Pontifical Academy
for Life

Prospects for Xenotransplantation

Scientific aspects and ethical considerations

VATICAN CITY 2025

Pontifical Academy for Life

Documents 1

Prospects
for Xenotransplantation

Collana
"Pontifical Academy for Life
Documents 1"

Pontificia Accademia per la Vita
Piazza San Calisto
00120 Vatican City
Tel: +39 06 698 95201
www.academyforlife.va
X: @PontAcadLife

Finito di stampare
nel mese di novembre 2025

Pontifical Academy
for Life

Prospects for Xenotransplantation

Scientific Aspects and Ethical Considerations

Updated Version 2025
Vatican City

Preface to Second Edition

Over the past two decades, research on xenotransplantation has made remarkable progress, suggesting the possibility of concrete clinical applications.

As early as 2001, the Pontifical Academy for Life published a document addressing the issue through a necessarily dual perspective: both scientific and humanistic.

In that occasion, St John Paul II sent a message in which he wrote:

"The goal of your work is, first of all, of human interest, since it is prompted by the necessity of resolving the problem of the grave insufficiency of human organs which are suitable for transplants: it is known that such an insufficiency means the death of a high percentage of sick people on waiting lists, who could be saved by the transplant. The transplants could prolong a life which is still good.

Certainly the passing of animal organs and tissues to people through transplants implies new problems of a scientific and ethical nature. You have raised these problems with responsibility and competence, simultaneously taking to heart the benefit and the dignity of the human person, the possible medical risks, which are not always quantifiable or foreseeable, the attentive consideration for animals, which is always a duty even when they are operated on for the greater good of man, who is a spiritual being in the image of God.

In these sectors, science is a necessary guide and valuable light. Scientific research must nevertheless be placed in the right perspective, being directed to the good of man and the safeguarding of his health.

Anthropology and ethics, in their turn, are ever more called to intervene in order to offer a necessary and complementary contribution, defining values and criteria to follow and, at the same time, establishing the conditions for an harmonious ordering of priorities, which must exist among them".

Twenty-five years later, the decision has been made to offer a second edition of that document, providing an updated synthesis of scientific advancements and restating, in a manner suited to recent innovations, a number of ethical criteria that may guide and accompany this important field of medicine.
I wish to express my heartfelt gratitude to the international Working Group that, with particular expertise and dedication, has prepared this new version of the document. I entrust the text to the scientific community and all the people involved in healthcare system, in the hope that it may serve as a valuable resource in the pursuit of our shared and noble commitment to the service of human life.

Msgr Renzo Pegoraro
President
Pontifical Academy for Life

Vatican City, September 26, 2025
Sts. Cosmas and Damian, physicians

In drafting its contents, the Academy received input from an international working group with specific expertise in the various disciplines connected with xenotransplantation.

Members of the Working Group are the following:

for the Scientific Section:

Prof. Umberto Agrimi
(Expert in Animal Welfare)
Department of Food Safety
and Veterinary Health, Italian National Institute of Health - Rome, ITALY

Dr. David K.C. Cooper MD, PhD, FRCS
(Xenotransplantation, Heart Surgeon)
Center for Transplantation Sciences,
Massachusetts General Hospital/Harvard Medical School - Boston, USA

Prof. Emanuele Cozzi, MD, PhD
(Xenotransplantation, Transplantation immunologist)
Dept. of Cardiac, Thoracic and Vascular Sciences - Padua University Hospital - Padova, ITALY

Prof. Jay A. Fishman, M.D.
(Xenotransplantation, Infectious disease and safety expert)
MGH Transplantation Center
Massachusetts General Hospital/Harvard Medical School - Boston, USA

Prof. Cesare Galli
(Animal genetic engineering expert)
AVANTEA srl, Laboratorio di Tecnologie della Riproduzione - Cremona, ITALY

Prof. Richard N. Pierson III, M.D.
(Xenotransplantation, Thoracic Surgeon)
Center for Transplantation Sciences
Massachusetts General Hospital/Harvard Medical School - Boston, USA

Prof. Mario Picozzi
(Forensic Doctor)
University of Insubria - Varese, ITALY

Prof. Franciscus van Ittersum
(Nephrologist)

Department of Nephrology
Amsterdam University Medical Center - Amsterdam,The Netherlands

for the Anthropological-Ethical Section:

Prof. Daniel J. Hurst, PhD, ThM, MDiv, MSc
(Xenotransplantation, Ethicist)

Department of Medical Education and Scholarship
Rowan-Virtua School of Osteopathic Medicine - Stratford, USA

Prof. Sigrid Müller
(Theologian)

Catholic Theological Faculty
University of Vienna - Vienna, AUSTRIA

Dr. Maria Concetta Pelliciari
(Expert in Communication)

LUMSA University - Rome, ITALY

Msgr. Renzo Pegoraro
President of the Pontifical Academy for Life – VATICAN CITY

Dr. Carlo Maria Petrini
(Bioethicist)

Bioethics Unit, Italian National Institute of Health - Rome, ITALY

Editorial Contributions and Support:

Dr. Monica Consolandi
(Researcher)

Fondazione Bruno Kessler – Trento, ITALY
Pontifical Academy for Life – VATICAN CITY

Index

Second Part: Theological, Anthropological and Ethical aspects of Xenotransplantation 37

Glossary

Acute vascular rejection - Acute vascular rejection (also termed delayed xenograft rejection) is an immune response against the graft, that usually occurs within days or weeks after the transplant, precipitated by elicited xenoreactive antibodies and by the activity of host inflammatory cells that invade the xenograft.

Allograft - A transplant of organs, tissues or cells between individuals of the same species, e.g., from a human to another human.

Allotransplantation - The transplantation of organs, tissue or cells between individuals of the same species.

Antibodies - Antibodies are proteins produced by the immune system whose role is to protect the body against foreign agents. For instance, antibodies recognize pathogenic microorganisms, such as viruses or bacteria, and contribute to their destruction. In transplantation, antibodies may recognize the transplanted organ as foreign and trigger an immune response that will damage the organ.

Chimerism - The presence in an individual of genetically distinct cell populations belonging to two different individuals, such as animal-derived cells in a human recipient after xenotransplantation.

Chronic Rejection - A long-term rejection process characterized by the gradual loss of function of a transplanted organ, tissue or cells, occurring in both allografts and xenografts.

Coagulation cascade activation – is a step-by-step process that occurs in the body usually in response to an injured blood vessel.

Complement - is a group of proteins present in the blood circulation. When activated these proteins help antibodies to clear invading microbes and foreign cells.

Decedent model - a research approach involving deceased individuals, who are brain-dead, but whose organs are still functioning. The decedent model is occasionally used in transplantation research.

Hyperacute rejection - A rapid, often severe, immune response against the graft that occurs within minutes to hours after transplantation, caused by pre-existing xenoreactive antibodies and complement of the recipient acting against the vascular endothelial cells of the transplanted organ.

Immunological barriers - Factors such as the immune system's response to foreign tissue that challenge the success of organ transplantation, leading to rejection of the transplant.

Immunosuppression - Medical therapy used to suppress or modulate the recipient's immune system to prevent rejection.

Infectious agents - Pathogens such as viruses, bacteria, fungi or parasites that can cause diseases and are tested in both organ donors and recipients to prevent post-transplant infections.

Nonhuman primate - A primate species other than humans that can be used in scientific research due to the anatomical and physiological similarities with humans.

Organ Donor - Individuals (or animals in the case of xenotransplantation) that provide organs, tissues or cells for transplantation

Recipient - An individual who receives a transplanted organ, tissue, or cells from a donor in the context of transplantation.

Rejection - The the process by which the body of the transplant recipient attempts to rid itself of the transplant.

Transgenesis - The process of introducing a foreign gene or genetic material into the genome of an organism

Xenograft - A transplant of organs, tissues or cells between individuals of different species (e.g., from a pig to a human).

Xenotransplantation - The transplantation of organs, tissues or cells between individuals of different species, such as from animals to humans.

Xenozoonosis - Infection transmitted from a donor animal to a human recipient by xenotransplantation.

Zoonoses - Infectious diseases transmitted from animals to humans.

Introduction

Transplantation represents a highly successful means of treating a variety of human diseases. However, the number of transplants performed is limited by a shortage of human organs, tissues and cells [1]. Xenotransplantation, the transplantation of organs, tissues or cells from one species to another, if applied to human being, would offer the possibility of an unlimited supply of organs, tissues and cells for transplantation thereby relieving the "chronic" shortage of human donors.

However, even as xenotransplantation is becoming a clinical reality, some practical challenges have yet to be fully addressed.

One is represented by rejection, the process by which the body of the transplant recipient attempts to rid itself of the transplant.

Another is to ensure the correct functioning, across species barriers, of the transplant in its new host.

Also, there is the need to minimize the risk of introducing infectious agents into the human population via the xenotransplant.

In addition, xenotransplantation raises theological, anthropological, psychological and ethical issues for consideration, as well as legal issues and procedural concerns.

First Part

Scientific Aspects

Historical background

1. To date, there is only very limited experience in transplanting animal-derived organs, tissues or cells (or xenografts) into humans. Several primate-to-human kidney transplants in the 1960s and early 1970s used the rudimentary immunosuppressive therapies available at that time to prolong survival of the organ. The most striking success was the nine-month survival of a pair of chimpanzee kidneys transplanted into a human by REEMTSMA and colleagues [2]. In the 1980s, a baboon heart was transplanted into a baby (Baby Fae) who survived for 20 days [3]; of four other baboon or chimpanzee heart transplant recipients, only one survived for 4 days. In the 1990s, STARZL and colleagues transplanted baboon livers in two patients [4]; one patient survived for 70 days and the other for 26 days. The first patient was placed on an oral diet on the fifth post-transplant day and spent most of his time in a regular ward, leaving the hospital briefly on one occasion [5]. In one case, a baboon pathogen (cytomegalovirus) was apparently transferred to the patient, even though this did not have any clinical consequences [6]. In both patients there was evidence of an adequately functioning liver mass, sufficient to sustain life. The baboon livers led to the presence of baboon proteins synthesized by the transplanted liver; in some cases, those proteins reached blood levels that are those observed in baboons and not in humans.

Between 1968 and 1995, one pig liver and two pig and one sheep heart transplants were attempted; in no case did the recipient survive for more than 24 hours [7]. In the following years, only a limited amount of clinical data was reported whilst xenotransplantation activities were primarily conducted in non-human primates.

Since 2022, five transplants of pig organs in living patients have been publicly announced. Two human recipients of pig hearts with a constellation of 10 gene edits exhibited life-supporting graft function for over a month before the heart xenograft failed [8,9]. The recipient of a kidney from a genetically engineered pig carrying a total of 69 gene edits had stable life-supporting function until dying from cardiac complications at 52 days [10]. A genetically engineered pig kidney transplanted 10 days after implantation of a heart pump lost function and was removed after six weeks [11]. A genetically modified pig liver was implanted as an auxiliary graft after removal of most of the patient's own liver containing a large tumor [12]. Ten days following transplantation the patient was alive and in good clinical condition.

In summary, pilot clinical experiences (and preclinical experiments in decedents; see section 10) show that pig organs can provide life-supporting function in humans for days or weeks and continue to yield invaluable new information regarding remaining barriers to longer-term success for each organ.

While in the past non-human primates were thought to be the preferred animal source of organs for human recipients, currently the scientific community and the regulatory agencies have ruled out their use because of the increased risk of transmission of infection and because of additional ethical and practical concerns. Indeed, based on practical and ethical considerations, the pig has been chosen as the source animal species for the clinical application of xenotransplantation [13]. In this context, the use of genetically engineered pigs has enabled a considerable improvement in survival of pig organs transplanted into nonhuman primates receiving immunosuppressive therapy [14, 15,16]. However, survival of pig organs in nonhuman primates has not yet approached results of human organs transplanted into other humans (allotransplantation). Difficulty in achieving long-term

pig organ xenograft survival in preclinical models suggests that obstacles to clinical success may exist that have yet to be fully overcome.

Further genetic engineering and cloning of source pigs and/or the use of new immunosuppressive strategies are the two main approaches that have been attempted to prolong the survival of a xenograft [17]. Clearly more preclinical and clinical research in xenotransplantation is still needed.

Current Situation

Rejection of a pig solid organ xenograft

The four immunological barriers to xenograft survival

There are four described immunological barriers that must be overcome to achieve successful organ xenotransplantation from pig to primate (human and non-human), though the mechanisms behind these barriers partially overlap [18].

2. First, hyperacute rejection is caused by xenoreactive natural antibodies and complement of the recipient acting against the vascular endothelial cells of the pig organ. Second, acute vascular rejection is caused by the combined effect of elicited xenoreactive antibodies and activated host cells, e.g., natural killer cells and monocytes. In combination, these stimuli (anti-graft antibodies and activated host cells) result in activation of the endothelial cells of the pig organ, which in turn results in inflammation and thrombosis (platelet aggregation and activation of the coagulation cascade) and organ rejection. Third, the xenograft counterpart of classical T cell-mediated rejection of allografts (transplantation between individuals of the same species) occurs, but this has been documented relatively rarely to date. Finally, xenografts may also be subject to chronic rejection in a manner analogous to that which occurs in allografts.

Hyperacute rejection is defined as rejection that occurs within 24 hours. Recipient xenoreactive natural antibodies and complement are the two major factors that result in hyperacute rejection of an immediately-vascularized organ. Pre-existing xenoreactive natural antibodies bind to the vascular endothelial cells of the pig organ [19,20]. The bound antibodies activate complement, leading to rapid graft injury (rejection), usually within minutes.

Acute vascular rejection (also termed delayed xenograft rejection), that usually occurs within days or weeks after the transplant but can be later, is precipitated by elicited xenoreactive antibodies and by the activity of host inflammatory cells, e.g., monocytes and natural killer cells, that invade the xenograft. Graft vascular endothelial cells are again activated, resulting in thrombosis, compromised blood flow and rejection. Until recently, acute vascular rejection represented the principal immunological barrier to successful xenotransplantation.

If acute vascular rejection is prevented, the effect of a T cell response may be seen (the counterpart of allogeneic T cell rejection). There are disagreements whether the xenogeneic T cell response is more difficult to overcome than the allogeneic response, which today is relatively easily controlled. However, novel immunosuppressive agents, hitherto not administered to patients with allografts, appear to control the T cell response to a xenograft fairly successfully.

As with allotransplants, there is evidence that, even when a xenograft survives the above rejection phases, graft vasculopathy (chronic xenograft rejection) characterized by diffuse narrowing of the arteries in the xenograft will develop over the following months or years. Its mechanism is poorly understood, but antibody directed to antigens on the vascular endothelium of the organ (whether an allograft or xenograft) are believed to play a major role.

Despite the above "classification", there are often histopathological features of a mixed rejection response, e.g., features of hyperacute and acute vascular rejection or of acute vascular and T cell-mediated cellular rejection. Furthermore, at this stage the contribution of the innate immune response in rejection has yet to be clarified.

Prevention of xenograft rejection

3. Two major approaches have demonstrated effectiveness to prevent rejection, namely (i) genetic engineering of the organ-source pig and (ii) the administration of novel immunosuppressive regimens based on agents that block the CD40/CD154 T cell co-stimulation pathway [21]. Genetic engineering consists of two main approaches – (i) deletion of expression of the 3 known glycan xenoantigens against which humans have natural anti-pig antibodies [22], and (ii) the introduction into the pig of human genes [22,23] that provide additional protection against the human immune response, e.g., complement-regulatory or coagulation-regulatory genes.

The respective roles of genetic engineering and novel immunosuppressive therapy remain unclear. However, several combinations of gene edits prevent early antibody-mediated rejection, and the novel CD40/CD154-based immunosuppressive therapy prevents T cell activation and therefore contributes to the absence of both cellular and elicited antibody-mediated rejection.

Treatment of xenograft rejection

4. Until recently, reversal of antibody-mediated rejection of a pig xenograft proved very difficult [23, 24]. However, the administration of an agent that inhibits complement activation has reversed rejection in a very small number of pig organs in nonhuman primates and in one decedent kidney recipient [Montgomery, personal communication]. Nevertheless, maintenance of therapeutic levels of immunosuppressive agents to prevent xenograft rejection would appear to be preferable.

Advances in Biotechnology and Molecular Genetics

5. The last 25 years have seen major advancements in molecular and cellular biology as well as in techniques regarding assisted reproduction. Such advancements have led, first, to the ability to engineer the genome of pig cells in vitro and, second, to the ability to generate from such cells live pigs through cloning (somatic cell nuclear transfer) [25]. The development of the concept of "gene targeting" by homologous recombination [26], an event that exploits the DNA molecular machine of the cell to modify a gene sequence or to introduce a human gene at a specific location in the pig genome, has been a major step forward. Together these gene editing techniques have allowed the inactivation of the enzymes synthesizing the sugar residues that are known to be highly immunogenic in humans and are responsible for hyperacute and acute vascular rejection of a xenograft and the insertion of various human genes, defined also as "transgenes", intended to improve xenograft function. This work has been greatly facilitated by the discovery of programmable nucleases, DNA cutting enzymes that can be precisely delivered to required sites in the genome [27,28]. The latest programmable nuclease is the CRISPR/Cas9 system [29] that is widely used to edit the pig genome for many applications including xenotransplantation. The advantages of these new molecular tools are many, including the high efficiency and precision in cutting specific DNA sequences for both inactivating undesirable genes or for inserting human genes that are helpful to protect a xenograft from activation of the complement or coagulation cascades, from inflammation or other undesirable events. These very precise genome engineering techniques associated with cloning have led

to an exponential growth in the number of pig lines produced for xenotransplantation studies while minimizing the number of animals required to accomplish the research, an acceleration of activity that was not even conceivable before these gene editing advances were developed. In addition, methods to regulate the expression of transgenes have been devised [30]. For example, expression of a certain transgene may be highly desirable at a given moment following transplantation but may become undesirable under different circumstances. Being able to regulate the expression of a transgene in the recipient, or confining expression to a specific tissue or cell type represents a great advance in the development of xenotransplantation [31].

Xenotransplantation and the Biological Identity of the Recipient

6. The use of animal-derived products as medication or for therapeutic purposes in human patients has a long history. Before the era of recombinant proteins, pig insulin was used to treat diabetes and even today heparin is sourced from animal tissues. Likewise, bioprosthetic heart valves, i.e., valves manufactured using bovine or pig pericardium, currently represent the preferred therapeutic option for many patients requiring cardiac valve replacement [32].

In most of the circumstances listed above that are currently part of routine medical practice, it is possible that donor-derived fragments of DNA originating from the death/lysis of cells from the graft are released in the circulation [33]. This is not different from that which occurs, for example, in a pregnant woman where fetus-derived DNA is found in the maternal circulation and can even be used for diagnostic purposes [34]. It is likely that the same will happen in the case of solid organ xenotransplantation where animal-derived

DNA (along with RNA, proteins, and lipids) released from cell lysis will be released in the circulation with no known detrimental impact on the recipient.

As for DNA fragments, similar considerations are valid in the case of microchimerism, where cells from the animal organ will enter the recipient circulation, as occurs in allotransplantation [35]. Therefore, in the case of chimerism a human being has cells originating from another individual. Animal-derived cells have been detected for several years following xenotransplantation in humans [36] and, to date, no detrimental impact on the recipient has been reported.

Importantly, animal-derived cells released in the recipient circulation will not have an impact on the recipient germline. Indeed, the germline of an individual is set before birth and there is no convincing in vivo evidence that even autologous stem cells can contribute to the germline [37], let alone somatic cells coming from a transplanted pig organ.

Xenotransplantation and the Biological Identity of the Donor Animal

7. As stated above, donor pigs used for xenotransplantation may be subjected to various degrees of gene editing that range from a few to a large number of gene edits [15]. It must be pointed out that even in the case of pigs with a large number of gene edits the level of genetic engineering is far from having an impact on the "pigness" of the pig as it will only affect a minor number of the genes present in the pig genome. On the other hand, even a limited number of gene edits can affect the viability of the animal, depending on the type of modification introduced [38]. This must be assessed case by case and gene-

tic engineering must be adapted to ensure the health and welfare of the pig. Irrespective as to whether the genetic engineering procedure performed in the pig involves a Knock Out (KO, inactivate a gene) or Knock In (KI, insert a new gene in the genome; also known as transgenesis) approach, genetic modifications are stable. KO mutations are inherited in a mendelian fashion [39]. Eventually KI genes can have multiple integrations or copy numbers and being foreign to the genome could potentially be silenced by methylation, but the sequences integrated will not change in the genome of the pig and segregate in the progeny also in a mendelian fashion.

Recently, a novel approach called embryo (or blastocyst) complementation [40] that ultimately generates chimeric animals has been developed. It is a promising technique that in theory could allow a human organ to develop in a 'host' animal such as a pig. However, embryo complementation is still far from a possible clinical application as many questions have yet to be answered. These include the generation of pig embryos lacking specific organs (i.e. the kidneys), the need to learn how to facilitate the integration and proliferation of human cells, as well as how to control the fate of human cells into the pig embryo [41]. At this stage, there is no objection in principle to conduct studies using the embryo complementation approach as long as the ethical rules and principles of medical research will be applied (as discussed later in this document). Still, further ethical and cultural reflections on this model are needed.

Experimental systems

Xenotransplantation of organs and cells has been studied primarily in small animal models and in pig-to-nonhuman primate combinations.

Small animal models

8. Initial xenotransplantation studies were mainly conducted in rodents [42,43]. In particular, the principal xenotransplantation model used involved xenotransplantation of hamster or mouse hearts into rats. These studies proved to be very helpful to understand the basic obstacles to successful organ transplantation between different species. However, whilst initially these models proved to be very advantageous from both a logistics and economics standpoint, they were eventually perceived as inadequate surrogate models of pig-to-primate xenotransplantation [44]. Indeed, their limitations include major differences in the onset of the anti-xenograft immune response [for instance, rats do not hyperacutely reject mouse or hamster xenografts]. Furthermore, the impossibility to conduct studies to investigate physiological compatibility between donors and recipients encouraged investigators to explore xenotransplantation science in the most relevant model for clinical xenotransplantation, namely the pig-to-nonhuman primate model.

Large animal models

9. The principal animal model used today remains transplantation of gene-edited pig organs into immunosuppressed nonhuman primate recipients. Gene-edited pig hearts have been shown to survive for up 945 days when they are not asked to do life-supporting work (heterotopic transplant) [45]. When placed in the position of having to support life (orthotopic transplant), the longest survival period has now reached 15 months for a cardiac xenograft [46] and more than 2 years for a renal xenograft [15]. These exceptional results accompli-

shed in the last decade are the ultimate outcome of two different approaches that have been combined to extend survival of pig organs transplanted into primates. As stated above, gene-edited pig organs have undergone modifications that render them less "foreign" to primate recipients, a condition that dramatically reduces the activation of the recipient's immune system and the onset of rejection [47]. Additionally, specifically gene-edited organs are less susceptible to the damage deriving from the activation of the recipient coagulation cascade and are more resistant to inflammatory events. Furthermore, novel immunosuppressive strategies have been developed that more efficiently prevent the immune response responsible for the rejection process [23]. Unquestionably, pig organs are anatomically and physiologically different from their human counterpart. However, the evidence that a gene-edited life-saving pig heart or kidney can sustain the life of a nonhuman primate for more than 1 year [46] and almost 3 years [15], respectively, is clear demonstration that the existing inter-species differences between pigs and primates are not insurmountable. Similarly, very encouraging results have also been obtained when pig islets were transplanted into preclinical surrogate models of diabetes [48].

Altogether current results suggest that genetically-engineered pig organs and cells may indeed represent a valid alternative to the human counterpart. Still the initiation of well-designed clinical trials appears indispensable to address all the remaining unanswered questions.

Studies in human decedents

10. It is a widely accepted cultural and behavioural norm across most if not all human societies that the human body should be treated with respect and dignity before and after death.

All contemporary biomedical research takes into account the expressed or presumed wishes of the patient or decedent, and, where feasible, all research on living persons, or disposition of their body after death, requires the consent of the subject or of their legally authorized representative [49]. Some persons experience death of the brain while the heart continues to function and to provide blood flow to the other organs. In most legal jurisdictions, a person whose brain no longer exhibits any appreciable level of consciousness and has irreversibly lost basic functions including breathing and other brainstem reflexes is considered 'brain dead', a 'decedent' [50]. Since the concept of brain death became widely accepted in the 1960's, decedents whose hearts and other organs are functioning have constituted the main current source of hearts, lungs, livers and kidneys for life-saving organ transplants, a condition that is also accepted by the Roman Catholic Church. Recently some investigators have proposed to perform experimental procedures using decedents who are not medically suitable to provide their organs for transplantation [51,52]. In this context, as for organ transplant donation, research experimentation involving decedents has been conducted with the consent of their family or their legally authorized representative.

The use of the decedent model may have various limitations related to brain death such as systemic inflammation, dysregulated coagulation and hemodynamic instability, the length of time for observation and logistical challenges (such as cost, resource utilization, infectious disease considerations) [53,54].

However, observations made in such systems will supplement preclinical and clinical experiences. Hemodynamic instability is usually manageable with vasopressin and thyroid hormone repletion to address hypothalamic endocrine disruption. Likewise, dysregulated coagulation is reversible in some cases with supportive care. Nonetheless, a heart-beating decedent's physiologic milieu is in some cases a hostile environment for the xenograft, which may bias results to underestimate the actual expected clinical efficacy (functional capacity, durability) relative to clinical application in physiologically stable, medically optimized patients with end-stage organ failure.

Since 2021, 9 transplants of pig organs into brain-dead human decedent research subjects have been publicly announced. Six transplants of pig kidneys into decedents used 'conventional' immunosuppressive drugs -- treatments that have earned regulatory approval for use in recipients of human organs [55]. Using pigs with one gene modification, knockout of Galα1-3Gal transferase (GalTKO) that prevents expression of the principal carbohydrate target recognized by human anti-pig antibodies, life-supporting kidney function was preserved for over 61 days in one case, and a rejection episode was reversed using a treatment regimen similar to that used to treat antibody-mediated rejection in humans [56, 57]. In two of three recipients of pig kidneys with a constellation of 10 gene edits designed to prevent known mechanisms of xenograft injury (10-GE), life-supporting kidney function was observed despite histologic evidence of varying amounts of graft damage. In one of two decedent recipients of 10-GE pig hearts, stable life-supporting heart function was observed for about three days, while the second developed progressive evidence of graft injury and hemodynamic instability [58]. Another team used a gene-edited liver in an extracorporeal (external) circuit in a deceased individual to examine liver function in that setting [59].

Studies conducted in decedent recipients may represent a novel tool to generate new information to progress science in general, including that related to xenotransplantation. At this stage, from the Roman Catholic perspective there is no objection in principle to conduct studies in decedents as a bridge to clinical trials. Still, further ethical and cultural reflections on this model are needed.

XENOZOONOSES: THE TRANSMISSION OF INFECTIOUS AGENTS FROM ONE SPECIES TO ANOTHER

Microbiologic safety in clinical trials of xenotransplantation

11. In human allotransplantation, screening of organ donors and recipients for possible infectious agents (e.g., for cytomegalovirus, CMV, or hepatitis C virus, HCV) provides the basis of post-transplant monitoring or surveillance protocols and for antimicrobial prophylaxis. Allotransplant microbiologic screening prior to transplantation is limited due to the short time between organ procurement and implantation; microbiologic culture data may be unavailable until after organ implantation [60].

Zoonoses are infectious diseases of animals transmitted to humans. "Xenozoonosis" describes infection transmitted from the source animal to the human recipient by xenotransplantation. In the immunosuppressed human xenograft recipient, risk may be due to both organisms existing in the recipient and, potentially, organisms derived from the porcine source animal. Thus, the safety goal is to determine a list of potential human pathogens from swine to exclude from isolated (biosecure) breeding colonies of pigs [61]. While diagnostic tools (micro-

biology) and therapies exist for most bacteria, fungi, and parasitic infections, fewer diagnostic and therapeutic tools exist for viral infections which are common in transplant recipients.

Screening of donor swine: porcine organisms and animal breeding

12. Many porcine organisms have a potential to cause disease in humans, notably in the presence of immune suppression for transplantation [62]. Such information is being used in the development of "clean" lines of source animals with documented exclusion of potential human pathogens. Special, biosecure facilities are required to protect swine raised for xenotransplantation. Swine bred to be free of organisms felt to be of some risk to swine health or to human recipients are called "designated pathogen-free" (DPF) [63]. DPF animals may be derived by hysterotomy (caesarean derived) or cloning in sterile environments with routine microbiological monitoring of pigs and their handlers. These steps appear to have excluded almost all known infectious agents of concern. However, it cannot be ruled out that an unknown porcine virus might exist which causes no pathology in pigs but which may cause disease in humans. Of the potential pathogens, the greatest concern surrounds viruses for which limited diagnostic assays or documented therapies exist. Few common viruses are known to infect pigs and humans, including hepatitis E virus (HEV) and swine influenza virus. The pig viruses for which the most information exists seem to infect only pig cells and not humans. One of these, porcine cytomegalovirus/porcine roseolovirus (or PCMV) is restricted to porcine cells, but causes systemic inflammation, clotting disorders and contributes to graft rejection [64]. Assays exist to test for the presence of PCMV; these include serologic tests (antibodies) and nucleic acid tests (NAT). Other viruses (e.g., porcine circovirus, porcine lymphotropic herpesvirus) are not

known to cause systemic effects in other species. As these viruses do not infect normal human cells, spread to the general public is considered unlikely.

As is true for all other mammalian species, pigs have sequences in their DNA that encode retroviruses (PERV A, B, C, and AC - Porcine Endogenous Retroviruses). PERV replicate without symptoms in normal pigs [63,65]. Patience and colleagues showed that pig retroviruses could infect certain human cells in vitro [66]. This raises the possibility that xenograft-derived PERV could infect human cells and insert into the host genome causing effects such as altered gene regulation or cancer [67,68]. However, the three similar PERVs (A, B, and C) do not appear to infect normal human cells [67,68]. No PERV infection of humans has ever been identified [36, 69]. There are no satisfactory animal models to test the pathogenicity of PERV. The blood of 160 patients exposed to living pig tissues was studied for the presence of PERV. In 135 patients exposure was for only one hour or a little more. In a few of the remaining patients exposure was for longer periods, in one case for 460 days. None of the patients showed evidence of PERV infection, although pig cells containing retroviral sequences were found even several years after exposure to the pig tissue [36]. It is a matter open to conjecture the extent to which these data on limited exposures to pig cells predict the level of risk associated with xenotransplantation of pig organs carrying PERV sequences; years of exposure would presumably occur if an organ were successfully transplanted into a human. However, as PERV infection of normal human cells does not occur, spread to the general public is considered unlikely [70,71]. Various strategies have been developed to exclude PERV from source pigs, including genetic modifications that

inactivate PERV in all pig cells [72]. PERV is also susceptible in vitro to available antiviral agents used to treat HIV infection if infection were to occur [73].

Moving to the clinical phase

13. In the last few years convincing preclinical data have been generated in clinically relevant animal models showing that, following xenotransplantation, genetically-edited pig organs may sustain the life of immunosuppressed nonhuman primates for months (in the case of hearts) or even years (in the case of kidneys) [15,46]. Similarly, preclinical data have also been obtained showing that pig islets can provide excellent control of sugar metabolism and enable insulin-independence of nonhuman primate recipients exceeding one year [48]. Indeed, together such preclinical data are very convincing as they demonstrate the capacity of pig organs and cells not just to sustain the life of nonhuman primates but also provide evidence that these pig-derived xenografts meet the key physiological needs of nonhuman recipients. Furthermore, the data currently available suggest that the use of designated pathogen-free animals grown in biosecure breeding colonies should be required as a source of pig organs for clinical xenotransplantation [61].

Together these considerations, primarily based on efficacy and safety evidence, have acted as the trigger for the recent, cautious resumption of clinical xenotransplantation in a limited number of patients who did not meet the criteria to undergo transplantation with human organs [8-11] or faced a high probability of death while waiting for a human organ [74]. Clearly, we are at a very early stage of clinical xenotransplantation. Indeed, clinical xenotransplantation is still an uncharted territory with still many “unknowns” that will only

be clarified once xenotransplantation is performed in human clinical trials. However, the very convincing and encouraging data generated in the last few years in preclinical models and in humans suggest that a cautious clinical translation of xenotransplantation into carefully selected human beings at this moment in time is morally and ethically defensible.

Second Part

Theological, Anthropological and Ethical Aspects of Xenotransplantation

Theological Aspects of Xenotransplantation

Theological Reflection Envisaging Present Challenges of Xenotransplantation

14. The recent discussion on xenotransplantation is motivated by how close biotechnology developed during the past decades appears to be to successfully bringing this treatment option close to clinical viability. If this aim will be reached, it is hoped to prolong human life with xenotransplantation in a situation in which human organs available for transplantation are scarcely available.

Ethical questions regarding Xenotransplantation cannot be answered without reflecting on the human person and the animals providing the transplant. The understanding of human persons and their role in creation shapes the way in which we evaluate the aim and ways of their engagement in the world. Theological ethics looks at the human person and creation in relationship to God as it is described in the light of the Gospel and interprets the text in dialogue with today's human experience and knowledge as it is offered by sciences and humanities. The relevant biblical texts and the insight of the Christian tradition deserve refreshed consideration and renewed interpretation as scientific research and theological discourse advance to be able to offer some guidance with respect to the specific challenges that arise over time as the consequence of human ingenuity and related evolving technology.

At the same time, in other areas such as climate change and ecology human technological intervention at present is under critique for unbalancing the ecological system. Growing concern

about the extinction of species has also prompted reflection about the dignity of creation and especially of entire species of animals. Dignity of animals and the entire creation is used in an analogical way to the dignity of the human being. Analogy means that there are comparable elements but yet a fundamental difference remains. Pope Francis in his encyclical "Laudato si'" uses "intrinsic value" when he speaks about animals and creation [75]. This critique not only refers to how technologies have been used but addresses also religious belief and reproaches Christianity for supporting an exaggerated anthropocentrism, thereby neglecting the dignity of other creatures and explicitly promoting the exploitation of the environment. This makes a careful re-examination of biblical resources necessary.

Pope Francis, in his encyclical "Laudato si'", reacts to the accusation and argues that the Bible has been misinterpreted when the command to "subdue" the earth (Gen 1:28) was understood as absolute domination [76]. He refers to the double task of "tilling" and "keeping" which leads to a caring relationship of humans towards animals and the entire creation: "'Tilling' refers to cultivating, ploughing or working, while 'keeping' means caring, protecting, overseeing and preserving. This implies a relationship of mutual responsibility between human beings and nature. Each community can take from the bounty of the earth whatever it needs for subsistence, but it also has the duty to protect the earth and to ensure its fruitfulness for coming generations" [76]. In addition, the felt results of human intervening in nature have highlighted the fact that human beings cannot be regarded apart from the ecological system but need to be seen as part and major factor within, as well as dependent on it. The position of the human being in creation and human ability to intervene in its character and functioning, as well as the responsibility for animal welfare are some of the resulting anthropological and ethical topics which also, to some extent, impact on the question of xenotransplantation [77].

Anthropological Aspects

The Human Person's Dignity and Responsibility

15. The biblical text offers two "creation accounts" (Gen 1:1-2:4a and Gen 2:4b-25), which are the most important source describing the position of the human person in the context of creation. Especially the sentence "Then God said, 'Let us make mankind in our image, after our likeness. And let them have dominion over the fish of the sea and over the birds of the heavens and over the livestock and over all the earth and over every creeping thing that creeps on the earth.'" (Gen 1:26) has been used in Christian tradition to argue that the human person stands at the top of creation and that all other creatures were created to serve their well-being. When reading the account more closely, however, one can discover that the land animals were created on the same day as humans (Gen. 1:24) and therefore are closely related to them in the order of creation [78]. Also, it is argued that according to the biblical text creation is completed only on the day after the creation of the human person and therefore does not entirely culminate in her, but orients her towards God (Gen 2:2).

These observations highlight that the important position given to the human person in the biblical text cannot be understood without taking into consideration her relation to other creatures and towards a higher being, namely God the creator. As a result, the human person is not endowed with arbitrary liberty, but rather responsibility for creation. She is given the task to keep God present in the life of the earth, which means to act with responsibility and care for human beings and the environment [79].

This account of the human task can be confirmed by the first part of Gen 1:26 and its repetition in Gen 1:27: "So God created mankind in his own image, in the image of God he created him". This is a singular position that has, along the history of Christianity, been equated with the rational capacities of the human being which excel all other creatures and to the creative capacity in all fields of culture and science which presupposes freedom and will: "Developing the created world in a prudent way is the best way of caring for it, as this means that we ourselves become the instrument used by God to bring out the potential which he himself inscribed in things: "The Lord created medicines out of the earth, and a sensible person will not despise them" (Sir 38:4)" [80; 81].

The excellence of the human person is, however, balanced by a precautionary reservation in the biblical text. Biblical scholars point out that the second half of the description of the human position exactly denominates the difference between God and the human being. To be created "after our likeness" (Gen 1:26) expresses that the human person is not just an equivalent to God, but rather a substantial difference remains, since the human person is substantially fallible. This is, among other aspects, due to the impossibility for human persons to foresee all long-term effects of their interventions in the world. They are always in danger of being contrary to God's good intentions for creation.

These precautionary observations make it clear that a full-fledged anthropocentrism without respect for the surrounding nature is not viable from a biblical perspective [82]. It needs to be replaced by at least a moderate, methodological anthropocentrism which acknowledges the dignity of all creatures and creation while maintaining a difference between human persons and animals due to the demand of responsibility, which can be attributed only to human persons who alone can be held responsible for their actions. Also, the human person should be understood as part of an ecological system or network which enables her to live and flourish.

Human Stewardship: Preserving Human Life and Avoiding Animal Suffering

16. Apart from the creation accounts, a second approach to the human being can be taken by the reports talking about Jesus Christ's activities in which he healed the sick. From there, Christian tradition has developed initiatives to create hospitals and hospices to take care of the physical as well as for the spiritual well-being of human persons. Such caring attitude has been also related to the relational character of human beings, the love of the neighbor and of oneself being intrinsically related with the love of God (Matthew 22:37 40).

Such love and care for human persons and God can be extended to other creatures. From our point of view, supported by the biblical perspective, we reaffirm that humans have a unique and higher dignity. However, humans must also answer to the Creator for the manner in which they treat animals. As a consequence, the sacrifice of animals can be justified only if required to achieve an important benefit for the human person, as is the case with xenotransplantation into human beings, even when this involves experiments on animals and/or genetically modifying them.

However, even in this case, there is the ethical requirement that in using animals, humans must observe certain conditions: criteria of real necessity and reasonableness must be respected; genetic modifications that could significantly alter the biodiversity and the balance of the species in the animal world must be avoided; unnecessary animal suffering must be prevented.

Biomedical research community has prioritized environmental enrichment for most mammalian species. In particular as related to xenotransplantation using pigs and nonhuman primates, nonhuman primate research programs have shown the benefits to ani-

mal health (reduced stress hormone levels) and behaviour from providing training (positive reinforcement for behaviours that enable or simplify sample collection), companionship (pair housing), environment (visual and/or auditory entertainment) conducive to normal-for-species social interactions, within the limits of experimental requirements to accomplish study goals.

The theological and moral point of view sees no substantial problem in the utilization of different animal species (e.g. non-human primates) but leaves open the question of differing levels of sensibilities between animals of different species and that of equilibrium among species and within a species.

A moderate anthropocentrism allows to see other creatures also as endowed with intrinsic value. Nevertheless, according to the Bible, this does not mean an absolute prohibition on killing: "It is true that it is only to mankind after the Flood that flesh is given for food (Gen 9:3)" [83]; however, both the clothing of Adam and Eve and the sacrifice of Abel (Gen 4:4) presuppose the killing of animals [84]. While the use of force in order to protect life can be legitimate [85], mass killings of animals without any responsibility and respect cannot be brought into equation with the human task to intervene in the world in the spirit of care and responsibility.

Intervention in human and animal life in the context of xenotransplantation is, therefore, not fundamentally different from other interventions in nature that are life-sustaining for human persons, such as eating animals for survival, while it can be considered different in urgency because of the life-threatening character of organ failure and a lack of other options [86]. Nevertheless, even using animals for one's survival is seen by a growing number of persons as a painful experience. To observe animal welfare, avoidance of suffering and avoiding the extinction of a species are some of the criteria of general concern, which are also relevant in this context.

Also, with respect to the dignity of creation, research in animals should not take place at the mere expense of the animals, but with their help, i.e. not for the sake of satisfying the curiosity of the human person alone, but with respect for their intrinsic value, they are not of mere instrumental value [87]. Interventions in animal life are therefore bound by respect for the intrinsic value of the animal and the application of moral reasoning. Among the ethical criteria, the adequate relationship of aim and means with respect to foreseeable consequences, virtue ethical principles like justice and temperance, but also derived criteria as the "Three R Rule" (reduction, replacement, refinement) could be applied. Human intervention in nature needs to be purposeful, proportionate and sustainable.

The point should also be made that Catholic theology does not have preclusions, on a religious or ritual basis, in using any animal as a source of organs, tissues or cells for transplantation to human beings. The question of the acceptability of an animal organ, – once it has been established that personal identity is not affected by xenotransplantation, and once all the general ethical requirements of transplantation have been met, – becomes cultural and psychological. Therefore, it may be possible to overcome initial misgivings by providing the necessary support in an effective manner.

Human Creativity and Responsibility: Challenges for the Researcher and Physician

17. Biotechnical research in the context of xenotransplantation is an example of the creativity of the human person which is indispensable and belongs to his/her character. Therefore, it is often argued that humans are co-working with God's creational

power and can modify other animals and nature [88]. This is obvious with regard to many inventions and innovations which have turned human life more humane, safe and healthy. However, since human beings can easily underestimate or not foresee side-effects of their interventions in animal life and the environment, it is important to communicate both positive and negative results of relevant research and to apply the precautionary principle in its application.

In the context of xenotransplantation, the main question of concern is the genetic adaptation of the animals whose organs are used for transplantation by inserting elements of the human genome, to overcome "anatomical and physiological barriers preventing or impairing the functionality of the implanted xenograft" [89].

A first concern is that continuing modifications of the genome of the animal do not lead to violating the currently accepted ethical barrier of creating hybrids between human and other species. Genetically modified pigs currently proposed to provide organs for human use do not violate this barrier. So far, genetic changes caused by inserting human genes into the animal are still minimal and restricted to changing biochemical and molecular features, but not, for example, its physical appearance or the biology of its brain, thus preserving the pig's fundamental identity as a member of its species.

Also, it is the responsibility of researchers and physicians to overcome the physiological barriers between humans and pigs in order for the transmission of animal material into the body of the human person to accomplish its therapeutic intent. Modification of the pig and treatments given to the human are needed to prepare the patient's body for the reception of the xenotransplant. Based on the evidence to date, there is no known or expected change in the genome or fundamental biologic identity of a human person who receives a pig xenograft. With respect to

self-identity and self-perception, which are at the center of 'person-hood' and individual humanity, the transmission of animal genes across the human recipient's body-brain barrier or into their embryonic stem cells (oocytes, spermatozoa) is extremely unlikely to occur as a consequence of xenotransplantation or related recipient treatments. Consequently, with regard to human identity and especially in view of possible offspring, it is essential that xenotransplant activities minimize any chance that the recipient's genome be altered or intentionally influenced as a consequence of the organ or cell xenograft and related procedures. By example, it is of utmost importance to reject xenotransplantation of those brain cells associated with cognition from animals into the brain of humans if the personal identity of the patient cannot be safeguarded; cell treatments into the brain intended to correct physiologic defects, such as Parkinson's disease by pig adrenal cell injection, are very unlikely to pose such a threat, and could be considered ethically justifiable [90].

Challenges in this context regard secondly the responsibility for the animals which are used for transplants. One immediate challenge consists of avoiding such bodily effects in the animal of "anatomical, physiological, behavioral" [91] nature that cause suffering of the animal. Another aspect to be considered is that the animals must be kept in an artificial living environment to prevent, e.g., the transmission of animal diseases to the human recipient of the organ (xenozoonosis).

It is true that many animals, especially for food production, are kept under restricted living conditions. However, this does not excuse us from taking responsibility for the best possible animal welfare. The argument that only a very limited number of animals is concerned is also true for this phase of experimental treatment. However, should a commercial use of genetically-en-

gineered animals begin, much larger numbers of animals would be kept under these conditions, and challenges regarding safety and maintaining animal comfort and dignity under commercial pressures would increase.

Medium-term challenges are the effects that genetically changed animals could have on the ecosystem if they could reproduce outside their closed research environment. In the light of these challenges, the responsibility of researchers is also to maintain the barrier between wild-type and genetically-engineered pigs to avoid an increase of danger of xenozoonoses.

Integration of the Transplant into the Body-Image – Challenges for the Identity of the Patient

18. The question of who a human being is and how a human person can be defined can lead to answers which change according to the academic disciplines. From the perspective of genetics, no difficulty seems to exist in accepting a xenotransplant because the recipient of the xenograft remains a "normal" human person: there is no change of genetic, physical or psychological identity.

Difficulties in self-identifying as a human person (psychological and spiritual effects) after a xenotransplantation can originate from psychological difficulties to accept such an organ [92]. On the one hand, such problems can be regarded as a variation of a similar problem that can occur after transplantation of a human organ because a change in the body can provoke a crisis of identity, though this is not necessarily the case [93].

A more specific crisis of identity can be caused due to the animal origin of the transplant which can also cause adverse reactions by other people. Human beings are relational beings

and therefore the reaction of others can influence personal attitudes towards the organ. However, these challenges of perceiving human identity can be overcome. What makes a human person humane is a human character and way of behaving, not the physical material of a specific organ. It is therefore the task of the patient to address the psychological challenge to accept the pig organ into her/his own bodily self-awareness [94]. This happens usually when human organs are transplanted: "the transplanted organ […] is integrated relatively quickly into one's own body image, especially when patients quickly notice an improvement in their physical well-being" [95].

Yet it also needs to be mentioned that, since self-awareness belongs to the core of the human person and is related to their personal conscience, there can be no obligation to consent in accepting a xenotransplant if such a psychological integration is not possible, or when it is opposed by strong moral or religious conviction regarding animal ethics. Therefore, patients need to be well informed and supported psychologically and spiritually to lay secure grounds for informed consent and optimal shared decision making [96].

At the same time, information policies and medical education should be implemented at a broad societal level to diminish the danger of social stigmatization of xenograft recipients. Balanced information about xenotransplantation within the diverse faith communities can also contribute to help patients in accepting a xenotransplant and diminishing the danger of stigmatization by others. Theologians have stressed the aim of "saving and preserving life" [97], while also arguing in favor of continued research for further alternatives which could avoid conflicts with animal ethics [98].

Caring for the Vulnerable and the Dying

19. In the medical context, researchers and physicians make every effort to save and preserve human life, while human condition is vulnerable and death a reality which cannot and should not be denied. From a Christian point of view, death is a transition to the fullness of life in God's presence. Human persons by accepting unavoidable death can transform the physical evil of death and integrate it into a broader vision of life. Therefore, the preservation of life should not be regarded as unconditioned, but always in close relationship with the dignity of the vulnerable and dying person, which needs to be given priority over other possible interests [99].

Both in the case of survival with the help of xenotransplantation, and in the case of unavoidable death it is of immense importance to provide not only pastoral and psychological support of the patient, but to provide also a specific education of all those involved, especially care workers and the patients' relatives and close contacts [100]. Such education should include medical knowledge and psychosocial as well as spiritual insight in order to cope with the variety of emotional and affective aspects involved [101]. Also, it is recommended to create contact points in the hospital to deal with all kinds of problems related to medical aftercare [101]. In such a way, both the human task to correspond to the relational character of the human being, and to care for the vulnerable person, can be professionally met [102].

20. Further investigation and clarification is needed for a wider bioethical analysis. The ethical evaluation of the practicability of xenotransplantation, in light of the current situation as summarized in the first part of this document, requires the consideration of a whole series of factors, some of which are derived from the general moral norms valid for all transplants, and others of which are more specifically related to xenotransplantation.

Understanding Health Risk

21. One of the fundamental ethical questions that should be examined in evaluating xenotransplantation is that of the health risk or safety of such procedures. This risk is dependent on various factors which cannot always be predicted or assessed. Before going on, therefore, it may be useful to recall some general aspects of the ethics of risk.

Risk – understood as an unwanted or damaging future event, the actual occurrence of which is not certain but possible [103] – is defined by means of two characteristics: the level of probability and the extent of damage. The probability of the occurrence of a certain damaging event in particular circumstances can be expressed as a risk percentage or as a statistical frequency. Furthermore, the presence or absence of certain chance factors of risk can sometimes alter the probability that a certain event will take place. The extent of the damage, in contrast, is measured by the effects that the event produces. Naturally, a very probable risk is easily tolerated if the extent of damage associated with it is very small; on the contrary, a risk that causes a high level of damage, however improbable,

gives rise to much greater concern and require greater caution.

It is important to distinguish between a probable event (albeit with varying degrees of probability) and a possible event, i.e. one that could happen (event not theoretically impossible but which is so improbable as to require no change in behaviour or choices).

Together, these two criteria - probability and extent of damage - define the acceptability of risk, as reflected by the risk/benefit ratio. Only when a risk can be concretely assessed it is possible to apply criteria for evaluating its acceptability.

Lastly, it is necessary to distinguish acceptability from what we can define as the acceptance of the risk, as defined by the reaction of the individual or of the public to the existence of the risk. This is a response that has a significant subjective component, one which is not always completely thought out and which is influenced by culture, by the information available and how it is understood, by the way in which the information itself is communicated, and by common sensibilities. In the absence of data that allow a reliable assessment of such a risk, greater caution should be used; this does not mean, however, that a moratorium should be placed on all experimentation. Indeed, to move from ignorance to knowledge, from the unknown to the known requires the exploration of new approaches which, especially during initial experimental stages, will not be without some risks. In this situation, therefore, the imperative ethical requirement is to proceed by "small steps" in the acquisition of new knowledge, making use in experiments of the least possible number of subjects, with careful and constant monitoring and a readiness at every moment to revise the design of the experiment based on new data emerging.

It is important to consider the distinction between risk assessment and risk management. To achieve an ethical assessment, both elements must be carefully examined.

Health Risk in Xenotransplantation

22. This general discussion of the ethics of risk must be applied to the specific case of xenotransplantation. In xenotransplantation, there are known risks (e.g., risk of xenograft rejection; risk of transmission of known microorganisms harboured by pigs), unknown risks (e.g., the function of the xenograft within the human recipient; the risk of transmission of unknown porcine microorganisms), and unknown risks due to the early stages of clinical xenotransplantation (i.e., risks of which we are not currently aware). These categories of risk frame the discussion.

We note that there are issues connected with xenotransplantation, such as the probability of rejection and the increased possibility of infection because of immunosuppressive therapies, about which significant knowledge already exists, although further study is necessary. Pigs also carry microorganisms that might be human pathogens. These are known risks that can be mitigated through some combination of prevention (e.g., breeding of pigs lacking pathogenic organisms), vaccination or antibiotic prophylaxis, and careful monitoring. Existing scientific data and any new data can help to establish a threshold of risk that must not be crossed if a transplant operation is to be considered morally acceptable. Such data should be made available to the scientific community and to the public as they emerge to guide assessment of the risk posed by this technology [104].

Impact of Infectious Risk, Microbial Surveillance and Infection Control in Xenotransplantation

23. The assessment and evaluation of risks associated with the possible transmission to the recipient or to the public of infections arising from the xenotransplant (xenozoonoses) by known or un-

known pathogenic agents requires assessment [60,61,70]. A major consideration for clinical xenotransplantation is that infection might occur due to microorganisms harboured by pigs that are unrecognized or for which diagnostic assays or therapies may not exist [61, 63]. In the absence of standardized assays for such organisms, such infections could escape detection, with the consequent possibility of the spread of the infection to those having close contacts with the patient, leading eventually to spread to a greater population. At the same time, a major benefit of xenotransplantation includes the ability to screen source animals for such organisms during breeding compared with the limited time available for screening in human-to-human transplantation. Further, in human-to-human (allo-) transplantation, immunosuppressive regimens are standardized and there is a predictable timeline for infectious risk which provides a basis for vaccination and antimicrobial prophylaxis and for the evaluation of infectious syndromes [60]. Immunosuppressive drugs for clinical xenotransplantation target multiple aspects of the human immune system and may alter patterns of infection and require new preventative approaches to vaccination and to antimicrobial prophylaxis [61]. The impact of multiple genetic modifications of source animals regarding infectious risk is also unclear. Some of these risks may be defined in early clinical experiences. Proceeding with clinical xenotransplantation in a small sample of closely monitored patients would enable gain of knowledge and refine strategies for disease prevention and treatment.

Infections are common in immunosuppressed transplant recipients; most are due to community acquired infections. The magnitude of this risk in xenotransplantation is unknown in the absence of clinical studies [105]. Some of the ethical considerations for xenograft recipients are due to the requirement for recipients to accept life-long monitoring for infections [105]. Recipients and their social contacts will require education regarding the “un-

knowns" of xenotransplantation, including possible infectious risks. Patients with signs of infection may require hospital isolation until a specific microbial diagnosis is achieved. Such interventions may require guidance from, or participation by, local or national public health authorities in the development of clinical protocols. It is an ethical requirement to proceed with caution.

In the clinical application of xenotransplantation, the psychological and spiritual wellbeing of the patient should also play a central role. Protocols should address the possible repercussions for the recipient's psyche of the xenotransplantation procedure (e.g. because of the modification of one's "bodily schema") [106-109]. In the post-transplant stage, psychological and spiritual resources must be provided, as the patient requests, to support their holistic wellbeing. More data will be needed on the psychological and spiritual issues faced by xenograft recipients.

Ethical Implications of Genetic Engineering

The use of organs from engineered animals for xenotransplantation raises the need for certain reflections on genetic engineering and its ethical implications.

As we have already observed, carrying out such genetic modifications, including introducing genes of human origin, is morally acceptable if performed with respect for the animal and for biodiversity, and with the aim of bringing significant benefits to humans. Therefore, while recognizing that transgenesis does not compromise the overall genetic identity of the mutated animal or its species, and reaffirming human responsibility towards the created order and towards the pursuit of improving health by means of certain types of genetic mani-

pulation, we will now enumerate some fundamental ethical conditions which must be respected beyond the general rules already mentioned:

1. Concern for the well-being of genetically modified animals should be guaranteed so that the effect of a gene's expression or lack of expression, on the anatomical, physiological and/or behavioural aspects of the animal may be assessed, all the while limiting the levels of stress and pain, suffering and anxiety experienced by the animal.
2. The effects on the offspring and possible repercussions for the environment should be considered.
3. Such animals should be kept under tight control and should not be released into the general environment.

Informed Consent

24. In the ethical discussion on xenotransplantation, the subject of informed consent also deserves special attention [110].

Given the animal source of the organs which will be transplanted, this issue concerns only the recipient and, secondly, their close contacts. At the outset, recipients should be given every information regarding their pathology and its prognosis, the xenotransplant operation and subsequent therapy, and the probability of success and the risks of rejection. Special attention should be paid to making sure that the patient is informed about the real and hypothetical risks of zoonoses, in light of current data, and about the precautions to be adopted in the case of infection (in particular the possible need for quarantine should infection with a communicable disease be suspected, which involves avoiding physical contact with others while the risk of contagion is present). The patient must also be infor-

med about the need to remain under medical supervision for the rest of his/her life, so that the necessary constant monitoring for the health of the organ as well for infection from known and unknown pathogens following the transplant may be carried out. It has been proposed that potential xenograft recipients adhere to a "Ulysses contract," in which they provide consent to lifelong infectious disease monitoring. While lifelong monitoring is necessary, the legality of a Ulysses contract approach is uncertain, and likely to vary by jurisdiction. It is important for xenotransplantation clinicians and xenograft recipients to have a trusting relationship so that it is more likely that the recipient will adhere to post-transplant monitoring independent of local legal framework.

In addition, adequate information on possible alternative therapies to xenotransplant therapy should not be withheld. To this end, it may be necessary to involve an impartial external third-party subject matter expert who can independently advise the potential xenograft recipient on the risks and benefits of proceeding with xenotransplantation. This would seemingly eliminate any potential bias and conflict of interest that may be present.

This informed consent on the part of the patient should be understood as personal. Minors and those unable to provide valid consent are generally excluded from the experimental phase before safety and efficacy are defined in competent and consenting adults.

However, if a patient incapable of giving valid consent (e.g. a child or infant, or a patient in a coma due to liver failure) is in danger of imminent death, recourse to decision-making by an authorized representative (next of kin, court-appointed custodian) is legally accepted in most jurisdictions. In this case a

potentially lifesaving 'bridge' xenograft might represent the best available treatment option, and consent by proxy to a xenotransplant would seem ethically defensible as long as the procedure offered reasonable hope for patient benefit.

Family support of the xenograft recipient's decision to proceed with xenotransplantation is strongly advised. Similar to allotransplantation, family members or other close contacts will be needed by the patient post-transplantation to help with activities of daily living, transportation to medical appointments, and for other types of support. The patient's close contacts (e.g., family members) should also be informed about what the transplant could entail regarding their contact with the patient and about the possible risks of infection, as mentioned above, occur. It may be requested that close contacts provide blood samples that will be stored for future analysis and comparison should xenozoonosis be suspected. In a strict sense, however, consent cannot be requested from them, since it is the patient who is ultimately responsible for the choices concerning his/her own health.

Allocation of Health Care Resources

25. Xenotransplantation represents a form of possible treatment requiring a great outlay of both health care resources and economic resources. For this reason, some people have expressed doubts about its ethical validity; given the large amounts of resources that it would take away from the other forms of therapeutic treatment and from other areas of research, they consider both the uncertainty about its success and the risk entailed to be excessive. Faced with these doubts, it is important to remember that, even taken into due consideration the costs-benefits balance, the huge amount of health care resources used in this case are justified by the urgent need to try to save the lives of so many patients who would otherwise have no chance of survival.

Although pre-clinical and clinical applications of xenotransplantation use a large amount of research and healthcare resources, current therapies to treat organ failure are also expensive and do not contribute to increased quality of life. In the case of chronic kidney disease, dialysis can effectively filter impurities from a patient's blood. However, dialysis is an expensive therapy and is also very taxing on the patient. Studies have indicated that kidney allotransplantation results in cost savings over time compared to dialysis. The same is plausibly true for xenotransplantation [111].

It should also be added that as long as xenotransplantation on humans remains at an experimental stage it should not be subject to the criteria applied to treatment in a strict sense; rather it should be evaluated according to the criteria used for clinical trials.

Therefore, the foreseeable collective benefits that it may accrue in the future should also be taken into account. We do well to recognize here that the research into xenotransplantation which has taken place so far has also brought about greater medical knowledge in the area of allotransplantation.

Role of ethics committees

26. Xenotransplantation is, at present, an experimental treatment. As such, it has significant implications in terms of research ethics. Furthermore, the impact on the person, the peculiarities, the complexity, the invasiveness of the procedure imply critical issues from the point of view of clinical ethics.

Obviously, especially in situations such as xenotransplantation, research ethics and clinical ethics cannot be clearly separated: the area of overlap is considerable.

From both perspectives, a prior evaluation carried out by a competent ethics committee is necessary.

In many countries, experimental transplants may, by law, be subjected to evaluation by an ethics committee, until they become common practice with standardized procedures [112].

It is necessary that, among the members of ethical committees that evaluate xenotransplantation trials, there are experts with experimental and/or clinical experience.

Therefore, ad hoc committees could be appropriate, including all the necessary skills: clinical medicine, surgery, transplantation science, bioethics, law, psychology, genetics, etc.

In particular, the ethics committee should assure:

- The research has a robust rationale, respects a rigorous scientific method and is supported by pre-clinical data.

- The risk-benefit assessment is favourable.

- There is compliance with national Regulations and Guidelines: ethical requirements for human experimentation must be met

- There is compliance with the regulatory and ethical rules for the treatment of animals.

- Suitability of the structures [e.g. hospital] that perform the transplants is documented. Suitability refers to: capacity, institutional commitment, evidence of contingency planning, clinical experience.

- Medical healthcare personnel are suitable in terms of training, experience, commitment, and evidence of contingency planning.

- Verification of the selection of participants is adequate and follows published guidance, that vulnerable populations are excluded (with due exceptions) and that appropriate checks have been conducted on the reliability of the participants and close contacts in relation to compliance for post-study surveillance.

- Ensure that participants have received adequate informa-

tion regarding participation in the study, the risks and the possibility of abandoning the study.

- Ensure that the participant's consent is autonomous and informed, also in relation to psychological problems related to identity that could arise following the transplant.

- Ensure that participants have received adequate information in relation to post-transplant follow-up and the impossibility of withdrawing from this aspect of the trial.

- Ensure that the patient has been informed about the choice to proceed with an animal-to-human and not a human-to-human transplant in compliance with the principle of justice and fair allocation of scarce resources.

Patentability and Xenotransplantation

27. Research on xenotransplantation has hitherto in some countries been carried out in large measure by private biotech companies which have committed substantial economic resources to this endeavour; they have also been providing financing to public institutions for the purpose of obtaining better therapeutic results. It is therefore reasonable for them to expect an economic return on the investment made; one of the possible ways to do this is by acquiring patents [113]. In other countries, as within the European Union, such research has been largely state-funded. It is therefore up to the legal frameworks of the respective countries to establish rules which do justice both to the companies and to just conditions for the distribution of life-saving genetically engineered animal organs. To propose specific regulations for providing health care, however, goes beyond the specific task of this document.

Practical Guidelines

Practical Guidelines

28. Bearing in mind all that has been written above, we can now present a practical approach which will guide the path of research and development in the area of xenotransplantation as applied to humans.

Regarding the xenotransplantation of solid organs, it is of course necessary that pre-clinical experiments (from animal to animal) should continue for as long as scientists should require and until repeatable positive results are obtained, results which are considered sufficient to allow trials on humans to begin.

When the moment arrives, it will be ethically correct, respecting the rules of informed consent indicated above, to involve initially only a restricted group of patients, patients who cannot be chosen – in the given circumstances – for allotransplantation (whether because of waiting lists or individual counter-indications), and for whom no better alternative treatment is available.

A commensurate moral imperative is that of ensuring careful and detailed monitoring of the individuals who receive a xenograft, a situation which could foreseeably continue for the rest of the patient's life, watching for any sign of possible infection caused by known or unknown pathogenic agents.

In addition, every experimental clinical trial should be carried out in highly specialised centres with proven experience in pre-clinical pig-to-nonhuman primate models; these centres should be authorised and supervised by the competent health care authorities. When present, the approval of Ethics Committee (Research and/or Clinical Ethics Committee) is needed.

The results thus obtained, if unequivocally positive, would constitute the basis for extending the practice of xenotransplantation, making it an accepted surgical therapy.

Information of the Public

29. The questions and issues related to xenotransplantation have implications of a very wide social character [114]. There is thus an ethical need to acquire correct information on the topics of greatest public interest with regard to the potential benefits and risks. This information should be communicated to as large a segment of the public as possible. Moreover, by means of debates and public discussions in small and large groups, society itself, through its representatives, should help to identify the conditions under which they would find it acceptable to invest resources and hope in this new therapeutic approach, in light of the scientific uncertainties which are still present and the urgent need to increase the availability of organs which can be transplanted.

A serious ethical commitment on the part of scientists should not neglect to explore therapeutic paths which may represent alternatives to xenotransplantation, such as seem to be promised by many recent discoveries in the field of genetics, as in a longer period the therapeutic use of adult stem cells.

Scope of This Document

30. With respect to the specific fields of health-related policies and legislation on matters of xenotransplantation, it is our heartfelt hope that the considerations offered in the present document will provide a useful point of reference for all those who – at an international, national, regional and local level –

are responsible for leading society. Many countries have already developed guidelines to regulate this complex sector, offering helpful operational directives [115-118].

On our part, we do not believe that this document should enter into procedural political-legislative matters. We therefore limit ourselves to emphasizing the importance and desirability that a substantial convergence of international legislation in this area should be achieved as soon as possible, by means of a genuine coordination at different levels. On the one hand, such legislation must provide rules for the continuation of scientific research, guaranteeing its validity and safety. On the other hand, it must watch over the health of the citizens involved and the potential risks (especially infective) connected with xenotransplantation. Furthermore, it must offer criteria for public campaigns aimed at providing widespread information about the opportunities and risks of this treatment to the population.

We conclude this document with the sincere hope that the effort made on this study by those who have participated in it - scientists, clinicians, jurists, theologians and bioethicists – will represent a concrete contribution to the discussion on the important theme of xenotransplantation. May it also be seen as a further expression of the close attention which the Catholic Church pays on problems related to human disease and suffering.

References

References

1. DOMÍNGUEZ-GIL B, LÓPEZ-FRAGA M, MULLER E, ET AL. Santander Global Summit in Transplantation: Supporting Global Convergence in the Shared Goals of Sufficiency, Transparency, and Oversight. Transplantation. 2024 Online ahead of print.

2. REEMTSMA K., MCCRACKEN B.H., SCHLEGEL J.U., ET AL. Renal heterotransplantation in man, Ann Surg, 1964, 160:384.

3. BAILEY L.L., NEHLSEN-CANARELLA S.L., CONCEPCION W., ET AL. Baboon-to-human cardiac xenotransplantation in a neonate, JAMA 1985, 254:3321.

4. STARZL T.E., FUNG J.J., TZAKIS A.G., ET AL. Baboon to human liver transplantation, Lancet 1993, 341:65.

5. MARINO I.R., DOYLE H.R., NOUR B., STARZL T.E. Baboon liver xenotransplantation In: COOPER DKC, KEMP E, PLATT JL, WHITE DJG, eds. Xeno-transplantation. The Transplantation of Organs and Tissues Between Species. 2nd ed. Berlin: Springer-Verlag 1997: 793-811.

6. MICHAELS MG, JENKINS FJ, ST GEORGE K, ET AL. Detection of infectious baboon cytomegalovirus after baboon-to-human liver xenotransplantation. J Virol. 2001; 75:2825-8.

7. TANIGUCHI S., COOPER D.K.C. Clinical xenotransplantation – A brief review of the world experience. In: COOPER DKC, KEMP E, PLATT JL, WHITE DJG, EDS. Xeno-transplantation. The Transplantation of Organs and Tissues Between Species. 2nd ed. Berlin: Springer-Verlag 1997: 776-792.

8. GRIFFITH BP, GOERLICH CE, SINGH AK, ET AL. Genetically Modified Porcine-to-Human Cardiac Xenotransplantation, N Engl J Med. 2022, 387:35-44.

9. COOPER DKC, COZZI E. Clinical Pig Heart Xenotransplantation-Where Do We Go From Here? Transpl Int. 2024, 37:12592.

10. KOZLOV M. Pig-organ transplants: what three human recipients have taught scientists, Nature 2024, 629:980-981.

11. SEALY A. Transplant patient stable and on dialysis after pig organ removed due to 'unique challenges' with heart, kidney health, CNNHealth May 31, 2024.

12. MALLAPATY S. First pig-to-human liver transplant recipient 'doing very well, Nature 2024, 630:18.

13. RAZA SS, HARA H, EYESTONE W, AYARES D, ET AL. Pigs in Transplantation Research and Their Potential as Sources of Organs in Clinical Xenotransplantation, Comp Med. 2024,74:33-48.

14. ANAND RP, LAYER JV, HEJA D, ET AL. Design and testing of a humanized porcine donor for xenotransplantation, Nature 2023,622:393-401.

15. Kim SC, Mathews DV, Breeden CP, ET AL. Long-term survival of pig-to-rhesus macaque renal xenografts is dependent on CD4 T cell depletion, Am J Transplant. 2019 Aug;19(8):2174-2185.

16. MOHIUDDIN MM, GOERLICH CE, SINGH AK, ET AL. Progressive genetic modifications of porcine cardiac xenografts extend survival to 9 months, Xenotransplantation 2022 May;29(3):e12744. doi: 10.1111/xen.12744. Epub 2022 Mar 31.

17. COOPER DKC, HARA H, IWASE H, ET AL. Pig kidney xenotransplantation: Progress toward clinical trials, Clin Transplant. 2021, 35:e14139.

18. COOPER DK, EZZELARAB MB, HARA H ET AL. The pathobiology of pig-to-primate xenotransplantation: a historical review, Xenotransplantation. 2016, 23:83-105.

19. COOPER DKC, PIERSON RN 3RD. Milestones on the path to clinical pig organ xenotransplantation, Am J Transplant 2023, 23:326-335.

20. BÜHLER L, AWWAD M, BASKER M, ET AL, High-dose porcine hematopoietic cell transplantation combined with CD40 ligand blockade in baboons prevents an induced anti-pig humoral response, Transplantation 2000, 69:2296-2304.

21. COOPER DKC, HARA H, IWASE H, ET AL. Justification of specific genetic modifications in pigs for clinical kidney or heart xenotransplantation, Xenotransplantation 2019, 15:e12516.

22. COZZI E, WHITE DJ. The generation of transgenic pigs as potential organ donors for humans. Nat Med 1995;1:964-966.

23. HABIBABADY Z, MCGRATH G, KINOSHITA K,ET AL. Antibody-mediated rejection in xenotransplantation: Can it be prevented or reversed?, Xenotransplantation 2023, 30:e12816.

24. TECTOR AJ, ADAMS AB, TECTOR M. Current Status of Renal Xenotransplantation and Next Steps. Kidney 2023, 360: Feb 1;4(2):278-284. doi: 10.34067/KID.000715202

25. POLEJAEVA, I.A., CHEN, S.H., VAUGHT, T.D ET AL. Cloned pigs produced by nuclear transfer from adult somatic cells, Nature 2000, 407:86-90.

26. CAPECCHI MR. Altering the genome by homologous recombination, Science 1989, 244:1288-92.

27. CARROLL, D. Genome engineering with targetable nucleases, Annu Rev Biochem 2014, 83:409-439.

28. COX, DB, PLATT, RJ, ZHANG, F, Therapeutic genome editing: prospects and challenges. Nat Med 2015, 21:121-131.

29. HRYHOROWICZ M, LIPI SKI D, ZEYLAND J. Evolution of CRISPR/Cas Systems for Precise Genome Editing, Int J Mol Sci. 2023, 24:14233.

30. KALLUNKI T, BARISIC M, JÄÄTTELÄ M, LIU B. How to Choose the Right Inducible Gene Expression System for Mammalian Studies?, Cells. 2019;8:796.

31. GALLI, C., Animal engineering for xenotransplantation, EJT 2023, 1: 182-191.

32. BROWN JM, O'BRIEN SM, WU C, ET AL. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database, J Thorac Cardiovasc Surg. 2009, 137:82-90.

33. OELLERICH M, BUDDE K, OSMANODJA B, ET AL. Donor-derived cell-free DNA as a diagnostic tool in transplantation, Front Genet. 2022, 13:1031894.

34. MANOKHINA I, DEL GOBBO GF, KONWAR C, ET AL., Review: placental biomarkers for assessing fetal health, Hum Mol Genet. 2017, 26:R237-R245.

35. SPRIEWALD BM, WASSMUTH R, CARL HD, ET AL. Microchimerism after liver transplantation: prevalence and methodological aspects of detection, Transplantation 1998, 66:77-83.

36. PARADIS K, LANGFORD G, LONG Z, ET AL. Search for cross-species transmission of porcine endogenous retrovirus in patients treated with living pig tissue. The XEN 111 Study Group, Science 1999, 285:1236-41.

37. HORAN CJ, WILLIAMS SA. Oocyte stem cells: fact or fantasy?, Reproduction 2017, 154:R23-R35.

38. PHELPS CJ, BALL SF, VAUGHT TD, ET AL. Production and characterization of transgenic pigs expressing porcine CTLA4-Ig, Xenotransplantation 2009 Nov-Dec;16(6):477-85. doi: 10.1111/j.1399-3089.2009.00533.x. PMID: 20042047.

39. MACKAY TFC, ANHOLT RRH. Gregor Mendel's legacy in quantitative genetics, PLoS Biol. 2022 Jul 19;20(7):e3001692. doi: 10.1371/journal.pbio.3001692. PMID: 35852997; PMCID: PMC9295954.

40. MATSUNARI H, NAGASHIMA H, WATANABE M, ET AL. Blastocyst complementation generates exogenic pancreas in vivo in apancreatic cloned pigs, Proc Natl Acad Sci U S A. 2013, 110:4557-62.

41. WANG J, XIE W, LI N, ET AL. Generation of a humanized mesonephros in pigs from induced pluripotent stem cells via embryo complementation, Cell Stem Cell 2023, 30:1235-1245.

42. WANG H. Small animal models of xenotransplantation, Methods Mol Biol. 2012. 885:125-53.

43. LIN Y, GOEBELS J, XIA G, JI P ET AL. Induction of specific transplantation tolerance across xenogeneic barriers in the T-independent immune compartment, Nat Med. 1998, 4:173-80.

44. MEYERHOLZ DK, BURROUGH ER, KIRCHHOF N, ET AL. Swine models in translational research and medicine, Vet Pathol. 2024; 61:512-523.

45. MOHIUDDIN MM, SINGH AK, CORCORAN PC, ET AL. Chimeric 2C10R4 anti-CD40 antibody therapy is critical for long-term survival of GTKO.hCD46.hTBM pig-to-primate cardiac xenograft, Nat Commun. 2016, 7:11138.

46. Mitchell CB, Simmons J, Hodo CL, et al. Early Results of an Infant Model of Orthotopic Cardiac Xenotransplantation, J Heart Lung Transplant 2025, 44:503-510. Doi:10.1016/j.healun.2024.12.011.

47. COOPER DKC, HARA H, IWASE H, ET AL. Justification of specific genetic modifications in pigs for clinical organ xenotransplantation, Xenotransplantation 2019, 26e12 516.

48. COOPER DKC, MOU L, BOTTINO R. A brief review of the current status of pig islet xenotransplantation. Front Immunol. 2024, Feb 23:15:1366530. Doi: 10.3389/fimmu.2024.1366530.

49. PRICE D. Legal and Ethical Aspects of Organ Transplantation. Cambridge University Press. First Edition 2000.

50. SARBEY B. Definitions of death: brain death and what matters in a person, J LAW BIOSCI. 2016, 3(3):743-752.

51. PENTZ RD, COHEN CB, WICCLAIR M, ET AL. Ethics guidelines for research with the recently dead, Nat Med. 2005, 11:1145-9.

52. PARENT B, KATES OS, ARAP W, ET AL. Research involving the recently deceased: ethics questions that must be answered, J Med Ethics, 2024, 50:622-625.

53. TAKAHASHI C, HINSON HE, BAGULEY IJ. Autonomic dysfunction syndromes after acute brain injury. Handb Clin Neurol. 2015, 128:539-551.

54. KONSMAN JP. Cytokines in the Brain and Neuroinflammation: We Didn't Starve the Fire! Pharmaceuticals (Basel) 2022, 15(2):140. doi: 10.3390/ph15020140.

55. COOPER DKC, KOBAYASHI T. Xenotransplantation experiments in brain-dead human subjects-A critical appraisal, Am J Transplant. 2024, Apr;24(4):520-525. doi: 10.1016/j.ajt.2023.12.020. Epub 2023 Dec 28. PMID: 38158188.

56. MONTGOMERY RA, STERN JM, LONZE BE, ET AL. Results of Two Cases of Pig-to-Human Kidney Xenotransplantation, N Engl J Med. 2022, 386:1889-1898.

57. NYU LANGONE HEALTH, Two-Month Study of Pig Kidney Xenotransplantation Gives New Hope to the Future of the Organ Supply (Sept. 14, 2023), https://nyulangone.org/news/two-month-study-pig-kidney-xenotransplantation-gives-new-hope-future-organ-supply).

58. MOAZAMI N, STERN JM, KHALIL K, ET AL. Pig-to-human heart xenotransplantation in two recently deceased human recipients, Nat Med. 2023, 8:1989-1997.

59. MALLAPATY S. First pig liver transplanted into a person lasts for 10 days, Nature, 2024, 627:710-711.

60. FISHMAN JA. Infection in Organ Transplantation, Am J Transplant 2017, 17:856-879.

61. FISHMAN JA. Risks of Infectious Disease in Xenotransplantation, N Engl J Med 2022, 387:2258-2267.

62. ONIONS D, COOPER DK, ALEXANDER TJ, ET AL. An approach to the control of disease transmission in pig-to-human xenotransplantation, Xenotransplantation 2000, 7:143-55.

63. FISHMAN J, PATIENCE C. Xenotransplantation: Infectious Risk Revisited. Am J Transplantation 2004, 4:1383-1390.

64. GOLLACKNER B, MUELLER NJ, HOUSER S, ET AL. Porcine cytomegalovirus and coagulopathy in pig-to-primate xenotransplantation, Transplantation 2003, 75:1841-7.

65. DIECKHOFF B, KESSLER B, JOBST D, ET AL. Distribution and expression of porcine endogenous retroviruses in multi-transgenic pigs generated for xenotransplantation. Xenotransplantation 2009, 16:64-73.

66. PATIENCE C, TAKEUCHI Y, WEISS RA. Infection of human cells by an endogenous retrovirus of pigs, Nat Med 1997, 3:282-6.

67. ERICSSON TA, TAKEUCHI Y, TEMPLIN C, ET AL. Identification of receptors for pig endogenous retrovirus, Proc Natl Acad Sci U S A 2003, 100:6759-64.

68. Fishman JA. Patience C. Xenotransplantation: infectious risk revisited. Am J Transplant 2004, 4(9):1383-90. DOI: 10.1111/j.1600-6143.2004.00542.x.

69. Morozov VA, Wynyard S, Matsumoto S, Abalovich A, Denner J, Elliott R. No PERV transmission during a clinical trial of pig islet cell transplantation, Virus Res 2017; 227:34-40. DOI: 10.1016/j.virusres.2016.08.012.

70. NELLORE A, WALKER J, KAHN MJ, FISHMAN JA. Moving xenotransplantation from bench to bedside: Managing infectious risk, Transpl Infect Dis 2022, e13909.

71. FISHMAN JA, SCOBIE L, TAKEUCHI Y. Xenotransplantation-associated infectious risk: a WHO consultation, Xenotransplantation 2012, 19:72-81.

72. NIU D, WEI HJ, LIN L, ET AL. Inactivation of porcine endogenous retrovirus in pigs using CRISPR-Cas9, Science 2017, 357:1303-1307.

73. DENNER J. Can Antiretroviral Drugs Be Used to Treat Porcine Endogenous Retrovirus (PERV) Infection after Xenotransplantation? Viruses 2017, 9: 213.

74. KAWAI T, WILLIAMS WW, ELIAS N, ET AL. Xenotransplantation of a Porcine Kidney for End-Stage Kidney Disease, The New England Journal of Medicine 2025, 392: 1933-1940. Doi: 10.1056/NEJMoa2412747.

75. THE HOLY FATHER FRANCIS. Encyclical Letter Laudato si' of on Care for our Common Home (May 24, 2015), no. 140.

76. THE HOLY FATHER FRANCIS. Laudato si', no. 67.

77. Cf. THE HOLY FATHER FRANCIS. Laudato si', no. 68.

78. KEEL O., SCHRÖER S. Creation. Biblische Theologien im Kontext altorientalischer Religionen, Göttingen 2002, 182. Cf.

SAUTERMEISTER J, MATHIEU R., BOGNER V. Xenotransplantation—theological-ethical considerations in an interdisciplinary symposium, Xenotransplantation 2015, 22:174–182, 176.

79. Cf. LINTNER M. Der Mensch und das liebe Vieh. Ethische Fragen im Umgang mit Tieren, Innsbruck 2017, 44.

80. Cf. THE HOLY FATHER FRANCIS. Laudato si', no. 124.

81. PONTIFICIA COMMISSIONE BIBLICA. Che cosa è l'uomo? Un itinerario di antropologia biblica, Libreria Editrice Vaticana, Roma 2019.

82. THE HOLY FATHER FRANCIS. Laudato si', no. 68.

83. KEEL O., SCHRÖER S. Creation. Biblische Theologien im Kontext altorientalischer Religionen, Göttingen 2002, 182.

84. LINTNER M. Der Mensch und das liebe Vieh. Ethische Fragen im Umgang mit Tieren, Innsbruck 2017, 42.

85. Cf. SAUTERMEISTER J, MATHIEU R., BOGNER V. Xenotransplantation—theological-ethical considerations in an interdisciplinary symposium, Xenotransplantation 2015, 22:174–182, 176.

86. Cf. THE HOLY FATHER FRANCIS. Laudato si', no. 130. Cf. Lintner M, Der Mensch und das liebe Vieh. Ethische Fragen im Umgang mit Tieren, Innsbruck 2017, 45-46; Kernstock-Jörns, Abweichendes Votum, in: Kirchenamt der evangelischen Kirche in Deutschland/Deutsche Bischofskonferenz, eds. Xenotransplantation. Eine Hilfe zur ethischen Urteilsbildung (Gemeinsame Texte 13), Hannover/Bonn 1998, 25-27.

87. THE HOLY FATHER FRANCIS. Laudato si', no. 69. Cf. SEKRETARIAT DER DEUTSCHEN BISCHOFSKONFERENZ, ed. Zukunft der Schöpfung – Zukunft der Menschheit. Erklärung der Deutschen Bischofskonferenz zu Fragen der Umwelt und der Energieversorgung (Die Deutschen Bischöfe, Nr. 28), Bonn 1980, II, 2.

88. Cf. SAUTERMEISTER J. Xenotransplantation from the perspective of moral theology, Xenotransplantation 2015, 22:174–182, 186-187.

89. Cf. SAUTERMEISTER J. Xenotransplantation from the perspective of moral theology, Xenotransplantation 2015, 22:174–182, 185.

90. HALTER H. Organtransplantation aus ethischer Sicht, in: Münk HJ, ed. Organtransplantation. Der Stand der ethischen Diskussion im interdisziplinären Kontext (Theologische Berichte XXV), Freiburg Schweiz: Paulus-Verlag 2002, 174-245, 190.

91. PONTIFICIA ACADEMIA PRO VITA. Prospects for Xenotransplantation. Scientific Aspects and Ethical Considerations, Vatican City 2001, no. 15.

92. Cf. PONTIFICIA ACADEMIA PRO VITA. Prospects for Xenotransplantation. Scientific Aspects and Ethical Considerations, Vatican City 2001, no 10.

93. Cf. BECKMANN JP, ET AL. Xenotransplantation von Zellen, Geweben und Organen. Wissenschaftliche Entwicklungen und ethisch-rechtliche Implikationen, Berlin 2000, 247.

94. SAUTERMEISTER J. Xenotransplantation from the perspective of moral theology, Xenotransplantation 2015, 22:174–182, 189.

95. BUNZEL B, ET AL. Klinische Psychologie in der Chirurgie – Herzchirurgie, Transplantation, Kinderchirurgie, Plastische Chirurgie, in: Lehrner J, Stolba K, Traun-Vogt G, Volkl-Kernstock S, Eds. Klinische Psychologie im Krankenhaus, Wien: Springer-Verlag 2011, 169-183, 176 [transl.].

96. SAUTERMEISTER J, MATHIEU R., BOGNER V. Xenotransplantation—theological–ethical considerations in an interdisciplinary symposium, Xenotransplantation 2015, 22:174–182, 177. Hans Halter, Organtransplantation aus ethischer Sicht, in: Hans J. Münk (Ed.), Organtransplantation. Der Stand der ethischen Diskussion im interdisziplinären Kontext (Theologische Berichte XXV), Paulusverlag Freiburg Schweiz 2002, 174-245, 189.

97. HALTER H. Organtransplantation aus ethischer Sicht, in: Münk HJ, ed. Organtransplantation. Der Stand der ethischen Diskussion im interdisziplinären Kontext (Theologische Berichte XXV), Freiburg Schweiz: Paulus-Verlag 2002, 193.

98. Cf. Xenotransplantation. Eine Hilfe zur ethischen Urteilsbildung. Vorbereitet von einer Arbeitsgruppe im Auftrag des Kirchenamtes der Evangelischen Kirche in Deutschland und des Sekretariats der Deutschen Bischofskonferenz,

https://www.dbk-shop.de/de/publikationen/gemeinsame-texte/xenotransplantation.html (last consultation 11.9.2024); Ghazi M, et al. Barriers toward xenotransplantation in Arab World, Xenotransplantation 2024, 31:1-10, 2, https://doi.org/10.1111/xen.12852.

99. Value based decisions have been argued for, e.g. by FEDSON S, ET AL. Ethical considerations in xenotransplantation of thoracic organs – a call for a debate on value based decisions, Journal of Heart Lung Transplant 2024, 43:1033–1038.

100. HURST DJ, ET AL. Close contacts of xenograft recipients: Ethical considerations due to risk of xenozoonosis, Xenotransplantation 2024, 31:e12847, 1-5, https://doi.org/10.1111/xen.12847; HURST DJ, COOPER DKC. Pressing ethical issues relating to clinical pig organ transplantation studies, Xenotransplantation 2024: 31, e12848, 1-5, https://doi.org/10.1111/xen.12848.

101. EBNER K, OSTHEIMER J, SAUTERMEISTER J. The role of religious beliefs for the acceptance of xenotransplantation. Exploring dimensions of xenotransplantation in the field of hospital chaplaincy, Xenotransplantation 2020, 27, e12579, 1-6, 5. doi: https://doi.org/10.1111/xen.12579.

102. CONGREGAZIONE PER LA DOTTRINA DELLA FEDE SULLA CURA DELLE PERSONE NELLE FASI CRITICHE E TERMINALI DELLA VITA. Lettera “Samaritanus bonus”, Roma 2020.

103. SCHONE-SEIFERT B. Risk, in Reich TW (ed.), Encyclopedia of Bioethics, vol. 4, New York: MacMillan 2005: 2316-2321.

104. SYKES M, D'APICE A, SANDRIN M; IXA ETHICS COMMITTEE. Position paper of the Ethics Committee of the International Xenotransplantation Association. Xenotransplantation. 2003;10(3):194-203. doi:10.1034/j.1399-3089.2003.00067.x

105. HAWTHORNE WJ, COWAN PJ, BUHLER LH, ET AL. Third WHO Global Consultation on Regulatory Requirements for Xenotransplantation Clinical Trials, Changsha, Hunan, China December 12-14, 2018: “The 2018 Changsha Communique”. The 10-Year Anniversary of The International Consultation on Xenotransplantation, Xenotransplantation 2019, 26(2):e12513. DOI: 10.1111/xen.12513.

106. MOHACSI PJ, BLUMER CE, QUINE S, THOMPSON JF. Aversion to xenotransplantation. Nature 1995, 378(6556):434. DOI: 10.1038/378434a0.

107. MOHACSI PJ, THOMPSON JF, NICHOLSON JK, TILLER DJ. Patients' attitudes to xenotransplantation, Lancet 1997, 349(9057):1031. DOI: 10.1016/s0140-6736(05)62938-8.

108. HAGELIN J. Public opinion surveys about xenotransplantation, Xenotransplantation 2004, 11(6):551-558. DOI: https://doi.org/10.1111/j.1399-3089.2004.00172.x.

109. RIOS AR, CONESA CC, RAMıREZ P, RODRıGUEZ MM, PARRILLA P. Public attitude toward xenotransplantation: Opinion survey. Transplant Proc 2004, 36(10):2901-2905. DOI: https://doi.org/10.1016/j.transproceed.2004.11.012.

110. Cf. BARKER J.H., POLCRACK L. Respect for persons, informed consent and the assessment of infectious disease risks in xenotransplantation, Med Health Care Philos 2001, 4(1): 53-70.

111. ZHANG Y, GERDTHAM UG, RYDELL H ET AL. Healthcare costs after kidney transplantation compared to dialysis based on propensity score methods and real world longitudinal register data from Sweden, Sci Rep 2023; 13(10730). Doi: 10.1038/s41598-023-37814-6.

112. Accordo tra il Ministro della Salute, le Regioni e le Provincie autonome di Trento e Bolzano 14 febbraio 2002. Repertorio atti n. 1388 del 14 febbraio 2002. Accordo tra il Ministro della salute, le Regioni e le Province autonome di Trento e Bolzano sui requisiti delle strutture idonee ad effettuare trapianti di organi e di tessuti e sugli standard minimi di attività di cui all'articolo 16, comma 1, della legge 1° aprile 1999, n. 91 recante "Disposizioni in materia di prelievi e di trapianti di organi e di tessuti" (GU 3 ottobre 2002n. 232).

113. WIPO/OMPI. Introduction to Intellectual Property: Theory and Practice, London: Kluwer Law International 1998: 145-150; Accordo di Marrakech istitutivo dell'Organizzazione Mondiale del Commercio, Annesso 1C: Accordo sugli aspetti della proprietà intellettuale relativi al commercio (Marrakech 1994), art.31.

114. TALLACCHINI, M. Xenotransplantation: The Role of Public Involvement, in DJ HURST, L PADILLA, WD PARIS (eds.), Xenotransplantation. Ethical, Regulatory, and Social Aspects, Springer 2023: 17-32.

115. THOM R, AYARES D, COOPER DKC, ET AL. Update on the ethical, legal and technical challenges of translating xenotransplantation, J Med Ethics 2024, Aug 21;50(9):585-591. doi: 10.1136/jme-2023-109298.

116. TÖNJES RR. Aspects of Regulation of Xenotransplantation in Europe, Transpl Int. 2024, Dec 13;37:13349. doi: 10.3389/ti.2024.13349. eCollection 2024.

117. HAWTHORNE WJ. Ethical and legislative advances in xenotransplantation for clinical translation: focusing on cardiac, kidney and islet cell xenotransplantation, Front Immunol. 2024 Feb 7;15:1355609. doi: 10.3389/fimmu.2024.1355609. eCollection 2024.

118. KWISDA K, CANTZ T, HOPPE N. Regulatory and intellectual property conundrums surrounding xenotransplantation, Nat Biotechnol. 2021, Jul;39(7):796-798. doi: 10.1038/s41587-021-00976-7.

Stampato nel mese di novembre 2025
dallo Stabilimento Tipografico «Pliniana»
Viale F. Nardi, 12 - 06016 Selci-Lama (PG)
www.pliniana.it

VATICAN CITY 2025