispensability of XT—which cannot be discussed here[6]—are met it has to be examined, if strains are present in handling with an animal. If no strains are involved the dignity is regarded and the handling is permitted.

Level 2: If strains are present and the dignity of the animal is negatively affected, it has to be assessed, if the intervention on animals is proportionate. Several interests thus need to be weight against each other within an act of balancing of interests, to justify XT and its research.

For instance, the strains include *sentient harms* (pain and suffering anxiety), *nonsentient harms* (major interference with its appearance, resp. species-specific characteristics, functions, or ways of life), *humiliation*, and *excessive instrumentalization*. Among the human interests regarding XT are human health and quality of life. Hence, if the strains on the animal's side outweigh the interests on the human side, dignity is disregarded and the procedure is morally wrong. However, if the human interests outweigh the animal's strains, dignity is regarded and morally permitted or even demanded. The balancing of interests includes the following procedures:

- XT (xenogenic pig versus human recipient),
- breeding of xenogenic pig versus human recipient,
- testing of xenografts on nonhuman primates vs. human recipients, and
- basic and applied research in the fields of immunology, surgery, and so forth versus human recipient.

As outlined above, while XT affects important human interests such as quality of life and health, it is difficult to determine whether and, if so, for how long the xenografts will function in the human body. Data on the quality of life of xenotransplant recipients is also not yet available. Even if the dignity of creature approach is a hierarchical approach in which human interests count more than those of animals, human interests do not always outweigh those of animals. Firstly, because the strains on the animals also include moderate and severe strains (severity grades 2 and 3), the mere survival of a human patient—regardless of the quality of life and life span—will not justify the excessive instrumentalization and killing of healthy animals. This issue will be further elaborated in the discussion part. Preclinical research to test genome-edited pig hearts in nonhuman primates is thus crucial because these animals enjoy a high level of protection. Second, while the strains for the animals are very likely and predictable, the gains for patients are not (yet) predictable. This means the actual death and strains of the pig (sentient and nonsentient harms, excessive instrumentalization) and the severe strain of the nonhuman primate (sentient and nonsentient

harm, excessive instrumentalization) on the one hand contrast an indeterminate benefit (life span and quality of life) of the patient on the other hand.[7]

4.6 | XT in the Context of Contemporary Animal Ethics

The hierarchical biocentrism with a combination of neo-Kantian and consequentialist elements is a very unique position among other perspectives within the ethics of human–animal relationships. At the moment, over 10 different, sometimes overlapping, complementing but also competing and mutually excluding positions exist [56]. This diversity has not yet found its way into the ethical debate about XT. In other words, the current state of art is strongly neglected. To solve this problem, ethicists should consider current developments in XT and address ethical issues, while scientists should approach others to acquire ethical expertise. This is crucial because ethical permissibility is the precondition for pursuing XT as a research and treatment approach.

Regarding the balancing of interest procedure, it should be noted that it is not regularly applied and promoted in many other approaches as a regular instrument to assess what ought to be done. It is rejected and criticized because other positions claim stronger protection for members of the moral community, and this has a large impact on the evaluation of XT. In the following, XT is put into the context of animal ethics positions that reject the balancing of interest procedure, and their perspective on XT is outlined.

The British pacifist and co-founder of the Humanitarian League, Henry S. Salt drew the following conclusion as early as 1892: "Have the lower animals 'rights?' Undoubtedly–if men have" [57]. However, it took almost 90 years for the American philosopher Tom Regan (1984) to counter the previously dominant utilitarianism with his theory of animal rights. In contrast to utilitarianism and the Swiss dignity of creature position, the animal rights view protects the life and bodily integrity of all members of the moral community by means of a strong right of defense that can only be trumped in very few exceptional cases, such as self-defense [58]. Building on such a view, several philosophers demand a stronger moral, political, and legal consideration of animal interests. For the case of XT, this perspective—in conjunction with the claim that all sentient animals should be protected by moral rights—leads to the conclusion that XT and the research associated with it is not a morally permissible means of addressing the problem of organ demand.

The fact [59] that at least 10 companies worldwide consider XT and the breeding of GE-modified animals for the production of xenotransplants as a current or future business model—including Smithfield Foods [60], the largest pork producer in the world—shows that animals are regarded as an economic and scientific resource, whereby they are systematically institutionalized and legally harmed and killed. This presents a profound moral problem. Instead of claiming a relationship of morally condemnable instrumentalization or exploitation with animals, it is also possible to understand animals as friends, neighbors, fellow creatures, or companions (as can be the case with cats and dogs) or even fellow citizens [61] with whom we should be able to share the resources of this planet and live together with as little conflict as possible.

5 | Results and Discussion

XT is a complex research field that encompasses not only medical and scientific but also ethical issues. In the nonhuman realm, this concerns animal life and animal welfare, which are affected by the breeding, housing, and organ retrieval of genetically modified pig hearts, and the testing of these organs on nonhuman primates and animals that are used for fundamental XT research.

As in other biotechnological application fields, genome editing technologies (GE), notably CRISPR/Cas9, have revolutionized xenotransplantation (XT) research.

Do current developments in the field of XT raise new questions regarding ethics in the nonhuman realm? GE does not generate any qualitatively novel ethical issues concerning animal ethics in the context of XT and the dignity of creatures. This concerns especially sentient and nonsentient harms. While the scientific advantages and improvements of GE, there are hardly any improvements in ethically relevant parameters such as consideration of animal welfare, respect for inherent worth, or respect for physical and genomic integrity. Theoretically, due to the precision and higher efficiency of GE procedures compared to classical genetic engineering methods, fewer surplus animals might be generated in specific experiments. However, since the possibility of simultaneously performing multiple knock-outs and knock-ins on XT-relevant genes opens up a multitude of new scientific applications, an increase in animal usage is expected. Furthermore, the moral problem is that multiple edits to the animal genome increase the likelihood that the animal organism will not develop normally. This concerns both animal welfare (sentient harms) and species-specific characteristics, functions, or ways of life (nonsentient harms) only quantitatively.

Do existing questions have to be re-examined and answered anew? In terms of ethics in the human realm and criteria of instrumental suitability, PERVs can be inactivated through multiple genetic engineering edits, thereby reducing the risk to humans. This mitigates the criticism of xenozoonoses. In terms of ethics in the nonhuman realm, since the advent of GE technologies, the current developments and state of the art in animal ethics have been neglected in the recent XT debate. This presents a significant limitation in the discourse because animals are most negatively affected by XT. Thus the contemporary biotechnological developments must be used as an opportunity to discuss existing ethical issues in an intensified and urgent manner.

This concerns, for example, (i) the moral significance and value of the life of a pig or a nonhuman primate and that of a human. The ethical justification of XT in the future will hinge on two crucial questions: not only how long patients with xeno-organs will survive, but also what quality of life they will have. (ii) The challenge of hierarchical positions is further to justify a nonarbitrary gradation. This hierarchy concerns the distinction between humans (primates) and nonhuman primates, as well

as between nonhuman primates and pigs. These two issues especially relevant because the contemporary state of the art in animal ethics tends to consider and protect animals more strongly than in the past.

Because ethical permissibility is the precondition to pursuing XT as a research and treatment approach, it should be given appropriate consideration. (iii) In this regard, ethicists should consider current developments in XT and address ethical issues while scientists should approach the humanities to acquire ethical expertise. In terms of good scientific practice, the ethical analysis could be improved if scientific journals would provide and simplify access to ethically relevant data such as the number of animals used and severity degrees independently of national and international legislation. (iv) The subject of the expert report was the Swiss context. Due to the international interdependence of science, a comparative global study of ethical XT regulations and their relation to the current state of animal ethics would be beneficial.

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Endnotes

[1] The telos approach was developed by Bernhard E. Rollin (1995). It is based on the idea that every living being has a certain nature or life form that is characterized by specific genetically determined interests, which are expressed in the environment. Bart Rutgers and Robert Heeger define animal integrity as follows: "The wholeness and completeness of the animal and the species-specific balance of the creature, as well as the animal's ability to maintain itself independently in a species-appropriate environment." What both approaches have in common is that they do not reject genetic modifications per se, but they allow interventions to be declared as harm that lies beyond subjective feelings.See Rollin B.E. *The Frankenstein Syndrome. Ethical and Social Issues in the Genetic Engineering of Animals*, Cambridge: Cambridge University Press; 1995. Rutgers, Bart/Heeger, Robert (1999): Inherent Worth and Respect for Animal Integritiy. In: Dol M, Van Vlissingen MF, Kasanmoentalib S, Visser T, Zwart H. eds. *Recognizing the Intrinsic Value of Animals. Beyond Animal Welfare*. Assen: Van Gorcum; 1999: 45. See also Schmidt K. *Tierethische Probleme der Gentechnik. Zur moralischen Bewertung der Reduktion wesentlicher tierlicher Eigenschaften*. Paderborn: mentis; 2008. Harfeld JL. Telos and the Ethics of Animal Farming. *Journal of Agricultural and Environmental Ethics*. 2012; 26 (3): 691-709.

[2] Animals involved in XT research are very likely to experience various forms of strains (see Sections 4.2–4.4) and ultimately be killed. Patients run the risk of having the XT organs rejected and of being negatively affected by the side effects of immunosuppressive drugs and isolation conditions. Medical staff could be negatively affected by xenozoonotic diseases.

[3] The literature study *Alternativen zur Xenotransplantation. Grundlage für tierethische Abwägungen* was conducted by Anne Eckhardt. It is freely accessible here: https://www.ekah.admin.ch/de/externe-gutachten/weitere-externe-gutachten. Accessed March 6, 2024. The final report of the ECNH *Xenotransplantation. New opportunities, new ethical questions?* is available in German, French and English: https://www.ekah.admin.ch/en/ecnh-opinions-and-reports/ecnh-reports. Accessed March 27, 2024.

[4] According to article 24 of the Animal Experimentation Ordinance, the strain suffered by animals caused by interventions or measures taken as part of animal experiments is divided into four constraint categories:*Severity grade 0–no strain:* Procedures and actions performed on animals for experimental purposes that do not inflict pain, suffering, or harm on the animals, engender fear, or impair their general well-being;*Severity grade 1–mild strain:* Procedures and actions performed on animals for experimental purposes that cause short-term mild pain or harm, or a mild impairment of general well-being;*Severity grade 2–moderate strain:* Procedures and actions performed on animals for experimental purposes that cause short-term moderate or medium to long-term mild pain, suffering or harm, short-term moderate fear, or short to medium-term severe impairment of general well-being;*Severity grade 3–severe strain:* Procedures and actions performed on animals for experimental purposes that cause medium to long-term moderate pain or severe pain, medium to long-term moderate harm or severe harm, long-term severe fear, or a severe impairment of general well-being.

[5] In contrast, a study of the European Food Safety Authority (EFSA 2017: 4) on animal welfare aspects of the slaughter or killing of pregnant farm animals (including pigs) concludes that the probability that they will actually feel pain is considered low. See European Food Safety Authority (EFSA). Animal welfare aspects in respect of the slaughter or killing of pregnant livestock animals (cattle, pigs, sheep, goats, horses). *EFSA Journal*. 2017; 15 (5), 1-96.

[6] For a discussion of the criterions instrumental suitability and indispensability see Camenzind 2023 and the final report of the ECNH 2024.

[7] In the final report (2024, p. 20) the ECNH came to the following conclusion: "*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-in-ducing 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."

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