Ethical analysis of the first porcine cardiac xenotransplantation

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Abstract

In this article, we provide an ethical analysis of the first porcine cardiac xenotransplant, performed in Maryland, USA in early 2022. David Bennett was offered the experimental procedure after he was deemed ineligible for human heart transplantation and mechanical circulatory support, based on a history of non-compliance. It was reported that Mr Bennett's previous instances of non-compliance were for medically non-life-threatening conditions years earlier, where the risks of non-compliance were not as high. We argue that, in Mr Bennett's case, a history of non-compliance in a different context, should not necessarily rule him ineligible for a potentially life-saving treatment now. Furthermore, using previous non-compliance to exclude individuals from donor organs may have the unintended effect of placing the burden of testing xenotransplantation on those who are already disadvantaged. We then argue that it is not enough to rely on patient consent to ethically justify xenotransplantation research. Taking a broad ethical perspective is crucial when mapping a clinical pathway for xenotransplantation.

INTRODUCTION

At 57, David Bennett was dying. He had a decades long history of heart disease. Prior treatments, including surgery, had proved ineffective. In October 2021, he began experiencing severe shortness of breath during daily activities. In November 2021, he was diagnosed with uncontrollable arrhythmia and was admitted to the University of Maryland Medical Center. Despite the best efforts of clinicians, his condition continued to deteriorate, and after 23 days, he was placed on peripheral venoarterial extracorporeal membrane oxygenation (ECMO).[1]

Mr Bennett's best chance at long- term survival was to get a new heart. Unfortunately, he had a history of not following medical advice.[2] [3] Therefore, Mr Bennett was deemed to have poor compliance[i] [4] to treatment, which was an exclusion criterion for receiving a human heart for transplantation and life-sustaining mechanical circulatory support. He was assessed by four different heart transplantation programmes and deemed to be ineligible by all four for history of non- compliance.[1]

Just when it seemed he had no hope, Mr Bennett was approached with an unusual offer. While the Maryland transplant team could not acquire a human heart for transplantation (allotransplantation), they could offer him a bioengineered heart grown inside a pig (xenotransplantation). The heart would come from specially bioengineered pigs, which are genetically modified to 'humanise' their organs, and minimise the chance of patient's immune system rejecting it.[5] To reduce the chance of zoonotic infections, particularly cross-species viral transmission, the bioengineered pigs were kept in sterile conditions isolated from other pigs.

Scientists at the University of Maryland Transplant Center had spent years researching how to make pig hearts survive in human bodies. Recently, they had achieved great success with transplanting pig hearts into baboons and avoiding host rejection. One baboon with a transplanted pig heart survived close to 3 years in good health.[6] Researchers believed they were now ready to move from baboons to humans. Mr Bennett happened to be in one of the only hospitals in the world where cardiac xenotransplantation was an option.

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[i] The concept of compliance can be distinguished from the related concepts of adherence and concordance. Compliance can be defined as 'the extent to which the patient's behaviour matches the prescriber's recommendations'. Adherence can be defined as 'extent to which the patient's behaviour matches agreed recommendations from the prescriber'. This difference reflects concerns that the concept of compliance represents a situation where clinicians simply dictate orders to patients, who are expected to follow. Adherence refers to a situation where patients have agreed with clinicians on a treatment plan. However, given the power- imbalance between clinicians and patients, adherence may still not ensure that a treatment plan has incorporated the perspectives of a patients adequately. This has led to the idea of concordance, which can be defined as 'the extent to which the patient's behaviour matches agreed recommendations that arise in a discussion between the clinician and the patient, where the views of both parties, especially the patients, were considered. For more information on see Chakrabarti's "What's in a name? Compliance, adherence and concordance in chronic psychiatric disorders' (2014). We use the term 'compliance' in this paper, because both xeno and allotransplantation come with strict protocols which are unlikely to vary because of patient input. However, many of the same underlying ethical issues could be discussed in terms of adherence or concordance.

Mr Bennett had limited options. ‘It was either die or do this transplant,’ Mr Bennett said before his surgery. ‘I want to live.’[7]

The clinical team was granted approval to conduct the surgery via the Food and Drug Administration (FDA) Expanded Access programme (also referred to at the compassionate use programme) and Mr Bennett underwent xenotransplantation of a pig heart.[8] Within 2 days, Mr Bennett was no longer reliant on ECMO. Despite initial complications requiring complex aortic reconstruction and abdominal surgery, the cardiac transplant seemed successful. Doctors reported that the heart was beating well and performing like a ‘rock star’.[9] Unfortunately, this success would be short-lived.

Tests taken after the operation showed traces of porcine cytomegalovirus (PCMV) in Mr Bennett’s blood. Initially doctors did not know what to make of this. The pig who provided Mr Bennett heart was supposed to be raised in conditions free from PCMV. Doctors thought the test might be an error. But then, Mr Bennett began to deteriorate. Forty- nine days after the transplant, he was experiencing abdominal pain and presented with high blood pressure. Further tests showed that the heart had begun failing, although no signs of rejection were noticed. A surgeon at the hospital suspected that an underlying PCMV infection may have caused a capillary leak, which contributed to the heart failing. At 60 days after he received the xenotransplant, Mr Bennett’s life- sustaining treatment was turned off and he passed away.[1]

BRIEF HISTORY OF XENOTRANSPLANTATION LEADING TO THE FIRST PIG-TO-HUMAN HEART TRANSPLANTATION

Xenotransplantation has a long history. As early as the 17th century, clinicians in France began experimenting with transfusions of animal blood into humans.[10] This practice led to many deaths and was subsequently banned by the French and UK parliaments.[11] In the 1960s, the first kidney xenotransplantations using chimpanzees were performed by Dr Keith Reemtsma. He performed 13 transplants, in each case transplanting both kidneys from a chimpanzee into a human recipient.[12] Most of the patients died 4–8 weeks after the operations either when the transplants were rejected or the patients died from non- zoonotic infectious complications as a result of the transplant. However, one of the patients went on to live for 9 months after the operation, remaining in relatively good health. At the time of the patient’s death, the kidney appeared to be functioning. In 1964, the first cardiac xenotransplant was performed again using chimpanzees. Unfortunately, the patient only lived for a couple of hours after that xenotransplant.[13] A more successful trial of cardiac xenotransplantation occurred in 1983, when a baboon heart was transplanted into an infant girl, Fae, with a congenital heart abnormality. While Fae survived the surgery, the rejection occurred after 20 days.[14]

Mr Bennett was the first human recipient of a porcine cardiac xenotransplant. Partly because of the above experiments with primates, there has been a growing consensus that pigs are the most promising species for xenotransplantation in human.[15] There is an in- depth understanding of pig biology and extensive experience in genetically modifying pigs in agriculture. Pigs can be genetically modified to control organ growth, remove known triggers

of immune rejection, and express certain human proteins to reduce graft injury and inflammation following transplantation.

Although Mr Bennett only lived for 60 days postoperatively, the xenotransplantation itself has been considered a success.[16] The heart showed no signs of rejection, a key determinant of long- term survival in xenotransplantation. Following Mr Bennett's case, there have been calls for clinical trials of porcine xenotransplantation, and in June 2022, the FDA took initial steps to initiate clinical trials into xenotransplantation.[17]

In this paper, we explore the ethical implications of the decision to perform the xenotransplantation in Mr Bennett's case. We first look in detail at Mr Bennett's eligibility for allotransplantation, and by extension, his eligibility for xenotransplantation through the FDA's Expanded Access programme. We then look at considerations regarding Mr Bennett's informed consent to undergo the procedure.

Should Mr Bennett have been on the FDA's Expanded Access programme?

The FDA's Expanded Access programme is designed to facilitate access to investigational medical products for patients who have life- threatening medical conditions. There are several criteria that must be met for a procedure to be authorised under this scheme. The most controversial of these in Mr Bennett case is 'there is no comparable or satisfactory alternative therapy to diagnose, monitor or treat the disease or condition'.18 For individuals with heart failure, there are at least two alternative treatments to xenotransplantation—a deceased donor organ transplantation, and the use of artificial devices to support or replace the function of the heart by durable mechanical support—such as a ventricular assist device (VAD) or totally implantable artificial heart (TAH). If Mr Bennett was eligible for either of these treatments, then xenotransplantation should not have been authorised by the FDA, and the procedure shouldn't have gone ahead.

The journal article describing Mr Bennett's xenotransplantation states that he was deemed to have poor compliance to treatment, and that this made him ineligible for both allotransplantation and durable mechanical support. With regard to allotransplantation, it is stated his case was reviewed by 'two regional and two prominent national heart transplantation programmes, and the request for a transplant was denied by all four programmes.[1] Mr Bennett's son told journalists that he had a history of incorrectly taking medications and missing follow- up appointments, which might help explain the finding.[19] In other words, Mr Bennett was physically a candidate for allotransplantation, but was ruled ineligible because he was deemed to be someone who would not follow medical advice. This raises questions about the ethics of denying people access to lifesaving therapies based on their past behaviour and lifestyle.

Non-compliance and the allocation of hearts

There is currently a shortage of human hearts. In the USA, as at 2020, there were 7386 people on the deceased cardiac donor waiting list.[20] Each year that number grows as the number of new listings outstrips the number of hearts donation (in 2020 there were 4000 new listings on the waiting list and 3761 hearts donated). Approximately 9% of those who go on the waiting list, die before they get a transplant. However, for those fortunate enough to receive a donor heart, the outlook is very good. Over 75% of patients who receive a heart transplant are alive after 5 years.[20]

As the need for human hearts outstrips their demand, it is necessary to make decisions about how to best allocate available hearts.[21] Certain physical conditions make individuals unlikely to survive the surgery itself or survive long after surgery. Some individuals are, therefore, denied a place on the deceased donor waitlist because they have significant physical comorbidities which reduce the benefit they will get from the heart. Allowing a heart to go to someone who is likely to die soon can be criticised from both utilitarians and non- utilitarian perspectives.[22] In addition to reducing the impersonal benefits (such as total life-years gained), transplantation programmes that do not consider life- years gained can be seen as disrespectful to the donor and their families, who often donate with the assumption their gift will provide many additional years of life for others. Some cognitive or behavioural disabilities may also influence how many years of life someone can expect to live after transplantation. After an organ transplant, patients must take a regime of drugs to make sure the organ is not attacked by the immune system (called rejection). One study looking into the consequences of non- compliance showed that 91% of kidney transplant recipients who were non- compliant with follow- ups and medications, either rejected the graft or died, within 12 months.[23] Non-adherence has been identified as the second most important cause of graft loss following renal transplants[24] and is frequently cited as one of major causes of graft rejection in cardiac transplants.[25]

Excluding those who are unlikely to finish a regime of medicine can arguably be seen as equivalent to excluding those with physical comorbidities. For example, even if individuals with severe dementia could be good physical candidates for allotransplantation, their mental state makes it unlikely for them to comply with care after surgery, and therefore, to get as much benefit from the heart as others. Patients with severe dementia are often excluded from consideration for allotransplantation.[26] Just as is the case for someone with severe kidney disease, prioritising those who do not suffer from dementia, or other severe mental illness, this can be justified on utilitarian and non- utilitarian grounds.

Mr Bennett was in good mental health, and good physical health apart from his heart condition.[1] His capacities to consent were assessed by three institutional processes and one external independent psychiatric evaluation. He was also highly motivated to undergo allotransplantation. One of his stated reasons for undergoing the xenotransplant was to prove he could follow doctors' orders which would make him eligible for a deceased donor transplantation.[2] He was ruled ineligible because of his past behaviour, rather than his future intention or capacity.[2] This is a common reason why some patients may be denied transplantation. For example, guidelines produced by The International Society Heart and Lung Transplantation state that:

> Poor compliance with drug regimens is a risk factor for graft rejection and mortality. Patients who have demonstrated an inability to comply with drug therapy on multiple occasions should not receive transplantation.[26]

A 2016 survey of American transplant providers, found that a history of adherence to a medical regime was one of the most influential factors when prioritising hypothetical candidates for transplantation (along with long- term survival and adequate social supports).[27]

It is the future behaviour of a recipient that will determine how much benefit is gained from an organ donation, not their past. While in many individual cases, a history of non- compliance will be indicative of non- compliance in the future, using history alone as an exclusion criterion can be unfair. Previous non-compliance does not always predict future non- compliance. Mr Bennett's previous instances of non- compliance were for a valve implant, 10 years earlier.[2] Plausibly, Mr Bennett did not perceive his compliance after this procedure to carry the same weight as compliance after a transplantation. A meta- analysis looking at the predictors of patient compliance found that 'adherence is significantly positively correlated with patients' beliefs in the severity of the disease to be prevented or treated'.[28] While this does not show that individual patients always improve their compliance as their disease worsens, it indicates that such intrapatient changes in compliance behaviour do occur. If Mr Bennett only now perceives his life at threat from his disease, his history of non-compliance may not be a good indicator of his future non- compliance. Moreover, patients do not exist as 'islands' but are embedded in a network of social support. Media reports indicate Mr Bennett had regular contact with his children and five grandchildren.[29] If he had the support of his family, this would have increased his chances at successful compliance. Further, there are now many education programmes and health apps that can be used to increase a patients likely of future compliance,[30] and it is unclear if options such as these were considered as a way of mitigating Mr Bennett's previous non- compliance.

It can be argued that it is fair to use responsibility for illness as a criterion for allocation of limited resources when the patient has been given a 'golden opportunity' to modify their lifestyle.[31 32] It is far from clear Mr Bennett has been given a golden opportunity with full psychosocial support. Moreover, it is unclear whether he understood that if he did not comply with medications back then, he would greatly increase his chance of developing heart failure and needing a transplant in the future.

Furthermore, it is striking that Mr Bennett was denied an allotransplantation because of non- compliance, and then offered a xenotransplantation, indeed to be the first patient to receive a genetically modified pig heart. The consequences of non- compliance are greater for xenotransplantation than allotransplantation. Xenotransplantation requires more medications than allotransplantation to achieve a higher level of immunosuppression. Because of the hypothetical risk of cross- species viral infection, some have argued that recipients of xenotransplantation will need to be placed under particularly stringent monitoring, partly because of risks of zoonotic infections.[33] Indeed FDA guidelines on xenotransplantation suggest that patients should be selected as candidates

for xenotransplantation, partly based on their 'ability to comply with public health measures […] including long- term monitoring'.[34]

In Mr Bennett's case, the clinical team stated they would make- up for his history of non- compliance through 'enhanced post procedure oversight'.[1] But if this can be done in cases of xenotransplantation, then why not allotransplantation? This raises a related but distinct issue to those discussed above. Regardless of questions of scarcity for allotransplantation, there is a question how we should interpret the 'alternative therapy' clause of the FDA's Expanded Access Authorisation criteria. For David Bennet to have been eligible or xenotransplantation, it should have been the case that 'there is no comparable or satisfactory alternative therapy to [….] treat the disease or condition'.

If enhanced postprocedure oversight could overcome previous non- compliance, then why was not allotransplantations with enhanced postprocedure oversight considered as a satisfactory alternative for Mr Bennett? Although it is likely that there will be more resources for extensive postprocedure oversight in xenotransplantation than allotransplantation—because it is being carried out under a research protocol—it is not clear if any steps were taken to determine if Mr Bennett's previous lack of compliance could be mitigated in the case of allotransplantation.

This raises a general ethical question about the FDA's Expanded Access pathway. Should individuals be considered as meeting this criterion if alternate therapies exist, are accessible to some in the community, but are inaccessible to others? If so, the bulk of the risks of testing novel therapies will fall on those with poor access to the best medicines, and who become eligible for compassionate access because of these misfortunes, which may be no fault of their own. This would not be fair on a luck egalitarian perspective.[35] This raises concerns about justice more generally, and the fair distribution of the benefits and risk of research of undergoing experimental treatments will likely fall.

Non-compliance and long-term circulatory support

Another alternative treatment in Mr Bennett's case would have been circulatory support with an artificial device, including VAD or TAH. While durable VADs are often used as a temporary bridges to heart transplantation, there is emerging evidence that they are effective as destination therapies.[36] Some individuals were supported with VADs for over 15 years.[37]

In the journal article describing Mr Bennett's xenotransplantation, his ineligibility for mechanical circuitry support was also attributed to non- compliance. However, denying competent and motivated individuals access to VADs based on a history of non- compliance also raises questions. Like allotransplantation, VADs require intensive ongoing support and monitoring, and long- term outcomes are influenced by compliance. VADs are expensive, and so in conditions of scarcity, it can be justifiable to give priority to those will get more benefit from these devices. But it is unclear if there were limited VADs available that could have been used as a destination therapy for Mr Bennett.

Furthermore, Mr Bennett could have been placed on durable VAD support (or TAH, if persistent malignant arrhythmia had precluded VAD) as a bridge to

decision- making. This would give everyone an opportunity to test his compliance under changed condition, but also it would also allow Mr Bennett to make a truly informed decis ion without having to choose between imminent death or xenotransplantation.

As we move towards large clinical trials of xenotransplantation, we will need to carefully consider the eligibility for these trials. One factor to consider is whether potential participants are eligible for allotransplantation or long- term circulatory support. This makes a difference to risk/benefit calculus of participating in the trial. Those who are eligible for allotransplantation or long- term circulatory support risk more by entering experimental trials than those who are ineligible for standard treatments.

While it is crucial to consider a patient's compliance with when placing about allo(and xeno)- transplantation, it is the likelihood of future compliance that is important, not a history of past compliance. In many cases, a history of past compliance will be indicative of a low likelihood of future compliance, but not always. For example, if people have undergone noticeable changes in their character and/or motivation, then their history may be less relevant to future compliance.

Decisions about eligibility should be made in response to clear and rigorous reasoning and informed by accepted guidelines devised in advance.

THE LIMITS OF INFORMED CONSENT

A key requirement of informed consent is that it must be given voluntary and not under duress.[38] Was Mr Bennett under duress when he consented to xenotransplantation? Comments like 'it was either die or do the surgery…I want to live', support the view that he was under pressure when choosing xenotransplantation. But here we must distinguish choosing an option under duress, and having very poor options to begin with. Xenotransplantation may have been the best of two poor choices for Mr Bennett. It will often be the case that people have limited options with regard to late- stage medical treatments. If a patient must choose the lesser of two bad options, it does not mean that their consent to that option should be questioned.

However, Mr Bennett's case shows why we need to look beyond consent with assessing ethically controversial research. A central moral function of consent is to protect or promote autonomy.[39] In Mr Bennett's case, the prior decision not to offer him allotransplantation or long- term circulatory support, took valuable options away from him. Being deemed 'non- compliant' reduced his capacity to be the author of his own life and make choices in accordance with his preferences and values. Although it is good that he is given the option of xenotransplantation over certain death, the overall situation is not one where Mr Bennett's autonomy is being promoted.

This shows the need to move to formal clinical trials of xenotransplantation, where rules around eligibility and suitability can be transparently assessed in all subgroups of patients. Recently xenotransplantation has been performed in brain- dead patients whose families have provided consent.[40] Others have proposed conducting trials in neonates and infants with severe congenital heart

malformations because of the immaturity of their immune system and current poor alternatives to xenotransplantation.[41] These candidates also have least to lose from participation and such design minimises expected harm.[42] We must carefully consider the different ethical issues that will arise in trials in each of these different patient groups. An advantage of using component adults like David Bennett is that they can give active informed consent to xenotransplantation. A disadvantage is that xenotransplantation tends to have a worse risk/benefit ratio in these groups. There are plausible scenarios where component adults like David Bennett would have decades of relatively healthy life if they can access alternative treatments. This is not true for some patients who are brain- dead or who have severe congenital abnormalities. The question of how to balance the importance of risks, benefits and informed consent needs to be careful considered in the design of xenotransplantation clinical trials.

CONCLUSION

As the demand for organs outstrips availability and calls for clinical trials of genetically modified porcine xenotransplantation intensify, there is an urgent need to discuss and agree on clear frameworks around patient selection and consent processes, both in adult and paediatric settings. In this paper, we highlight two issues that need to feature in these ongoing discussions. First, we must ask whether it is fair to use a history of non- compliance to exclude individuals from allotransplantation, and thus make them eligible for experimental therapies such as xenotransplantation. It is future non- compliance, which is ethically important. In some cases, previous non- compliance will not predict future non- compliance. Using previous non- compliance to exclude individuals from allotransplantation may have the unintended effect of placing the burden of testing xenotransplantation on those who are already disadvantaged. Second, it is not enough to rely on patient consent to ethically justify xenotransplantation research. Just because patients have given informed consent to xenotransplantation research, does not mean they have had their autonomy respected. Taking a broad ethical perspective is crucial when mapping a clinical pathway for xenotransplantation.

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