Geoethics and Xenotransplantation

7

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Introduction

Geoethics is an extension of bioethics and medical ethics to a domain that extends over a greater geographic area than that of the subject of a medical or biotechnological intervention [1]. Bioethics and medical ethics are necessarily concerned with the immediate subjects of therapeutic or scientific interventions upon people [2]. The limitation is inherent in the basic principles of bioethics and medical ethics. These principles revolve around the autonomy of the patient or scientific subject, which is ascertained by obtaining from such person or persons their informed consent. In addition, the principles of medical ethics require a determination that the intervention is being accomplished for the benefit of the patient. When doubt exists, there must be equipoise, meaning uncertainty as to whether the intervention is as good as any alternative [3]. Furthermore, bioethical principles of justice require efforts to ensure that all patients able to participate in therapeutic modalities are being treated equitably. None of these principles can reasonably be satisfied when persons who may be affected by the therapeutic intervention are unknown and geographically distant. Geoethics is a broad moral philosophy that incorporates medical ethics and bioethics but applies across geography and in contexts when the persons who may be affected by a technological intervention are unknown.

Xenotransplantation is now the transplantation of organs or tissues from a genetically modified pig into people [4]. While organs from animals other than pigs could in theory be used, as in theory could genetically unmodified organs with novel pharmacologic tolerance-inducing protocols, in practice the term "xenotransplantation" has come to mean organs from pigs who have been genetically modified with the intent that their organs and tissues are tolerable in human transplant recipients. The exclusive reliance on pigs for xenotransplantation arises from the combination of

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their phylogenetic distance from humans by nearly 100 million years, their anatomical homology with human vital organs and their relatively large litter sizes.

Xenotransplantation has the potential to impact persons across a greater geographic area than the hospitals in which patients are receiving xenografts. This is because there is a theoretical possibility that pathogens or pathogenic viral sequences could inadvertently be transferred to patients along with a xenograft, and that such patients could inadvertently further transmit an infectious disease across broad geographic domains. Geoethics provides an appropriate analytical framework in which to assess the impact of xenotransplantation beyond the hospitals in which it occurs [5].

The key principles of geoethical analysis are diversity, unity and viability. Diversity in the context of xenotransplantation means that technologists should be granted the latitude to provide xenografts in accordance with medical direction. The geoethical principle of unity requires a determination that providing a new technology, such as xenotransplantation, does not put geographically distant individuals at materially greater risk than that to which they have agreed. The geoethical principle of viability requires third-party assurance of technologists' compliance with any agreements made with geographically distant populations.

Bioethics and medical ethics are subsets of geoethics in the context of an immediate doctor-patient relationship. Respect for the physician's right to offer a therapeutic intervention to a patient is an extrapolation of the geoethical principle of diversity. Limiting the physician's rights to such instances in which a patient consents to the therapy, if there is a risk of adverse effect on the patient, is a micro-implementation of the geoethical principle of unity. Finally, should the patient agree to a medical intervention, the existence of institutional review boards and medical practice certification committees to ensure compliance with informed consent practices, are examples of the geoethical principle of viability.

Geoethical Diversity as Practiced by Xenotransplantation Technologists

Xenotransplantation cannot be offered to patients without the approval of medical and healthcare authorities in a sovereign jurisdiction. Geoethical diversity requires that xenotransplantation technologists be unencumbered in developing safe and effective organ replacements. In order to determine whether a xenograft is therapeutically appropriate it will be necessary for it to tested in people [6].

There is no animal model that can replicate human biochemistry in all its immunological mystery, and, unfortunately, the field of computational biology is yet too immature to accurately replicate human physiology in all its relevant biomolecular complexity. Accordingly, geoethical diversity requires that promising xenografts be offered to appropriate patients for whom they promise a plausible chance of health improvement.

In January 2022, doctors at University of Maryland Medical Center offered an end-stage heart disease patient, Mr. David Bennett Sr., a xenoheart of a type that had previously worked for over 6 months in baboons, including showing no sign of rejection when used heterotopically with a native baboon heart for over 3 years [7]. While Mr. Bennett lived for only two further months with the xenoheart, there was a plausible basis to expect longer life and the 2 months was longer than he was expected to live without the xenotransplant.

The geoethical diversity principle is consistent with the environmental concept of precaution because the founding documents for the precautionary principle note that it can be satisfied without certainty. In other words, it is not necessary, for serious threats, to prove that a technology is certainly harmful before it can be mitigated. Reciprocally, though, for immaterial threats, it would not be necessary to prove that a technology is absolutely safe before it can be permitted. Were it otherwise, nothing could traverse from one country to another because in an interconnected biosphere there is nothing that is absolutely safe to everyone. As noted in the *Rio Convention*, "where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation." [8] There is a grey zone between the so-called precautionary and proactionary principles, with the latter requiring less a priori proof of safety than the former, but neither constituting a block on the diversity rights of technologists to develop therapeutics. The gist of the precautionary-proactionary continuum is that, even for serious threats, "full scientific certainty" is an irrational and hence inapplicable benchmark, and hence must be all the more inapplicable when a threat is minimal.

The geoethical question in every case is whether there are, in the words of the *Rio Convention*, "threats of serious or irreversible damage…." Where such threats do not exist, geoethics is permissive of the rights of biotechnologists to implement human trials of xenografts. Sovereign regulatory agencies such as the US Food and Drug Administration (FDA) do not permit anything to be offered as a therapeutic, outside of the gastro-intestinal tract, if it contains pathogens or is considered at all likely to cause infectious disease. Accordingly, in recent xenokidney-to-human cadaveric transplant cases xenografts were free of concerning pathogens because they came from pigs raised in a clinically appropriate facility (also known as specific pathogen free housing), and because the pigs were genetically unable to produce retroviruses of possible concern to humans [9]. Hence, there being "no threats of serious or irreversible damage", the geoethically right thing is supporting the diversity rights of the xenotransplantation team.

Geoethical Unity as Experienced by Xenotransplantation Participants

The geoethical principle of unity requires the assent of affected populations to any technological activity that places them at risk of material harm. When reduced to the microscopic geography of a hospital, this principle would require informed consent from the patient accepting a xenograft. As the circle of non-improbable harm widens, the number of people who must agree to a xenotransplant also widens. For example, for xenotransplantation, it might be sensible to include within the scope of geoethical unity any persons who might exchange bodily fluids with a xenograft recipient, or who might be in prolonged close contact with such a patient should they evidence a fever or cough. However, if there is no evidence of a meaningful risk of harm from xenotransplantation, then such prophylactics need not go further.

At one time it was thought that disease-causing porcine endogenous retroviruses (PERVs) could leap from pigs to people via xenotransplants [10]. However, it was later shown that just one type of PERV—called PERV-C—was essential to enabling an infection of human cells, albeit without causing any evidence of disease, and biotechnologists soon learned how to breed just PERV-C negative pigs as xenograft sources [11]. Consequently, geoethics would not require agreements to xenotransplantation procedures from third parties, either distant or nearby, so long as just PERV-C negative and otherwise clinically-appropriate pigs were used.

In the January 2022 xenoheart case described above, it is likely that the patient agreed as part of the informed consent procedures to not exchange bodily fluids with other persons, to report regularly to the hospital for biopsies and health monitoring and to consent to in-hospital quarantine should any infectious disease manifest. These requirements may have been adopted in part to protect the hospital from legal liability, in part to maintain the rigor of the scientific research into xenotransplantation and in part to further reduce the already very small risk of a pathogen spreading geographically. Since these additional requirements would not otherwise impede the development of xenotransplantation, their satisfaction in the interests of geoethical unity would not undermine geoethical diversity.

Geoethical Viability in the Context of Xenotransplantation

The geoethical principle of viability requires ongoing third-party compliance monitoring for any agreements reached between those at a risk of meaningful harm and the technologists who created the risk. Indeed, geoethics requires the actual control of any problematic technology be automatically transferred to the monitoring organization, either directly or via legal authority, in the event of deviation from the terms of geoethical agreement.

As discussed above, xenotransplantation activities as are likely to be carried out do not put persons other than the patient at a risk of harm. However, to demonstrate the applicability of the geoethical principle of viability, let it be supposed that a kind of xenotransplantation was proposed in which there was a material risk of zoonotic virus transmission. In such a case, geoethics would require a priori agreement to the activity by representatives of those who would be placed at risk of harm. Since 'viruses need no passports', the population of people placed at risk would be global, and the only representatives of worldwide populations are international organizations supported by national authorities representing their populations. Examples of sources of geoethical unity for such pandemic-prone xenotransplantation activities are the World Health Organization (WHO) or a new international organization arising from a xenotransplantation-specific treaty amongst the world's nations.

An international organization that was challenged with pandemic-prone xenotransplantation activities would likely condition its agreement with requirements that patients sign “Ulysses contracts” in which they agree to a prolonged period of post-transplant quarantine, ongoing biosurveillance and re-hospitalization with quarantine upon any sign of infectious disease. Ulysses contracts are non-cancellable agreements, and thus cannot be withdrawn as is generally the case for informed consents. In addition, such a global representative of the world’s peoples at risk of a pandemic-prone form of xenotransplantation might reasonably also require the technologists to fund a global pathogen surveillance network to look for incipient signs of a pandemic. Finally, it would be sensible pursuant to the geoethical unity principle to also require that a fair allocation of xenotransplants be allocated to a random selection of appropriate patients from countries other than where the surgeries are occurring, so that there might be benefits to counterbalance the risks.

Under the geoethical viability principle, third-party experts would be required to monitor and enforce any agreements reached between an international organization representing at-risk populations and xenotransplantation technologists. The viability principle requires these third-party experts to be funded in advance by the technologists and to be provided with legal authority to shut off the flow of problematic xenografts if the terms of agreement are not being followed. Examples of third-party experts would be international law firms or consulting companies that would retain subject-matter expertise in xenotransplantation and public health. New companies may classify themselves as geoethical audit organizations, or GAOs.

Practical Consequences of Geoethics for Xenotransplantation

The towering obligations imposed by geoethics for xenotransplantation makes it highly probable that only non-risky xenografts will be used. It is vastly easier to ensure that xenografts are from PERV-C negative pigs raised in designated pathogen-free conditions than it is to establish a new international treaty, or to fund a new global biosurveillance system. It is vastly easier to ensure that one’s xenografts do not create meaningful risks of harm to geographically distant populations than it is to manage the creation of such risks.

Consequently, it can be expected that the geoethical principles of unity and viability will not need to be deployed for xenotransplantation as it is likely to be practiced. Instead, the geoethical principle of diversity will prevail (freedom of technological innovation), implemented in the patient-focused micro-domain with the traditional bioethical principles of beneficence, non-malfeasance, autonomy and justice. In essence, the potential obligations of geoethical unity and viability create a “safe harbor” within which the field of xenotransplantation is free to develop xenografts that are safe both for the patient and for the greater geographic community.

Conclusion

Twenty-First century xenotransplantation looks nothing like historic examples of body part or fluid exchanges between sundry animals and humans. Xenografts are being tried, and with growing success, only from herds that pose no meaningful risk of infectious disease to the patient or to others, and that are phylogenetically distant, generally accepted food sources that coincidentally have some therapeutically relevant aspect of physiological or biochemical homology with humans. This situation prevails because the collective human consciousness that underlies geoethics raises extremely high barriers to any other form of xenotransplantation, while also being proactively encouraging of the safe types of xenografts now being tested.

Xenotransplantation provides an excellent example of how bioethics and medical ethics operate within a philosophical superset of geoethics. All require the consent of those affected by a therapeutic or scientific intervention, but geoethics extends the ambit of consent to geographically distant populations. All require that the intentions of the healthcare or scientific actor are beneficent, non-maleficent and just, but geoethics transfers those intentionality judgements to the representatives of geographically distant populations, like how an Institutional Review Board (IRB) operates within a hospital setting. Geoethics uniquely requires that the terms of consent between technologists and those facing material risks from the technology be independently monitored and enforced.

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