

6.3.1 Xenotransplantation

Physicians have an obligation to participate in efforts to increase the supply of organs available for transplantation. In fulfilling that obligation, they must also be mindful of their obligations to protect the interests of patients and the welfare of the public. Xenotransplantation, i.e., using organs or tissues from nonhuman animal species for transplantation into human patients, is a possible novel means of addressing the shortage of transplantable organs that can pose distinctive ethical challenges with respect to patient safety and public health.

Some forms of transplantation, implantation, or infusion into a human recipient of organs or tissues from a nonhuman animal source have a significant history in clinical practice—for example the use of porcine heart valves. Other proposed procedures are more controversial and are restricted to research protocols.

Physicians who choose to participate in clinical research that involves transplantation of organs or tissues from nonhuman sources should:

- (a) Encourage education and public discussion of xenotransplantation in light of the unique risks such procedures pose to individual patients and the public.
- (b) Ensure that research in which they participate is well designed and adheres to institutional review board requirements, applicable national guidelines, and ethical standards for research with human participants.
- (c) Ensure that research in which they participate is adequately funded to assure lifelong surveillance of xenotransplant recipients and treatment of medical complications related to transplantation.
- (d) Ensure that recruitment is restricted to patients with serious or life-threatening conditions for whom no adequately safe and effective alternative therapies are available unless there is documented, very high assurance of safety.
- (e) Ensure that if participation by individuals who lack decision-making capacity is contemplated, appropriate measures are taken to safeguard their interests. In exceptional circumstances, minors with substantial decision-making capacity may, with the informed consent of their legal guardians, be considered as recipients in xenotransplantation. When an unemancipated minor proposes to participate in xenotransplantation, it may be appropriate to seek advice from another adult trusted by the minor or to seek consultation with an independent body, such as an ethics committee, pastoral service, or other counseling resource.
- (f) Ensure that participants are informed about and consent to the unique risks and burdens posed by xenotransplantation, including:
 - (i) novel infectious diseases (zoonoses);
 - (ii) potential psychological concerns arising from receiving an organ or tissue from a nonhuman animal;
 - (iii) the need for lifelong surveillance and ongoing clinical and laboratory monitoring, with archiving of biological samples when appropriate;

(iv) the need to inform intimate contacts of potential risk to their health;

(v) the need for an autopsy when appropriate.

(g) Ensure that high standards of care and humane treatment of all animals used in research are upheld.

AMA Principles of Medical Ethics: IV,VII

Background report(s):

CEJA Report 3-A-16 Modernized *Code of Medical Ethics*

CEJA Report 4-I-00 The ethical implications of xenotransplantation

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Physicians have an obligation to participate in efforts to increase the supply of organs available for transplantation. *In fulfilling that obligation, they must also be mindful of their obligations to protect the interests of patients and the welfare of the public.* Xenotransplantation, i.e., using organs or tissues from nonhuman animal species for transplantation into human patients, is a possible novel means of addressing the shortage of transplantable organs that can pose distinctive ethical challenges with respect to patient safety and public health. *[new content sets out key ethical values and concerns explicitly]*

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- (c) Ensure that research in which they participate is adequately funded to assure lifelong surveillance of xenotransplant recipients and treatment of medical complications related to transplantation.
- (d) *Ensure that recruitment is restricted to patients with serious or life-threatening conditions for whom no adequately safe and effective alternative therapies are available unless there is documented, very high assurance of safety.* *[new content updates to reflect guidance from the U.S. Food and Drug Administration]*
- (e) Ensure that if participation by individuals who lack decision-making capacity is contemplated, appropriate measures are taken to safeguard their interests. In exceptional circumstances, minors with substantial decision-making capacity may, with the informed consent of their legal guardians, be considered as recipients in xenotransplantation. *When an unemancipated minor proposes to participate in xenotransplantation, it may be appropriate to seek advice from another adult trusted by the minor or to seek consultation with an independent body, such as an ethics committee, pastoral service, or other counseling resource.* *[new content addresses gap in current guidance]*
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AMA Principles of Medical Ethics: IV,VII

REPORT OF THE COUNCIL ON ETHICAL AND JUDICIAL AFFAIRS*

CEJA Report 4-I-00

Subject: The Ethical Implications of Xenotransplantation

Presented by: Herbert Rakatansky, MD, Chair

Presented to: Reference Committee on Amendments to the Constitution and Bylaws
(Nelson G. Richards, Jr., MD, Chair)

1 Resolution 505 (A-99), “Xenotransplantation Clinical Trials,” introduced by the Medical Student
2 Section, instructed the AMA to identify and address the scientific and ethical concerns associated
3 with xenotransplantation research. The resolution was forwarded to the Council on Ethical and
4 Judicial Affairs and the Council on Scientific Affairs which has prepared a report that addresses
5 the scientific implications of xenotransplantation.

6 7 Introduction

8
9 There have been remarkable advances in allotransplantation techniques and immunosuppressive
10 drugs in the last decade, but donation programs have not been able to meet the increasing demand
11 for human organs and tissue.¹ Xenotransplantation, which offers a renewable source of
12 transplantable organs and tissue, potentially could alleviate the current need for human organs
13 and be used to treat a wide variety of human disorders.² The Public Health Service (PHS) defines
14 xenotransplantation to include any procedure that involves the transplantation, implantation, or
15 infusion into a human recipient of either (a) live cells, tissues, or organs from a non-human
16 animal source or (b) human body fluids, cells, tissues or organs that have had ex vivo contact
17 with live nonhuman animal cells, tissues, or organs.³ However, such novel procedures pose
18 unique risks not only to the recipient but to the general public as well. Public discussion is
19 necessary regarding appropriate levels of risk and, if xenotransplantation techniques become
20 successful and acceptable, programs that would ensure fair allocation of this new resource.

21
22 Xenotransplantation is a matter for the medical profession’s attention because it may result in the
23 creation of new sources for organs, tissue, and cells that could be used to treat a number of human
24 disorders. It may also result in the emergence of infectious agents novel to human beings as well
25 as psychological conditions that would require professional care. Therefore, the medical
26 profession must evaluate the ethics of xenotransplantation and, in particular, the potential role of
27 clinicians. The Council offers the following report to assess the risks and benefits of
28 xenotransplantation. The report begins with an overview of the potential risks and benefits such
29 procedures pose and current policy guiding xenotransplantation research in the United States. It
30 then provides an assessment of concerns for individuals and society, discusses the use of animals
31 in xenotransplantation research, and touches on issues relating to organ allocation. Finally, the
32 report provides ethical guidance for continued research, considering the possibility of clinical
33 trials involving human beings.

* Reports of the Council on Ethical and Judicial Affairs are assigned to the Reference Committee on Constitution and Bylaws. They may be adopted, not adopted, or referred. A report may not be amended, except to clarify the meaning of the report and only with the concurrence of the Council.

Potential Risks and Public Health Concerns

As with any transplantation procedure, certain risks are involved. Beyond organ or tissue rejection, a heightened susceptibility to infection is a major cause of morbidity and mortality.^{2,4} In addition to the increased risk of infection inherent to any surgical procedure on an immunocompromised patient, organ/tissue recipients also risk infection by pathogens transmitted from the donor. For example, prior to available tests for HIV or hepatitis C, recipients receiving tissue or an organ from an infected donor risked becoming infected.²

For xenotransplantation, the horizontal transmission of these viral pathogens raises additional concerns of introducing novel infections into the human population. Zoonotic infections, or cross-species disease, have been of concern in the past with examples ranging from avian flu viruses in Asia to human immunodeficiency virus (HIV), which is believed to be derived from a related simian immunodeficiency virus (SIV) found in chimpanzees.^{5,6} The prolonged exposure to living non-human animal cells inherent to xenotransplantation may facilitate infection across natural species barriers, potentially resulting in diseases epidemic to humans.^{7,8} Some speculate that xenogeneic viruses could recombine with latent viruses already found in the recipient human tissue, resulting in a virus with increased pathogenic capacity toward humans. This process is thought to occur intermittently as new strains of the influenza virus continually emerge.² The discovery of endogenous retroviruses, or viral material that recombines into the host's genome and can be inherited by offspring, have been shown to infect human cells *in vitro*.⁹ This study was a major factor leading to the FDA's decision to place a moratorium on xenotransplantation research in 1997.⁵ However, there has been little evidence of endogenous retrovirus infection in humans since the initial *in vitro* study and scientists are unable to predict *in vivo* pathogenicity on the basis of these studies.¹⁰ These and other scientific concerns are more adequately addressed in the companion Report, "Xenotransplantation: Scientific Considerations," from the AMA Council on Scientific Affairs.²

Current Oversight in the United States

In September 1996, the Department of Health and Human Services (DHHS), in concert with the Centers for Disease Control, the Food and Drug Administration (FDA), the Health Resources and Services Administration (HRSA), the Public Health Service (PHS), and the National Institutes of Health (NIH) released a proposed "Guideline on Infectious Disease Issues in Xenotransplantation" (61 FR 49920-49932). Although a final guideline has yet to be released, another draft of the Guideline was issued in May of 2000.³ The FDA has also drafted several guidelines directed toward industry to reduce the risk of transmission by xenozoonoses. In July 1996, the Institute of Medicine presented recommendations that augment the proposed PHS guidelines. In summary, the two guidelines make recommendations regarding: clinical protocol reviews and IRB composition; FDA protocols for investigational new drugs; informed consent protocols; clinical facility requirements including hospital infection control practices; procedures for pre-transplant animal procurement and source screening; methods of continued post-transplantation surveillance of recipients and health care providers; and the establishment of registries archiving biological samples from source animals and recipients for long-term public health investigation.^{2,3}

Ethical Analysis

Currently, there is a great deal of uncertainty surrounding the potential risks of xenotransplantation as well as the degree of benefit. There has been considerable debate about whether the research and technology are sufficient to progress to human clinical trials. The

1 ambiguity concerning the risks and benefits of continued xenotransplantation research has been
2 used both as a justification for continued research and as a reason to halt it temporarily.¹¹
3 However, the argument that research must proceed in order to assess the risks involved has
4 profound implications. The discovery of actual risk in this case might be made once the risk has
5 manifested itself in some form. Uncertainty surrounding the magnitude of risk does not justify
6 proceeding with research.⁷ Moreover, although individual informed consent is important in the
7 clinical setting, it alone is not sufficient to allow research involving an experimental procedure to
8 go forward, especially where risks extend beyond the individuals directly involved in the
9 procedure.¹² Even if the risks and benefits involved were deemed acceptable on an individual
10 level, the unique risk xenotransplantation poses to the public health requires approval not just on
11 scientific and individual grounds but also by the community at large.

12 *Societal Concerns*

13
14
15 The 1996 IOM recommendations state that once the scientific foundation for specific types of
16 xenotransplants is judged to be sufficient, and the appropriate safeguards are in place,
17 xenotransplantation trials would be justified and should proceed.¹³ However, as one author notes,
18 “[s]ocial acceptability may prove to be a greater barrier to xenotransplantation than
19 immunology.”⁵ Many beliefs about animals and humans are ingrained deeply within some
20 cultures. Because the risk of zoonoses will never be zero, some benefit-to-harm analysis will
21 be required to assess what level of risk is acceptable.

22
23 The prerogative of individual informed consent does not preclude recognition of the prerogative
24 of communities to obtain information on risks and precautionary measures.¹⁴ Accordingly, the
25 medical and scientific communities should encourage public discussion of the issue in order to
26 educate the public and to garner a general consensus about when to proceed. Involving the
27 community is not meant to slow or hinder scientific progress, but rather it is a way of respecting
28 lay opinion, thus preserving general trust in medicine and science.¹⁵

29
30 There has been considerable discussion concerning a mechanism for public involvement and the
31 risk assessment in this context. Many authors have proposed the formation of a multidisciplinary
32 board to facilitate the direction of further research or forums for public discussion.¹⁶ The FDA
33 has taken steps to create the Secretary’s Advisory Committee on Xenotransplantation (SACX) to
34 assist in developing guidelines for research oversight in this field.² In the case of
35 xenotransplantation, assessments must be iterative because new developments may alter the
36 nature or extent of the risks involved.¹⁷

37
38 Considering the financial stakes involved in xenotransplantation, the decision-makers responsible
39 for determining whether continued research is justified and appropriate should be free of any
40 potential conflicts of interest. The potential for such conflicts are great and have already made
41 themselves apparent as indicated by the high level of self-interest surrounding the comments
42 submitted to the proposed FDA guidelines.¹⁸ This is reiterated in the 1996 IOM report with the
43 caveat “a real danger exists that the commercial applications of xenotransplantation technology
44 will outstrip both the research base and the national capacity to address special issues raised by
45 xenotransplantation.”¹³

46 *Individual Concerns*

47
48
49 For the individual xenograft recipient, as for all participants in clinical trials, the primary
50 safeguard and concern remains informed consent. Physicians must ensure that patients receive
51 adequate information to ensure an informed choice. In the context of xenotransplantation, the

1 traditional standard of informed consent may have to be modified to account for the possible risk
 2 to third parties and the long-term experimental nature of the trial.¹⁹ For instance, recipients may
 3 have to agree to post-operative measures such as life-long surveillance, disclosure of sexual
 4 contacts, and an autopsy after death, and waive the traditional right to withdraw from a clinical
 5 trial,¹⁸ at least until the risk of late zoonoses is reasonably known not to exist. Therefore,
 6 careful attention should be paid both to the content and format of the consent disclosure. In all
 7 cases emphasis should be placed on both the known risks and, particularly important in this
 8 context, the unknown or uncertain risks.

9
 10 Children and incompetent adults require special consideration because they cannot directly
 11 consent to be research subjects, and some of the risks of xenotransplantation have lifelong
 12 implications. The World Medical Association has suggested that these groups be excluded from
 13 research that can be performed on competent, consenting adults. Investigation of
 14 xenotransplantation is a special case, however, because the procedure will often be the only life-
 15 saving treatment available for some patients with end-stage vital organ failure. In the earliest
 16 phases of research, therefore, it would be ethical to include children and incompetent adults in
 17 xenotransplantation protocols only when the patients are terminally ill and alternative treatments
 18 are not available.

19
 20 Disclosure should also include a discussion of psychological concerns associated with lifelong
 21 medical monitoring and receiving an organ or tissue graft from an animal. Although emotional
 22 problems associated with xenotransplantation are not well understood, patients receiving
 23 allografts often report trouble in accepting the grafted organ.⁵ In some cases, these problems may
 24 be exacerbated by xenotransplantation, since some culturally inviolate boundaries between
 25 animals and humans may become blurred.^{20,21} At the onset of clinical trials, researchers should
 26 consider offering counseling services for their patients to address these concerns as well as
 27 emotional problems associated with extensive post-operative surveillance.

28 29 *Use of Animals*

30
 31 There has been some concern on scientific and moral grounds about the use of non-human
 32 primates as a source of transplantable organs versus using pigs, which seems to be more socially
 33 acceptable.²¹ For the purposes of research, primates have disadvantages such as slow breeding, a
 34 tendency toward single births, and, theoretically, increased risk for zoonoses because of a
 35 relatively small phylogenetic distance between humans and primates. On the other hand, pigs
 36 have large litters, possess organs roughly the same size as humans, and breed quickly thus
 37 facilitating the creation of gnotobiotic, or germ-free, lines.¹⁴ Moreover, with the recent effort to
 38 clone pigs, scientists have taken a step, albeit a small one, towards creating lines of transgenic
 39 pigs that could provide organs that are not as susceptible to rejection as their wild type organs.²²
 40 Although the AMA has taken the stand that biomedical research using animals is essential to
 41 improving the health and well-being of humans, it supports policies to protect animals from
 42 unnecessary pain or inappropriate use.²³ In this case, determining the most appropriate animal
 43 model to use in xenotransplantation is primarily a scientific matter, but regardless of the species
 44 used, researchers should maintain their “commitment to ethical principles that promote high
 45 standards of care and humane treatment of all animals used in research.”²⁴

46 47 *Allocation*

48
 49 Although xenotransplantation may someday offer an alternative source for organ and biological
 50 tissue, it may not eliminate the need for transplantable organs from human sources and,
 51 therefore, will not remove allocation decisions altogether. Allocation protocol will depend, in

1 large part, on the comparative effectiveness of tissue and organs from human and non-human
2 sources. Currently, human tissue and organs are a preferred source for transplantation. However,
3 with the advent of transgenic or chimeric animals, organs may be produced that are more suitable
4 for potential recipients than available human organs. In any case, decisions for the individual
5 allocation of organs or tissue (human or non-human) should be made in accordance with Opinion
6 2.03, “Allocation of Limited Medical Resources” [Appendix 1] which provides ethically
7 appropriate criteria based on medical need.²⁵ Criteria include likelihood of benefit, urgency of
8 need, change in the quality of life, duration of benefit, and, in some cases, the amount of
9 resources required for successful treatment.

10
11 Much of the justification for proceeding with research in xenotransplantation is to increase access
12 to transplantable organs and tissue. At the onset, the early trials will most likely use non-human
13 organs as a bridge until suitable human organs become available.¹⁸ Given the risks of
14 xenotransplantation to the public and to the individual subjects in early trials, the justification for
15 its continued research should be significant in benefit and realistic. For example, if the eventual
16 goal of whole organ xenotransplantation is simply to serve as a means to prolong the wait for
17 human organs, physicians and society must decide if the risks are worth the benefit. As
18 demonstrated by the use of artificial hearts in the 1980’s, options for bridge organs do not help
19 alleviate the overall shortage of transplantable organs and caused many ethical dilemmas as
20 supposed bridge organs resulted in permanent replacements.²⁶

21
22 On a broader level, physicians and the rest of society should view xenotransplantation in the
23 overall context of distribution of health care resources when discussing issues related to
24 allocation. Initially, the financial cost of xenograft transplantations will be substantial. Many
25 people argue that the money being spent on research on xenotransplantation could be better spent
26 on enhancing current human donation programs as well as increasing public health awareness in
27 hopes of decreasing the eventual demand for transplantation.²¹

28 29 Conclusion

30
31 Physicians have an ethical obligation to consider the harms and benefits of new medical
32 procedures and technologies. Potential physical and psychological harms and risks to the public’s
33 health are all legitimate concerns. Before physicians would be justified in participating in
34 xenotransplantation, the harms and benefits need to be evaluated further, with some issues
35 requiring discussion on a societal level.

36
37 Therefore, physicians and the medical community need to encourage public dissemination of
38 information related to xenotransplantation. Physicians also should encourage the discussion of
39 special ethical issues including informed consent, allocation of health resources, and the
40 psychological and social impact of receiving animal organs. Until these issues are brought to
41 closer resolution and the potential benefits clearly outweigh the potential for harm, it would be
42 inappropriate for physicians to participate in xenograft procedures outside existing federal
43 guidelines.

44
45 In order to protect the public health, all on-going xenotransplantation research should, at a
46 minimum, adhere to the 1996 PHS and IOM guidelines as well as the 1999 FDA
47 recommendations regarding precautionary measures to minimize potential risks posed by
48 xenotransplantation (e.g., clinical facility requirements, infection control practices, and post-
49 transplantation surveillance protocols). Any additional factors that would minimize potential risk
50 further should be implemented as well. For instance, as we learn more about the pathogenic
51 capacity of endogenous retroviruses, additional precautionary measures may be necessary.

1 Beyond clinical practice guidelines for xenotransplantation, clinical xenograft trials should adhere
2 to Opinion 2.07, “Clinical Investigation” and House of Delegate Policy 460.979, “Use of Animals
3 in Research (AMA Policy Database).”
4

5 Recommendations
6

7 The Council recommends that the following be adopted and the remainder of the report be filed:
8

9 Xenotransplantation includes any procedure that involves the transplantation, implantation, or
10 infusion into a human recipient of either (a) live cells, tissues, or organs from a non-human
11 animal source or (b) human body fluids, cells, tissues or organs that have had ex vivo contact
12 with live non-human animal cells, tissues, or organs. Although xenotransplantation offers a
13 potential source of tissue and organs for medical procedures, research in this area may uncover
14 physical and psychological conditions that require medical attention. As such, physicians need to
15 be involved in developing and implementing guidelines for continued research. Therefore, the
16 following guidelines are offered for the medical and scientific communities:
17

- 18 1) Physicians should encourage education and public discussion of xenotransplantation because
19 of the potential unique risks such procedures pose to individual patients and the public.
20
- 21 2) The medical and scientific communities should support oversight for the development of
22 clinical trial protocols and of ongoing xenotransplantation research.
23
- 24 3) Given the uncertain risk xenotransplantation poses to society, participants in early clinical
25 trials may have to agree to post-operative measures such as life-long surveillance, disclosure
26 of sexual contacts, an autopsy, and waive the traditional right to withdraw from a clinical trial
27 until the risk of late xenozoonoses is reasonably known not to exist. These requirements may
28 continue even if the transplanted tissue is rejected or removed. The informed consent process
29 should include a discussion of the above issues as well as potential risks to third parties and
30 psychological concerns associated with receiving an organ or tissue graft from an animal.
31 Careful attention must be paid to both the content of the consent disclosure and the manner in
32 which consent is obtained.
33
- 34 4) It would be ethical to include children and incompetent adults in xenotransplantation research
35 protocols only when the patients are terminally ill and alternative treatments are not available.
36
- 37 5) Allocation protocols must be fair and in accordance with Opinion 2.03, “Allocation of
38 Limited Medical Resources,” which recommends that decisions regarding the allocation of
39 medical resources among patients be based only on ethically appropriate criteria relating to
40 medical need. These criteria include, but are not limited to, the likelihood of benefit, the
41 urgency of need, the change in quality of life, the duration of benefit, and, in some cases, the
42 amount of resources required for treatment.
43
- 44 6) Sponsors of xenotransplantation research should assure that adequate funding exists for life-
45 long surveillance and treatment of complications arising from xenotransplantation procedures
46 on research subjects.
47
- 48 7) At a minimum, all on-going research should adhere to the *Public Health Service Guideline on*
49 *Infectious Disease Issues in Xenotransplantation*, FDA guidelines relating to
50 xenotransplantation, Opinion 2.07 “Clinical Research,” and any additional precautionary

- 1 measures believed to minimize potential risks to the public or to patients. It is inappropriate
2 to participate in xenograft procedures outside federal guidelines.
3
- 4 8) All xenotransplantation research should continue to promote high standards of care and
5 humane treatment of all animals used in research (H-460.979) and to apply these standards to
6 the care and treatment of animals used as sources of transplantation material.

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