Xenotransplantation: The Role of Public Involvement

3

Mariachiara Tallacchini

Introduction

Public involvement, namely including the general public, for health regulations and policies has gained momentum and has been deemed increasingly relevant in the past few decades in most democratic societies. This chapter illustrates the meaning and the evolution of public involvement in xenotransplantation (XTx) from a science policy perspective—that is, how scientific knowledge and normative requirements merge in decision-making—and with an interest for the current changes as to how democratic societies think of themselves [1]. Xenotransplantation represents a unique case as debates about the role of the public, from people's attitudes to citizen consultations, have been extensive and controversial. The chapter starts by briefly considering the role of the public in transplantation technologies in order to highlight that, while sharing a public health dimension, transplants and xenotransplants seem to look at the public for different purposes. In transplantation, the public has been considered crucial to support organ donation; in xenotransplantation, public involvement has gained momentum and then has become an international regulatory requirement as a strategy both to assess the acceptability of its risks and to better legitimize its implementation. As xenotransplantation carries potential risks of spreading xenozoonotic pathogens, its regulation involves traditional medical principles as well as environmental and public health approaches, such as the precautionary principle, which will be explained further in this chapter.

The chapter proceeds with an analysis of how "the public" has become relevant in the recent regulatory history of xenotransplantation. More precisely, different publics have been taken into account by making them the object of surveys and interviews where their positions are quantified; but they have been also addressed as

M. Tallacchini (✉)
Department of Legal Studies, Università Cattolica S.C., Piacenza, Italy
e-mail: mariachiara.tallacchini@unicatt.it

D. J. Hurst et al. (eds.), *Xenotransplantation*,
https://doi.org/10.1007/978-3-031-29071-8_3

subjects of deliberative interactions—with a special reference to the public consultations that took place in Canada and Australia at the turn of the millennium.

The overall knowledge and experience that has been acquired through all these theoretical and practical exercises has the potential to provide new ways of collaboration among citizens, scientists, and institutions. Also, from this perspective, transplantation and xenotransplantation can be looked at in a continuum as to public involvement, because they share the necessity of connecting individual and public health. The COVID-19 experience has added new insights to these forms of interactions in terms of using knowledge and sharing uncertainties responsibly, revealing the need for a more deeply committed citizenship from all parts of society.

Individual and Public Health in Transplantation Technologies

The contemporary history of transplantation of human organs, including its first surgical successes and increasing promises in the mid-twentieth century, seemed to suggest that transplants would become a viable therapy for a large population of patients. However, somehow paradoxically, despite their achievements, transplantation medical technologies and policies have had to face some major obstacles since their beginnings. On the one hand, successful campaigns to create social acceptance of donation—including acceptance of the concept of brain death [2]—and to forge a culture of human awareness and solidarity have not always achieved optimal results. On the other hand, even with more refined organ donation programs, the shortage of available, adequate, and compatible organs to be transplanted has been persistent and perhaps structural.

Indeed, as the former point is concerned, several well-organized donation campaigns all over the world have turned out to be capable of increasing organ availability—with the case of Spain becoming paramount [3, 4]—by combining a variety of medical and policy measures, including legal measures, financial incentives, expanding donors, and education.

More inclusive criteria for donors with potentially suboptimal organs depend on a complex set of technical factors and medical decisions, and financial incentives have remained somehow marginal, due to their potential ambiguities. Legal measures have been considered as one of the most relevant steps to be taken. In order to promote donations, legislations have either asked their citizens to provide express informed consent to donation in case of death (opt-in systems) or presumed their consent if individuals do not explicitly disagree (opt-out systems). Providing legal certainty to support transplant policies has definitely helped [5, 6] However, even in regulatory contexts where consent to donation is provided in advance, still medical personnel keep consulting with families and close contacts before proceeding. As the Spanish experience has shown, public confidence is not simply related to legislation encouraging donation, but is connected to the broader dimension of trust towards institutions [4, 7].

This is why increased attention has been paid to education processes raising knowledge and awareness in school programs [8, 6]. Education is deemed essential

as organ shortage represents an "inadequate societal response to organ donation" [6]. Indeed, the comparison between public attitudes and organ availability has consistently shown that, while the results of interviews and surveys reveal high levels of support to transplantation, the actual organ supply remains significantly lower [8]. This is why, according to some scholars, the educational message should introduce conceptual changes in encouraging organ donation. An efficient revision in transplant and organ donation education programs "may be a challenge to change the inadequate people's behavior" [6]. Citizens should be made aware that organ shortage is a health emergency, an "unjustifiable damage to public health" [8].

However, as said, also with optimized programs for organ donation the mismatch between the need for transplants and donor supply may remain. This can happen because: (1) some organs are more prone (like lungs) to be damaged due to trauma, disease or deterioration; (2) the rising prevalence of health problems, such as diabetes mellitus and obesity, can reduce the number of eligible donors; and (3) major public health problems, such as the COVID-19 pandemic, also have an impact on organs' safety [6].

The paradox of human organ transplantation is that, while an increasing number of patients will survive and thrive long-term after organ transplantation, the limited number of organs available is reducing the percentage of patients that successfully complete transplant surgery. This unavoidable conclusion often represents the premise for considering xenotransplantation, even with their complex set of scientific, technical, and normative issues [9].

From the public involvement point of view, the two domains seem different. Transplantation remains within the traditional boundaries of medical ethics in terms of free and informed consent of the transplanted, and with close contacts and/or family involved on the donor's side. The public dimension of transplantation, aimed at encouraging donation, despite its implicit meaning of public acceptance, support, and commitment, as well as its public health implications, has never led to the forms of public involvement triggered by xenotransplantation regulation.

Xenotransplantation introduced a discontinuity and an anomaly in medical ethics as it resulted after WWII, namely centered on the rights and the autonomy of the individual, primarily expressed through informed consent [10]. Because of its potential for transmission of xenozoonotic infections, on the one hand, lack of information about unknown risks was making informed consent contradictory; on the other hand, these threats were calling for harmonizing individual and collective rights, thus challenging the individually-oriented paradigm for medical ethics. The uniqueness of xenotransplantation, at least when it started becoming an applicable technology potentially concerning a large number of patients, consisted in its involving not only the informed and consenting patients who are willing to accept the risks, but also their contacts and families, and eventually also the general public [11].

In the 2000s a group of bioethicists started reflecting on the widely unexplored ethical implications of pandemics and the prolonged bioethicists' negligent behaviors in looking at public health issues [12, 13, 14]. In order to highlight the situation, Michael Selgelid forged the word "pandethics" to refer to the ethical context where

the patient is both the victim and the vector of an infection [15]. Although Selgelid explored the context of (unexpected) outbreaks of infectious diseases, a medical technology with potential pandemic effects was not different. In the aftermath of the September 11, 2001 terrorist attacks against the United States by al-Qaeda members and the 2003 severe acute respiratory syndrome (SARS) outbreak that was first identified in China, Jay Fishman argued that "(m)eaningful distinctions do not exist for the medical community between epidemics caused by natural causes, new technologies or bioterrorism". He added, as a pragmatic more than a prophetical conclusion, that if we were to fail in coordinating better international reporting about infectious diseases, "we will always be a little bit too late. And with the next outbreak, we will, once again, be surprised" [16].

Therefore, xenotransplantation found itself at the crossroad between medical and public health regulatory issues. This intersection explains how it seemed relevant that the most directly impacted subjects (close contacts), but also society at large may have a say about the acceptability of this technology and its risks.

Risks, Precaution, and the Public: From the Environment to Health Technologies

A brief summary of the main passages and events that have accompanied and framed the rise and the expanding role of the "public" helps provide the context for understanding how this requirement has emerged in xenotransplantation regulation and has been considered as a source of democratic legitimacy and transparency.

Recognition that the public at large should be given a right to 'a say' about science and technology has been part of both scholarly reflection and science policy since the early 1970s in the environmental domain, and with the growing impact of techno-science in daily life. The involvement of specific fractions of the public was initially theorized and introduced in the United States with the National Environment Protection Act in 1969, while an industrial accident releasing dioxin in a chemical plant in Seveso (Italy) in 1976 triggered the 1980s European legislation on public information and participation [17].

In the mid-1970s public consultation was more widely proposed in relation to all technological domains within the context of the US Congress Office of Technology Assessment (OTA). Its first director, Joseph Coates, argued that public participation in technology assessment was essential for several reasons. First, it allows understanding the actual impacts of new technologies and their different forms of implementation. Second, it provides early awareness of failures and issues. Third, it prepares citizens for unexpected outcomes [18].

The issue of involving the public in the discussion also emerged in the context of the first two Asilomar conferences in 1974 on genetic engineering, where the term "public" was initially used (by bioethicist Alexander Capron) to refer to government and the law. During the same period, town meetings discussing the potential unintended release of genetically modified micro-organisms (MGMs), and directly launched by the scientific community, involved the population of Cambridge, Massachusetts [19].

In 1992 the Rio Declaration on Environment and Development internationally introduced the precautionary approach (and later "principle" in the European formulation of it [20]), stating that: "lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures" of prevention (Principle 15) [21]. The principle framed the idea that potential risks should be considered as actual risks in case of serious environmental threats. And, in 1996, the United Kingdom Nuffield Council of Bioethics, in a dedicated opinion that coincided with the 1996 draft Regulation on Xenotransplantation issued by the Food and Drug Administration (FDA) [22], for the first time connected xenotransplantation to the precautionary principle, thus extending its scope from the environment to health protection [23].

However, the implications of the precautionary principle remained open to a variety of interpretations, from calling for a moratorium to assessing public acceptance of risks. The former suggestion was taken up after a study in 1997 reported that human cells could be infected in vitro by porcine endogenous retroviruses (PERVs) [24]. In 1998 a group of leading xenotransplantation scientists in the US briefly called for a moratorium [25, 26], but later some of them shifted toward highlighting the need for public consultation [27]. In 1999 the Council of Europe, the institution in charge of human rights in the enlarged European context, also temporarily suggested a moratorium [28].

In the US regulation the precautionary principle was never favorably received—as precautionary measures have been mostly interpreted to refer to preventing actual risks [29]. The 2001 Public Health Service (PHS) Guidance on xenotransplantation quite marginally recognized that "public discourse on xenotransplantation research is critical and necessary" and that "public awareness and understanding of xenotransplantation is vital because the potential infectious disease risks posed by xenotransplantation extend beyond the individual patient to the public at large" [30]. The US never deemed necessary to launch a public consultation, even though the PHS Guidance was open to public comments, and public hearings with a limited participation from the public were held.

In Europe the meaning of the precautionary principle, extended to include all threats to human, animal, plant and environmental health, remained paternalistic as a "political responsibility" about the "high level of protection of citizens" [20].

In the past two decades, however, reflection on precaution has increasingly focused on the need not to stop emerging technologies, but to assess them carefully through an appropriate regulatory process, including public willingness and preparedness to accept potential risks when outweighed by substantial benefits.

Consulting Citizens on Xenotransplantation

At the beginning of the twenty-first century the US PHS Guidance set the regulatory conditions for the delicate passage from the preclinical to the clinical phase, thus normalizing and legitimizing xenotransplantation [31]. The US measures were rapidly followed by other countries, with different legal approaches towards experimenting with governance of emerging and controversial biomedical technologies.

The US approach primarily focused on mitigating the potential risks of infections. The major assumption was that the most likely potential form of infectious disease would be similar to the Human Immunodeficiency Virus (HIV) [30], a pathogen controllable through patients' responsible behavior. The guidance aims at protecting all involved subjects, but still relies only on patients' consent to inform their intimate contacts about potential risks [30, 32].

The Council of Europe (backed up by a favorable opinion from the European Commission) grounded its recommendations on the assumption of the worst case scenario of an airborne disease and suggested compulsory constraints for non-compliant patients and third parties (family and close contacts) (Article 21) [33]. According to the recommendation, patients and third parties should accept to "waive some fundamental rights" [34].

With a completely different approach, between 1999 and 2004, Canada and Australia equally interpreted the public health challenges posed by xenotransplantation severe enough to impact on the constitutional level of their societies and have the population contribute to the decision. Both governments went through extended forms of public consultation (through the mail, emails and the web, focus groups, and several town meetings) and translated the theoretical concept of scientific citizenship, namely citizens participating in science-based public policy, in operational terms. Later, in the mid-2000s, another participatory approach was endorsed by New Zealand, where the Maori population was consulted as a minority whose cultural values could matter in techno-scientific innovation.

Starting in 1999, the Canadian government launched an extensive public program on xenotransplantation, culminating in the release in 2001 of the report "Animal to-Human Transplantation: Should Canada Proceed? A Public Consultation on Xenotransplantation" [35]. The government was not primarily looking for approval, but was experimenting in strengthening democracy in health policy. The initiative shaped the role of citizens as "lay scientists", by providing them with the relevant information on xenotransplantation and waiting for their informed opinions. After a long and articulated process involving several deliberative experiences, citizens ended up by arguing that "Canada should not proceed" [35], thus challenging the so-called "knowledge deficit model" [36]. According to this model, uninformed people tend to disagree with science, while well-informed people tend to agree with it. Canadians reversed this theoretical assumption: having started with a favorable position towards xenotransplantation, the more they knew about its complexities and risks, the less ready they became in accepting it as a viable option. Though not opposed in principle, citizens argued that scientists and the health industry should more clearly demonstrate that benefits would outweigh risks, asking for continued public discussion on xenotransplantation.

In 2001, the Australian National Health and Medical Research Council (NHMRC) established a Working Party to provide advice on the scientific and normative aspects of xenotransplantation, to produce guidelines on clinical trials, and to consult with the community. In the next 2 years, an informed community discussion was organized [37, 38]. The Australian initiative was quite critical of the Draconian

safety measures introduced by other regulations, arguing that a challenging technology cannot primarily rely on patients' constraints and infringement of fundamental human rights: this does not correspond to sound science. Compulsory measures should not be used as a surrogate for scientific evidence of safety; therefore, "investigators should provide sufficient evidence of safety to show that there is no undue risk to the community if some participants choose to leave the trial" [37]. The final document suggested that Australian socially responsible scientists and citizens should cooperate to keep the community safe even if some patients may not comply with safety measures.

The results of both participatory exercises were disparate. After Canadians asked the government not to proceed with xenotransplantation, the government went back to a more science-based policy and set up an expert working group to further analyze the situation.

Australia accepted its citizens' concern about xenotransplantation, and in 2004 adopted a 5-year moratorium [39]. At the end of 2009, however, the Australian government expressed a favorable inclination toward proceeding with xeno-cell therapies, looking at the EU framework on Advanced Therapies [40] as a reassuring template that "risks, if appropriately regulated, are minimal and acceptable" [41].

In 2005 a more limited public consultation among the Maori population took place in New Zealand on the acceptability of a single clinical trial proposed by Living Cells Technology (LCT), a biotech company [42]. The trial concerned the implant of alginate encapsulated porcine islet cells into 8 type 1 diabetic patients [43]. Despite a long international controversy, the results of the consultation turned out favorable to xenotransplantation and to the proposed trial, also because the Maori felt that their opinion about innovative technologies had been taken into account by the government. Eventually, the New Zealand Minister of Health authorized the trial [44] that took place in 2009 [45].

The World Health Organization (WHO) attributed international recognition to these democratic experiences. Since the late 1990s the WHO had been very active in the field of xenotransplantation regulation [46]. In the early 2000s the increased threats of pandemics [47], and the risks of 'xeno-tourism' (patients traveling to countries where transplants can be easily performed without controls) [48] made the global situation more challenging. In 2004 the WHO warned against the absence of regulatory frameworks in countries where unauthorized experimentation could take place [49].

Finally, in 2008 the WHO Changsha Communiqué, following the first 'Global Consultation on Regulatory Requirements for Xenotransplantation Clinical Trials' held in China, published a refined general framework and explicitly endorsed a democratic governance of xenotransplantation [50]. After having set the existence of effective regulatory frameworks as an essential condition to legitimately proceed with XTx, the WHO added that "the regulatory system should be transparent, must include scientific and ethical assessment and should involve the public" [50]. The Second and Third WHO Global Consultation of 2011 and 2018 have confirmed the same principles [51, 52].

Debating the Public Dimension: Publics or Citizens?

The roles of non-experts in contributing to public discussion in science policy has been at the core of philosophical, sociological, and political analysis in the past two decades [53, 54] and has been widely debated in the context of xenotransplantation. Xenotransplantation represents an outstanding case of how theories and techniques about making sense of the "public" have changed through time, and how diverse perspectives have fought against each other in order to have the specific attitudes of certain groups to represent the views of the general public.

The first inquiries about public feelings towards xenotransplantation are especially relevant in order to understand the evolution of the public's role. They began in the early 1990s, when the potential for genetic engineering of pigs to partially overcome the issue of hyperacute rejection of their cells and tissues made clinical trials more safely feasible and realistically close. In 1993 a US Gallup poll reported 51% acceptance among 6127 people asked through a telephone survey whether they would accept an animal organ if a human organ was not available [55]. Very quickly the issue of public response became highly debated and controversial. In 1995 and again in 1997 and 1998 [56, 57, 58] a group of Australian researchers, while recognizing the relevance of xenotransplantation, made the point that accurate and extensive analysis of public attitudes was "mandatory" to avoid replicating the problems already raised by human organ transplantation. According to the group, public attitudes "will undoubtedly determine whether or not xenotransplantation gains general acceptance" [58].

Through a questionnaire in Australian hospitals the researchers reported high rates of aversion to xenotransplantation among 1956 acute care nurses (only 19% in favor of animal organs) and also from a group of 113 patients with renal diseases or in dialysis waiting for a kidney transplants (42% willing to receive a nonhuman organ). The reasons for aversion were not specified and the interpretation of data remained open to different interpretations, with some authors arguing that 40% did not show aversion, but was a positive result [59]. The Australian data was not contested, but most researchers in the field reacted by providing their findings in support of xenotransplantation. The skepticism of Australian patients was immediately contrasted by a survey in the United Kingdom (UK) reporting the "scientific enthusiasm" (78% willing to receive a nonhuman organ) of 850 patients with renal failure [60]. The initial debate on public attitudes and its relevance for xenotransplantation to proceed suddenly became a war of numbers and regional attitudes (UK and US against Australia). In 1997, after evidence showed human cells infected in vitro with PERVs [24], quantitative analyses of xenotransplantation rapidly grew in scientific journals, where survey and attitude literature had already earned a relevant space that has constantly expanded since. The main purpose for these sociological approaches has been, and still is, measuring the strength of public support for xenotransplantation, and sometimes also providing implicit forms of advertisement to it. Here the "knowledge deficit model" is often assumed: namely, that the more knowledgeable, aware, and educated the public, the more willing they are to accept xenotransplantation [36].

Besides providing an understanding of public feelings (or perceptions, attitudes, etc.) towards the new technology, this vast literature also introduced a wide range of "publics" by constructing a variety of different relevant fractions of the population (nurses, students, people with religious beliefs, etc.) [61, 62, 63]. In fact, if initial consideration was primarily given to patients, their contacts, health personnel, and students in medicine, the focus has widened to include several stakeholders and non-stakeholders (individuals without a precise interest in the subject), including religious groups, non-Western countries, minorities, disadvantaged and under-represented communities [64]. Through the years, research on public attitudes has substantially changed both with an increased opening to multiple sociological approaches and a more complex vision of the public [65].

Moreover, new research methods have been framed that compare different ways of engaging lay-people and scientists, with individuals retrospectively reflecting on their initial positions and how these have changed through the participatory process [66].

Still, a divide seems to remain between these exercises and the forms of public consultation launched in Canada and Australia. The two different categories of research have been described as "one-way" and "two-way" communication: one aimed at collecting information from the public, the other providing room for dialogue and discussion between scientists and the public [36].

Though with subtleties, the former remains "descriptive"—or should remain as numbers may be used to express tendencies—the latter is meant to produce "normative" suggestions. Indeed, "How do specific fractions of the public perceive xenotransplantation?" and "What do citizens suggest when addressed as potential co-regulators?" highlight different ways of looking at how innovation should legitimately take place.

Publics can be seen as objects of research, with quantifiable positive and negative attitudes towards XTx; but they can also be empowered as subjects of decisions.

In the mid-2000s the "momentum" for large public involvement was over, but the Canadian and Australian participatory experiences continued, developing toward broader institutional forms of public involvement. Canada has kept working on providing opportunities for citizens to participate in decision-making processes, especially in the field of health. In doing so, Health Canada has clarified and codified the language of public involvement. According to the current Guidelines on Public Engagement, the term "public" refers to "any individual or unorganized group (…) that is interested in or affected by, or has the potential to be affected by, an issue, decision or action". The word "citizen" is not explicitly defined, but is subsumed in the term "Canadians". Also, two different ways of addressing the public are defined. First, "public engagement" refers to planned 'two-way' (bidirectional) discussions with all individuals, organizations, or groups affected by the decision-making. Second, "public opinion research" (POR) concerns the planned, 'one-way' systematic collection of opinion-based information of any target audience using quantitative or qualitative methods and techniques such as surveys or focus groups [67]. The two different categories of public involvements—the former based on dialogues, discussions, and fora; the latter based on expressions of opinions—far from

excluding each other, are instead deemed complementary for better regulation and decision-making.

Australia has also devoted a big effort towards grounding participatory exercises in a vision of political philosophy, with National Action Plans "jointly developed by Government and Civil Society to help make Governments more transparent, accountable and publicly engaged" [68]. In this vision the concept of "public" has been reframed as "the citizens" "whose agency matters"; and "concepts such 'co-creation' and 'co-production' have been introduced to describe this systematic pursuit of sustained collaboration" between institutions, communities, and individual citizens, towards "a citizen-centric public service" [69].

Responsible Collaboration and Commitment: Merging Individual and Public Health After COVID-19

Xenotransplantation can be properly defined as a re-emerging technology since it has appeared and reappeared through time with increasingly adequate answers to problems of both feasibility and reduction of risks. In the 2010s successful developments with xenocell therapies seemed to allow overcoming several obstacles, with more harmonized regulatory approaches, and more manageable and acceptable risks [70, 71]. However, some disruptive factors in the recent times seem to have wiped out this reassuring landscape. COVID-19 unveiled a general lack of preparedness (even though the outbreak of a pandemic has been long expected); and the xenotransplantation scientific community was again confronted with assessing known and novel risks, while coping with supposedly skeptical public reactions [72, 73]. Then, toward the end of 2021 and the beginning of 2022, some partially unexpected experimental procedures with xeno-organs have revamped interest in xenotransplantation.

Three procedures were performed on brain dead subjects (two at NYU Langone Transplant Institute and one at the University of Alabama at Birmingham) [74, 75], and one on a living patient with end stage heart failure (at the University of Maryland School of Medicine) [76]. While the cases showed substantial progress in dealing with hyperacute rejection and added knowledge about the proper functioning of xeno-organs [77], they also renewed questions and concerns. But, while the ethical and social aspects of research on brain dead subjects have been already discussed in recent years and consensus has been reached about the ethical conditions that should be met in order to proceed [78], the xeno-heart transplant in a living patient, although authorized, was received in bewilderment. Commentators have harshly criticized the acceptability of informed consent, the absence of ethical approval due to the emergency situation, the authorization justified as compassionate use, and the complete absence of public awareness (not to mention public discussion) [79].

How has the role and meaning of the public dimension changed under the current circumstances? Reflection on, and practice of, the relations among institutions, researchers, and citizens have evolved greatly in the past few years. The overall perspective resulting from this evolution has led to making the most of both research

on public opinions and the dialogues with citizens. Currently, from the perspective of better innovation policy, both strategies can concur in gaining knowledge and building trust, and have become synergic factors towards improving the quality of decision making. On the one hand, research on public attitudes has the potential to add relevant knowledge on social acceptance of xenotransplantation by exploring the new issues raised by the recent experimental procedures. People, for example, could be asked: (a) if they were surprised or not by these forms of experimentation; (b) if they think that xenotransplantation is still a big challenge; (c) under which circumstances it could become a standardized treatment. On the other hand, it has been observed that the recent cases of experimental procedures reveal the relevance of public involvement for xenotransplantation to proceed as a widely accepted technology. "Increased public awareness and full transparency during clinical trial planning and execution will be needed to generate support for organ xenotransplantation trials" [77]. Surveying the public and creating awareness through an open dialogue represent converging strategies in legitimizing innovation.

Moreover, as uncertainties are concerned, the COVID-19 experience has provided relevant insights and practical evidence. What democratic societies have been experiencing is a collective learning process—involving regulators, experts, and citizens—in adequately absorbing knowledge and implementing it in daily behavior [80].

The crisis has shown that citizens' accurate understanding and implementation of scientific knowledge in everyday life have been at the core of infections containment strategies. Since the beginning of the pandemic citizens have been asked to acquire a lot of information about behaving safely in every aspect of their daily life: from washing hands to properly wear, and dispose of, masks; from keeping adequate distance to properly manage safety protocol at home or at work; from interpreting their symptoms to implementing procedures of self-isolation and quarantine.

All these new knowledge and practices require reciprocally trusted relations from both institutions and citizens. Institutions can offer clear and reliable information and have to rely on lay people's ability to adopt and properly use it with a crucial impact on keeping social life safe. But institutions are also learning from their collaborations with citizens. Several activities of so-called "citizen science" have been launched, for example, by the US National Institutes of Health (NIH), asking patients to collect evidence on long-haul COVID-19 for further studying the disease [81]. Collaborative research has become common in several fields [82, 83] and, increasingly, lay individuals are expected to properly manage sophisticated knowledge and technology. As some scholars in science policy commented, "the whole world becomes an extended peer community", because the appropriate behavior and attitudes of populations become crucial for a successful response to the virus [84]. The experience of COVID-19 showed that risks already are a daily part of contemporary life and that living with uncertainties has been largely acquired rationally and even emotionally. This is more than just expressing a hypothetical opinion or participating in a consultation exercise on new technologies. This is about how people live with risks.

Collaborative knowledge and exchange of knowledge make risks constantly redefined, clearer, and more manageable. This collaboration concerns also xenotransplantation that is no longer unique and can be performed in highly controlled environments. For instance, patients and their contacts can manage knowledge, perform complex tasks, and can be early "sensors" and "interpreters" of conditions and symptoms in relation to potential adverse events; the public can be supportive of collective forms of experimental procedures in a climate of full legitimacy, clarity, and transparency.

Some Provisional Conclusions for a Work in Progress

This chapter summarized the meaning and evolution of the roles of the public in xenotransplantation, and its broader connection to transplantation. These roles have been associated with public support of new technologies, acceptance of potential and potentially unknown risks, better regulation, harmonizing individual and public health, more transparent and legitimate public decisions. These multiple roles have been assessed through a variety of methodological tools, from measuring public attitudes to launching public dialogues.

However, the seemingly big divide among these different approaches in making sense of how people should get involved in xenotransplantation is becoming, at least practically, blurred as these approaches increasingly appear complementary in the actual governance of risks.

A wide convergence exists in thinking that conditions of scientific uncertainty need to be opened up and shared to achieve better "preparedness" in protecting individual and public health as a matter of safety and solidarity as civic commitments.

In highlighting the role of public education on transplants, it has been observed that "(t)he decision of an organ donor is one of the most important and significant behavior of a current world citizen" [8]. From this perspective—even though other medical technology may emerge and result as more viable—transplantation and xenotransplantation similarly show the connection between individual and public health as a civic commitment toward safety and solidarity.

The COVID-19 experience has strengthened this perspective. Current democratic societies can be defined as "democracies of experience". The active search for an improved quality of public decision making has thus moved from theoretical exercises to involve citizens toward the actual experience of deeper meanings of citizenship, requiring collaboration, responsibility, and commitment from and among all parts of the society [85].

References

1. Jasanoff S. Science and democracy. In: Felt U, Fouché R, Miller CA, Smith-Doerr L, editors. The handbook of science and technology studies. 4th ed. Cambridge: MIT Press; 2017. p. 259–88.
2. Lock M, Young A, Cambrosio A, editors. Living and working with the new medical technologies: intersections of inquiry. Cambridge: Cambridge University Press; 2000. (Cambridge Studies in Medical Anthropology).

3. Matesanz R, Dominguez-Gil B, Coll E, de la Rosa G, Marazuela R. Spanish experience as a leading country: what kind of measures were taken? Transpl Int. 2011;24:333–43.
4. Matesanz R, Marazuela R, Coll E, Mahillo B, Dominguez-Gil B. About the opt-out system, live transplantation, and information to the public on organ donation in Spain… Y ole! Letter to the editor. Am J Transplant. 2017;17:1695–6.
5. Chatterjee P, Venkataramani AS, Vijayan A, et al. The effect of state policies on organ donation and transplantation in the United States. JAMA Intern Med. 2015;175(8):1323–9.
6. Vanholder R, Domínguez-Gil B, Busic M, et al. Organ donation and transplantation: a multi-stakeholder call to action. Nat Rev Nephrol. 2021;17:554–68.
7. EP (European Parliament). Organ donation and transplantation facts, figures and European Union action. European Union, 2020. https://www.europarl.europa.eu/RegData/etudes/BRIE/2020/649363/EPRS_BRI(2020)649363_EN.pdf.
8. Cantarovich F. The society, the barriers to organ donation and alternatives for a change. In: Tsoulfas G, editor. Organ donation and transplantation-current status and future challenges. London: IntechOpen; 2018. https://www.intechopen.com/chapters/59201.
9. Stevens S. Xenotransplantation. In: Tsoulfas G, editor. Organ donation and transplantation-current status and future challenges. London: IntechOpen; 2018. https://www.intechopen.com/chapters/60883.
10. Weindling P. The origins of informed consent: the International Scientific Commission on medical war crimes, and the Nuremberg Code. Bull Hist Med. 2001;75(1):37–71.
11. Kaiser M. Xenotransplantation–ethical considerations based on human and societal perspectives. Acta Vet Scand. 2004;45:S65. https://doi.org/10.1186/1751-0147-45-S1-S65.
12. Selgelid MJ. Ethics and infectious disease. Bioethics. 2005;19(3):272–89.
13. Francis LP, et al. How infectious diseases got left out – and what this omission might have meant for bioethics. Bioethics. 2005;19(4):307–22.
14. Selgelid MJ, McLean A, Arinaminpathy N, Savulescu J. Infectious disease ethics: limiting liberty in contexts of contagion. Cham: Springer; 2011.
15. Selgelid MJ. Pandethics. Public Health. Special Issue. 2009;123(3):255–9.
16. Fishman JA. SARS, xenotransplantation and bioterrorism: preventing the next epidemic. Am J Transplant. 2003;3:909–12.
17. De Marchi B, Funtowicz S, Ravetz J. Seveso, a paradoxical classic disaster. In: Mitchell JK, editor. The long road to recovery: community responses to industrial disaster. Tokyo-New York-Paris: United Nations University Press; 1996. p. 86–120.
18. Coates JF. Why public participation is essential in technology assessment. Public Adm Rev. 1975;35(1):67–9.
19. Asilomar FDS, Recombinant DNA. The end of the beginning. In: Institute of Medicine Committee to study decision making (Hanna KE, editor). Biomedical politics. Washington: National Academies Press; 1991.
20. EC (European Commission), Communication from the Commission on the precautionary principle, 2000, February 2. Brussels COM (2000)1.
21. United Nations Conference on Environment and Development. Rio Declaration on environment and development. Rio de Janeiro, June 3–14, 1992.
22. FDA (Food and Drug Administration), DHHS (Department of Health and Human Services), PHS (Public Health Services). Draft Public Health Service guidelines for xenotransplantation. Fed Regist. 1996;61(185):49919–32.
23. Nuffield Council on Bioethics. Animal-to-human transplants: the ethics of xenotransplantation. London: Nuffield Council on Bioethics; 1996.
24. Patience C, Takeuchi Y, Weiss RA. Infection of human cells by an endogenous retrovirus of pigs. Nat Med. 1997;3:282–6.
25. Bach FH, Fishman JA, Daniels N, Proimos J, Anderson B, Carpenter CB, et al. Uncertainty in XT: individual benefit versus collective risk. Nat Med. 1998;4:141–4.
26. Bach FH, Fineberg HV. Call for moratorium on xenotransplants. Nature. 1998;391:326.
27. Ivinson AJ, Bach F. The xenotransplantation question: public consultation is an important part of the answer. Can Med Assoc J. 2002;167:42–3.

28. COE (Council of Europe). Recommendation 1399 (1999) on xenotransplantation. Text adopted by the Council of Europe Assembly on 29 January 1999.
29. EEA (European Environment Agency). Late lessons from early warnings: the precautionary principle 1896–2000. Environmental issue report No 22, 2001. https://www.eea.europa.eu/publications/environmental_issue_report_2001_22.
30. PHS (Public Health Service). Guideline on infectious disease issues in xenotransplantation. 2001. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/phs-guideline-infectious-disease-issues-xenotransplantation.
31. Tallacchini M. Risks and rights in xenotransplantation. In: Jasanoff S, editor. Reframing rights. Bioconstitutionalism in the genetic age. Cambridge: MIT Press; 2011. p. 169–92.
32. FDA-CBER (Center for Biologics Evaluation and Research). Source animal, product, preclinical, and clinical issues concerning the use of xenotransplantation products in humans. Guidance for Industry. 2003, updated December 2016. https://www.fda.gov/media/102126/download.
33. COE (Council of Europe). Recommendation (2003)10 of the Committee of Ministers to Member States on xenotransplantation. Adopted by the Committee of Ministers on 19 June 2003.
34. EC (European Commission). Scientific Committee on medicinal products and medical devices. Health & Consumer Protection Directorate General. Opinion on the state- of- the- art concerning xenotransplantation. Doc.SANCO/SCMPMD/2001/0002 Final, 2001. http://ec.europa.eu/health/ph_risk/committees/scmp/documents/out38_en.pdf.
35. CPHA (Canadian Public Health Association). Animal- to- human transplantation: Should Canada proceed? A public consultation on xenotransplantation. 2001.
36. Wynne B. Misunderstood misunderstanding: social identities and public uptake of science. Public Underst Sci. 1992;1(3):281–304.
37. NHMRC (National Health and Medical Research Council), Xenotransplantation Working Party. Animal- to- human transplantation research: How should Australia proceed? Response to the 2002 public consultation on draft guidelines and discussion paper on XT. Commonwealth of Australia 2003.
38. NHMRC (National Health and Medical Research Council), Xenotransplantation Working Party. Animal- to- human transplantation research: A guide for the community. Public consultation on XT. 2003/04, Commonwealth of Australia 2003.
39. NHMRC (National Health and Medical Research Council). Communiqué from the NHMRC's 154th session 2004.
40. EC (European Communities) Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.
41. NHMRC (National Health and Medical Research Council). NHMRC statement on xenotransplantation. 2009.
42. Toi te Taiao, The Bioethics Council. The cultural, ethical and spiritual aspects of animal-to-human transplantation. A report on xenotransplantation by Toi te Taiao: The Bioethics Council, New Zealand. Ministry of the Environment 2005.
43. Living Cells Technology Announcement, 'First Patient In Living Cell Technologies' New Zealand DIABECELL® trial drops insulin dose without ill effects. http://www.asx.com.au/asxpdf/20120926/pdf/428z0ty9pjdq55.pdf.
44. Beehive.govt.nz. The official website of the New Zealand government. Living cell technologies trial approved, 2008. October 21. https://www.beehive.govt.nz/release/living-cell-technologies-trial-appoved/.
45. ScienceMedia. Xenotransplantation and the LCT trials in New Zealand, 2009. July 17. https://www.sciencemediacentre.co.nz/2009/07/17/xenotransplantation-and-the-lct-trials-in-new-zealand/.
46. WHO (World Health Organization). Xenotransplantation: guidance on infectious disease prevention and management. WHO/EMC/ZOO/98.1, 1998. http://apps.who.int/iris/bitstream/

handle/10665/65511/WHO_EMC_ZOO_98.1.pdf;jsessionid=952F9963F743E1326D82DD045BF17253?sequence=1.
47. Jones KE, et al. Global trends in emerging infectious diseases. Nature. 2008;451:990–3.
48. Cook P, Kendall G, Michael M, Brown N. Xenotourism and xenotravel: some notes on global regulation. In: Bailey C, Barnett K, editors. Social change in the 21st century conference proceedings. Queensland: Queensland University of Technology; 2005. p. 1–11. https://eprints.qut.edu.au/3449/1/3449.pdf.
49. WHO (World Health Organization). Fifty-seventh World Health Assembly, Agenda Item 12.14, 2004. Resolution 57.18. http://www.who.int/gb/ebwha/pdf_files/WHA57/A57_R18-en.pdf.
50. WHO (World Health Organization). First WHO global consultation on regulatory requirements for xenotransplantation clinical trials. Changsha, 2008. The Changsha Communiqué. http://www.who.int/transplantation/xeno/ChangshaCommunique.pdf.
51. WHO (World Health Organization). Second WHO global consultation on regulatory requirements for xenotransplantation clinical trials. 2011. http://www.who.int/transplantation/xeno/report2nd_global_consultation_xtx.pdf.
52. Hawthorne WJ, Cowan PJ, Bühler LH, Yi S, Bottino R, Pierson RN, et al. Third WHO global consultation on regulatory requirements for xenotransplantation clinical trials, Changsha, Hunan, China December 12–14, 2018. The 2018 Changsha Communiqué. The 10-Year anniversary of the international consultation on xenotransplantation. Xenotransplantation. 2019;26(2):e12513.
53. Nowotny H, Scott PB, Gibbons MT. Re-thinking science: knowledge and the public in an age of uncertainty. London: Wiley; 2001.
54. Funtowicz SO, Ravetz JR. Science for the post-normal age (1993). Common Places. 2020, May 5 (republished with a new foreword). https://commonplace.knowledgefutures.org/pub/6qqfgms5/release/1.
55. Gallup Organization, Inc. The American public's attitudes toward organ donation and transplantation, conducted for the partnership for organ donation. Midlothian: Virginia's Organ Procurement Agency, 1993.
56. Mohacsi PJ, Blumer CE, Quine S, et al. Aversion to xenotransplantation. Nature. 1995;378:434.
57. Mohacsi PJ, Thompson JF, Nicholson JK, et al. Patients' attitudes to xenotransplantation. Lancet. 1997;349:1031.
58. Mohacsi PJ, Thompson JF, Quine S. Attitudes to xenotransplantation: scientific enthusiasm, assumptions and evidence. Ann Transplant. 1998;3:38–45.
59. Cooper DKC. Organ transplants. Nature. 1996;379:578.
60. Ward E. Attitudes to xenotransplantation. Lancet. 1997;349:1775.
61. Michaels M. Publics performing publics: of pigs, pips and politics. Public Underst Sci. 2009;18:617–31.
62. Casabona CR, Jorqui Azofra M, Cozzi E, editors. Scientific, ethical, social and legal aspects of xenotransplantation. Padova: Zampieron; 2012.
63. Sobbrio P, Jorqui M. An overview of the role of society and risk in xenotransplantation. Xenotransplantation. 2014;21(6):523–32.
64. Padilla LA, Hurst DJ, Jang K, Rosales JR, Sorabella RA, Cleveland DC, Dabal RJ, Cooper DK, Carlo WC, Paris W. Racial differences in attitudes to clinical pig organ. Xenotransplantation. 2021;8(2):e12656.
65. Hurst DJ, Padilla L, Cooper D, Paris W. Factors influencing attitudes toward xenotransplantation clinical trials: a report of focus group studies. Xenotransplantation. 2021;28(4):e12684.
66. Burgess J, Stirling A, Clark J, Davies G, Eames M, Staley K, Williamson S. Deliberative mapping: a novel analytic-deliberative methodology to support contested science-policy decisions. Public Underst Sci. 2007;16:299–322.
67. HC & PHAC (Health Canada and the Public Health Agency of Canada). Guidelines on public engagement, Ministry of Health, 2019. https://www.canada.ca/en/health-canada/services/publications/health-system-services/health-canada-public-health-agency-canada-guidelines-public-engagement.html.

68. OGPA (Open Government Partnership Australia), National Action Plan 2020–22 (NAP3), 2020. https://www.opengovpartnership.org/wp-content/uploads/2020/03/OGPs-Implementation-Plan-2020-2022-FINAL.pdf.
69. Holmes B. Citizens' engagement in policymaking and the design of public services, Parliament of Australia, Research Paper 1, 2011–2012, 2011, Canberra: Parliamentary Library. https://www.aph.gov.au/about_parliament/parliamentary_departments/parliamentary_library/pubs/rp/rp1112/12rp01#_Toc299099864.
70. Cowan PJ, Tector AJ. The resurgence of xenotransplantation. Am J Transplant. 2017;17(10):2531–6.
71. Tallacchini M. Medical technologies and EU law: the evolution of regulatory approaches and governance. In: Cremona M, editor. New technologies and EU law. Oxford: Oxford University Press; 2017. p. 9–37.
72. Knoll MF, Cooper DKC, Bottino R. How the COVID-19 pandemic may impact public support for clinical xenotransplantation in the United States? Xenotransplantation. 2020;27(5):e12623. https://doi.org/10.1111/xen.12623.
73. Opriessnig T, Huang Y-W. Coronavirus disease 2019 COVID-19 outbreak: could pigs be vectors for human infections? Xenotransplantation. 2020;27(2):e12591. 2020 03.
74. Montgomery RA. Results of two cases of pig-to-human kidney xenotransplantation. N Engl J Med. 2022;386:1889–98.
75. Porrett PM, et al. First clinical-grade porcine kidney xenotransplant using a human decedent model. Am J Transplant. 2022;00:1–17.
76. Jee C. A gene-edited pig's heart has been transplanted into a human for the first time. MIT Technology Review. 2022. https://www.technologyreview.com/2022/01/11/1043374/gene-edited-pigs-heart-transplant.
77. Pierson RN III. Progress toward pig-to-human xenotransplantation. N Engl J Med. 2022;386:1871–3.
78. Parent B, Gelb B, Latham S, Lewis A, Kimberly LL, Caplan AL, (NYU Medical Ethics Working Group on research on the recently deceased). The ethics of testing and research of manufactured organs on brain-dead/recently deceased subjects. J Med Ethics. 2020;46(3):199–204.
79. Caplan A, Kimberly L, Parent B and Schiff T. Here are some questions about the pig heart transplant that people actually should be asking, The Washington Post. 2022. January 14. https://www.washingtonpost.com/opinions/2022/01/14/questions-about-the-pig-heart-transplant.
80. Tallacchini M. Through the lenses of the pandemic: three short reflections on science policy and citizens' rights. Epidemiol Prev. 2020;44(2):341–2.
81. Collins F. Citizen scientists take on the challenge of long-haul COVID-19, NIH Director's blog. 2020. https://directorsblog.nih.gov/2020/09/03/citizen-scientists-take-on-the-challenge-of-long-haul-covid-19.
82. Holdren JP. Memorandun to the Heads of Executive Departments and Agencies, Executive Office of the President Office of Science and Technology Policy, Washington, D.C., 2015.
83. Boucher P, Nascimento S, Tallacchini M. Special issue on: Emerging ICT for citizens' veillance: theoretical and practical insights. Sci Eng Ethics. 2018;24(3):821–1021.
84. Waltner Toews D, Biggeri A, De Marchi B, et al. Post-normal pandemics: why COVID-19 requires a new approach to science. STEPS Center. 2020. https://steps-centre.org/blog/postnormal-pandemicswhy-covid-19-requires-a-new-approach-to-science.
85. Funtowicz S and Ravetz JR, Peer review and quality control. In: Wright J, editor-in-chief. International Encyclopedia of the Social & Behavioral Sciences, 2nd ed, Amsterdam: Elsevier; 2015. p. 680–684.