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RESEARCH ARTICLE

# Xenotransplantation Clinical Trials and Equitable Patient Selection

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**Abstract**
Xenotransplant patient selection recommendations restrict clinical trial participation to seriously ill patients for whom alternative therapies are unavailable or who will likely die while waiting for an allotransplant. Despite a scholarly consensus that this is advisable, we propose to examine this restriction. We offer three lines of criticism: (1) The risk–benefit calculation may well be unfavorable for seriously ill patients and society; (2) the guidelines conflict with criteria for equitable patient selection; and (3) the selection of seriously ill patients may compromise informed consent. We conclude by highlighting how the current guidance reveals a tension between the societal values of justice and beneficence.

**Keywords:** allotransplantation; clinical trial; consent; ethics; equity; fairness; justice; research subjects; xenotransplantation

## Introduction

There is broad agreement that research participant selection should be fair, both at the individual and collective levels. According to the *Belmont Report,* researchers should not "offer potentially beneficial research only to some patients who are in their favor or select only 'undesirable' persons for risky research," and researchers should be cautious about placing undue burdens on already burdened classes of individuals.[1] The *Report*'s insights on just patient selection have been echoed in guidelines the world over. With recent advancements in genome-editing technologies, phase 1 clinical trials of solid organ xenotransplant (XTx) are increasingly likely to begin within the next decade, and one intending to recruit 20 participants with end-stage kidney disease is currently under consideration in the United States but is not yet recruiting.[2] More controversial is the Food and Drug Administration's (FDA) expanded access pathway, which was how the first heart xenotransplant was approved. Additional xenotransplants are likely to be approved—or at least sought—under this pathway in the absence of the approval of a phase 1 trial. The consensus across XTx guidelines offered by regulators and major medical organizations is that participation in these trials should be restricted to seriously ill patients for whom alternative therapies are unavailable. For example, FDA guidance states: "You should limit xenotransplantation to patients with serious or life-threatening diseases for whom adequately safe and effective alternative therapies are not available, except when very high assurance of safety can be demonstrated."[3]

While we believe that the pursuit of XTx research can be ethically defensible and are genuinely hopeful about its potential, we think that—in some cases—because of recent advances, the clinical research is progressing faster than the necessary ethical reflection. After explaining current selection guidelines, we offer three lines of consideration: (1) The risk–benefit calculation may well be unfavorable for seriously ill patients and society; (2) the guidelines conflict with criteria for equitable patient selection;

and (3) the selection of seriously ill patients could compromise the validity of their informed consent. We conclude by highlighting how the guidelines reveal a tension between the societal values of justice and beneficence. This requires that, as XTx research continues with human subjects, greater clarity, communication, and transparency are essential to help mitigate concerns of injustice.

## Current Selection Guidelines

Many individuals on a waitlist for an organ transplant are good candidates for allotransplantation—their clinical teams assess the likelihood of successful solid organ transplantation to be high. Some individuals are not deemed to be good candidates for allotransplantation, for one reason or another (e.g., the presence of one or more comorbidities and previous medical nonadherence). Current XTx guidelines favor the selection of a subset of such individuals, that is, those who are disadvantaged or otherwise excluded from receiving a human organ.[4] The Nuffield Council on Bioethics, for instance, posited in 1996:

> *7.11: As set out above, the initial trials to xenotransplant organs will be major and risky procedures. This suggests that it would be justifiable to offer organ xenotransplantation only to patients for whom there is no alternative form of effective treatment. This would apply to many heart patients, whose lives are at risk and for whom the shortage of human organs is acute. The lives of most kidney patients can be maintained, albeit uncomfortably, on dialysis. For some people with renal failure, however, accessing the vascular system becomes extremely difficult and, eventually, dialysis may no longer be possible. The potential, albeit small, risk that xenotransplantation will transmit new infectious diseases to the population at large must also be considered (paragraphs 6.16 - 6.19). It would be hard to justify posing any potential public health risk unless the first xenografts were used to save the lives of people with no alternative possibilities of treatment.*[5]

The Nuffield Report limits XTx clinical trial participation to individuals who have no viable alternative and whose lives are at risk and in need of saving. Similar guidelines have been offered in the World Health Organization's (WHO) first Changsha Communiqué in 2008:

> Investigators should select trial participants for whom there is no adequately effective alternative therapy available and who understand the risks and consequences of the procedure, including the need for compliance with life-long follow up and who are motivated to modify their behaviour accordingly.[6]

More recently, the American Medical Association (2017), affirming the FDA guidelines, recommends limiting XTx recruitment to "patients with serious or life-threatening conditions for whom no adequately safe and effective alternative therapies are available."[7]

The guidelines have been met with general scholarly consensus. Maria Jorqui-Azofra posits that initial XTx clinical trials ought to involve "patients with serious life-threatening disease for whom adequately safe and effective alternative therapies are not available or where there is a potential for a clinically significant improvement with increased quality of life, following the procedure."[8] Reichart et al. propose that "intensive care unit (ICU)-dependent patients with end-stage heart failure requiring continuous intravenous catecholamines" be good candidates for initial clinical cardiac XTx trials.[9] Some scholars have also considered expanding the inclusion criteria to include individuals who are allotransplant candidates but are so far down the waitlist that they will likely die before receiving one. The case can be made that such individuals satisfy current XTx guidelines, since they fall in the class of individuals, in the words of Jagdale et al., "for whom a living donor is not an option."[10] Pierson III et al. affirm that clinical trials should enroll "patients lacking timely access to an allograft or who are expected to be served poorly by currently available therapeutic alternatives."[11] Henry Silverman and Patrick Odonkor suggest that would-be participants should have "a high likelihood of dying while on the transplant list due to the

limited availability of organs,"[12] whereas Reese et al. write that suitable candidates may include patients "at high risk of wait-list mortality" or who are "medically unsuitable for transplant with a human organ."[13] Some have proposed further limitations on participants, for example, excluding those with suicidal ideation, those who previously displayed medical noncompliance, or those who lack adequate psychological resilience. What matters for present purposes is that XTx trial participation is limited to those who lack a viable therapeutic alternative and are at risk of dying.

There is a clear rationale present in the Nuffield Council on Bioethics recommendations for restricting participation to individuals with little to no hope for another therapeutic option and who are at serious risk of death. Human subject research is unethical if it involves excessive risk of harm with minimal benefit to the individual and society writ large, and greater risk to one's health should be accompanied by a direct and at least proportional benefit to the individual. XTx clinical trials will be invasive—as participants undergo surgery to replace one organ with another—and are likely to pose an unknown but probable high risk of organ failure and death. As such, the corresponding benefit to participants and society should be high, which *prima facie* appears to be the case if XTx trial participation is limited to those who lack viable therapeutic alternatives and are at risk of dying: If all goes well, participants will live; if it does not, they may die, which would be the case anyway if they did not participate in the trial. Such individuals, in the words of the FDA guidelines,"have potential for a clinically significant improvement with increased quality of life, following the procedure."[14] Those who are considered good candidates for allotransplantation, by contrast, have a lot to lose by participating in such trials. For them, the option is between undergoing a risky experimental treatment or allotransplantation, which is known to be a relatively safe and effective treatment. Lastly, phase 1 XTx clinical trials move society closer to realizing a scalable means of helping address the shortage of available organs for transplantation and, therefore, offer clear societal benefits. As many as 22 people a day die in the United States alone waiting for an organ transplant, and XTx may one day help significantly reduce this number.[15]

## Problems with the Risk–Benefit Assessment

Unfortunately, the case for a positive risk–benefit ratio in XTx clinical trials currently remains underwhelming, because it is exceedingly difficult to assess XTx risk in the first place, and there is at present insufficient evidence to support the alleged benefits for patients and society for certain kinds of XTx; however, this may change as more decedent and compassionate use studies are conducted. First, it is difficult to extrapolate from preclinical XTx research in animal models to XTx human subjects due to the significant physiological differences. Pig hearts, unlike human hearts, for example, have a left azygous vein that drains via the coronary sinus; the left atrium of a pig heart has 5–7 pulmonary veins, not 4 as in a human heart; and pig hearts enjoy twice as high systemic and pulmonary vascular resistance, which is why, in light of these and other differences, extrapolating information from pig-to-baboon XTx experiments is "greatly" complicated by physiological differences.[16] Pierson III et al. are even more pessimistic, writing: "The value of pig-to-baboon preclinical results to predict clinical performance of the heart xenograft in a human, and the patient's response to an experimental treatment regimen, are both unknown, and fundamentally unknowable in advance of the initial clinical attempt."[17] Although there is a closer physiological similarity between pig, baboon, and human kidneys, physiological differences remain. This is a more general challenge with translational research because, despite concerted efforts to enhance the predictability of animal testing, the failure rate has in fact gone up.[18]

Moreover, much of the preclinical XTx animal research is either terminated early or the animals die relatively soon after. For instance, Längin et al. transplanted genetically altered pig hearts into four baboons, two of whom died 90 days after transplantation and the other two survived 182 days and 195 days, respectively.[19] More recently, Reichart et al. transplanted genetically altered pig hearts into four baboons, two of which succumbed to a zoonotic infection at days 15 and 27, respectively, and the other two survived for three months.[20] Although impressive and suitable to establish proof of principle—still more recently, a baboon who received a genetically altered pig heart survived 9 months[21]—this is

unlikely to be favorable for trial participants. Rather than die while receiving hospice care, they are asked to undergo a psychologically stressful experimental and complex surgical procedure that involves invasive monitoring, and, in return, based on preclinical XTx research on animals, they may survive for a few months and (presumably) in some cases less than they otherwise would have.

Of course, preclinical XTx research on animals is not the only research available, because there is evidence gathered from human decedent studies and human XTx research. However, preclinical XTx research using brain-dead decedents has been brief and is thereby difficult to extrapolate from. For example, kidney XTx human decedent research in 2021 was terminated at 54 hours[22] and 74 hours,[23] which means that it has serious limitations for establishing the benefits for living human recipients and which is why David Cooper laments that the value of such experiments "will remain very limited."[24] However, it is worth noting that a recent kidney xenograft decedent study has shown promising results by demonstrating optimal functioning with no signs of rejection after 32 days.[25] The recent cardiac XTx in a severely ill patient, David Bennett Sr., lasted only 8 weeks before the patient died,[26] though this is an advancement on previous XTx human trials. The recipient of a baboon heart, "Baby Fae," survived only 20 days.[27] Again, although such research may establish proof in principle, it is a far cry from establishing that phase 1 clinical trial participants will themselves benefit in proportion to the suffering and invasive procedure being asked of them. In the context of kidney XTx, for instance, it is often pointed out that there is a backup; that is, the pig kidney can be excised and dialysis resumed, and so, the risk is not as severe. Thus, this is a significant undertaking for participants, especially when there are proven therapeutic options available.

There is also the ever-constant concern over the risk of transmitting zoonotic disease.[28,29] As noted already, there are reports of animals in preclinical XTx studies developing a zoonotic infection from the host source, and it remains unclear whether a confirmed zoonosis contributed to David Bennett Sr.'s death.[30] The concern of zoonotic disease is not limited to immunocompromised patients but could also extend to their close contacts, community, and the wider public health. As L. Syd Johnson explains, "Everyone in the world is at risk from an XTx-related infection, not merely the individual xenograft recipient"[31]; she goes on to say the "unknown and unquantifiable risks of XTx include the possible unleashing of zoonotic diseases that could potentially affect the entire world."[32] Although this research promises to inch us closer to a scalable means of addressing the organ shortage, there is at least a theoretical risk to public health, and this risk will remain unknown until clinical trials begin. However, as virologist Joachim Denner has pointed out, the risk of transmission of zoonotic disease to the immunocompromised xenograft recipient is extremely low when the appropriate methods for detection and elimination are implemented.[33]

So far, we have been assuming that XTx phase 1 clinical trials are intended to directly benefit participants and have argued that the risks are difficult to assess but appear to be quite high for participants—based on recent history and in light of what is being asked of seriously ill patients. This assumption that XTx phase 1 clinical trials are intended to directly benefit participants is false; however, phase 1 clinical trials are not intended to directly benefit participants at all. Rather, the purpose of phase 1 clinical trials with a medical device is primarily to assess its safety and efficacy.[34] These trials are therefore not designed to directly benefit XTx recipients, thereby undermining the requirement that significant risk requires a proportional benefit to the patient. This cuts at the heart of the very possibility of ethical XTx clinical trials with seriously ill patients—by design, they do not directly benefit participants, but they do involve significant harm and burden. Participants are invited to participate in a risky, invasive, and experimental trial that, by design, may provide only indirect benefit to them.

In sum, the case for positing a favorable risk–benefit ratio is underwhelming. Societal risks include a possible novel zoonotic disease, whereas societal benefit includes a step toward transplantable organs; however, there are other avenues to increase the availability of transplantable organs that do not pose a risk of zoonotic disease.[35] Moreover, societal benefit alone does not justify significant harm to individual participants. Regarding individual participants, these studies are not intended to directly benefit them, and evidence of indirect benefit (i.e., extended or significantly improved life) is lacking.

## Tension with Ethical Patient Selection Guidelines

When a clinical trial is proposed that limits participation to only certain individuals, a compelling justification is required for why this subset of individuals is eligible to participate and all others are excluded. Although a favorable risk–benefit payoff is necessary, it is not sufficient, and so, we should evaluate whether limiting participation in clinical XTx trials to individuals for whom no other therapeutic alternative exists and who are at risk of dying has a compelling justification. To help assess the ethical defensibility of the XTx guidelines, we draw on the work of Douglas MacKay and Katherine W. Saylor, who offer four considerations to use when determining the ethical defensibility of subject selection.[36] We explain why XTx guidelines are in tension with each.

The first criterion is that subject selection should be fair in its inclusion criteria: "*Fair inclusion,*" McKay and Saylor write, "requires that the selection of participants be sufficiently inclusive to ensure that the research in question is appropriately generalizable to clinically distinct populations."[37] Practically, this entails that if XTx impacts seriously ill individuals differently than non-seriously ill individuals (e.g., otherwise healthy people in need of an organ), but XTx guidelines restrict participation in phase 1 clinical trials to individuals who lack therapeutic alternatives, then such trials may "not produce clinically relevant knowledge for the former."[38] Since XTx guidelines favor patients who lack therapeutic alternatives and are at risk of dying, researchers might not be able to extrapolate data to otherwise healthy patients who also may benefit from participating in XTx research. This is an issue of fairness, since only a subset of people who stand to benefit from XTx research participation are able to benefit from this clinical research. It is likely that once enough data have been obtained from initial clinical trials, researchers will reach a point at which it is ethically permissible for them to permit patients to choose to enroll in an XTx trial or not. This would not *post hoc* justify the possibility that initial XTx clinical trials did not adhere to the fair inclusion criterion.

The second criterion is that the burden of participating in a clinical trial should be shared fairly. Practically, this entails that individuals who are not already burdened are best placed to bear the burdens of a trial: It is unfair to ask the already burdened to become even more burdened than they already are when there are others who can assume the burden more easily. McKay and Saylor explain that, "In the context of the cooperative project it is unfair to ask some individuals to bear excessive burdens for the purposes of benefiting others."[39] Burdens should be shared equally, and if the risks of participation are excessively high, then it is unfair to ask those already burdened to participate. Clearly, this condition is not met because current XTx guidelines favor those who are most burdened of all—those who are seriously ill and at serious risk of death. The *Belmont Report* classifies "the very sick" as a vulnerable group and they are being targeted for inclusion precisely because they have no other alternative, not because they are uniquely tied to the research. Existing XTx guidelines are also contrary to what is set forth in *the Helsinki Declaration*:

> 20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and *the research cannot be carried out in a non-vulnerable group*.[40]

If it is responded that XTx research is too risky for candidates for allotransplantation, then it could be responded that it is too risky for everyone. Otherwise, we risk unfairly burdening the already burdened with something we deem too burdensome for the not-so-burdened.

The third criterion is that of fair opportunity, which "requires that prospective participants be granted a fair opportunity to participate in research that is *ex ante* beneficial."[41] In other words, "investigators must recognize that all who meet the scientific requirements of the study have a *prima facie* equal claim to participate."[42] Before we explain the rationale for this criterion, it is important to note that researchers probably are not at a point of knowing for sure that phase 1 clinical trials are *ex ante* beneficial. We hope so, but the case was made above that preclinical studies are currently underwhelming, especially in heart XTx; indeed, in our view, the only way for us to know that XTx research is *ex ante* beneficial is by pursuing clinical trials. This is a problem, of course. Nevertheless, let

us assume the research promises to be *ex ante* beneficial. This criterion is grounded in the recognition of moral equality among people, which entails the equal consideration of interests. Thus, since otherwise healthy people in need of an organ may benefit from XTx research, and there is no reason inherent in the research itself why they should be excluded, XTx guidelines violate the fair opportunity criterion. Everyone who could benefit from XTx should be allowed to participate. If it is responded that the research is too risky for some, then it is presumably too risky for all—it is unclear to us that it has been shown to be *ex ante* beneficial.

The fourth criterion regards third-party risk and "demands that participants be selected to ensure a fair distribution of risks to bystanders."[43] The rationale for this condition is that the selection of participants "plays a role in the creation and distribution of these third-party risks," and there are reasonable limits to place on third parties.[44] The case can be made that this condition is unsatisfied for reasons already mentioned: XTx research carries a low but theoretically plausible risk of zoonotic transmission from the xenograft recipient to close contacts and to the wider public. This public health concern around emerging zoonotic diseases has been heightened following the COVID-19 pandemic, and there is a renewed interest in how they can be prevented[45]; it is therefore essential that patients and the public are sufficiently confident that everything possible is being done to keep this risk as low as possible. Alternatives to XTx research such as policy changes and increased donor awareness do not pose such serious third-party risk.

In sum, the case can be made that XTx research guidelines are unfair because they burden the already burdened and do not fairly include all who stand to benefit from the research; this is not to mention the bystander risk posed by the possibility of zoonotic disease and the risk of transmission from the xenograft recipient to the wider population. Again, although we acknowledge that the evidence suggests that the possibility is low, it is not zero. Some scholars expand XTx inclusion criteria to allotransplant candidates who, despite being otherwise healthy, are too far down on the transplant list and may likely die waiting for an organ. Although these expanded inclusion criteria may well address MacKay and Saylor's first two criteria, it is doubtful that these expanded inclusion criteria respond to the concerns about the third and fourth criteria—they are still limiting who can enroll, and third-party risk remains.

## Problem with Voluntariness

It may be reasonably considered whether individuals for whom no viable therapeutic alternative exists can voluntarily give informed consent to participate in XTx trials. We agree with Appelbaum et al., who argue that a decision is involuntary "only if it is subject to a particular type of influence that is external, intentional, illegitimate, and causally linked to the choice of the research subject."[46] Internal influences such as fear or confusion do not render the ensuing decision involuntary, nor do situational constraints such as a lack of therapeutic alternatives; instead, the influence has to come from an external agent, one who intends to influence the choice illegitimately, that is, against generally accepted moral norms. An example of pernicious influence would be a clinician who tells a person to enroll in a clinical trial or else she will cease caring for the person.

To evaluate whether severely ill patients are subject to illegitimate influence when offered the opportunity to become a participant in an XTx phase 1 clinical trial, we need to examine whether generally accepted moral norms are violated. It has been argued that a researcher proposing XTx as an option to would-be participants is not illegitimately influencing the decision, for there are other options for would-be XTx participants, for example, they can keep receiving dialysis, wait for a human donor, or accept death,[47] but this does not take into account that XTx guidelines limit participation to individuals with a serious, possibly life-threatening, condition and who have no viable therapeutic alternative. These individuals are *chosen* to be participants *precisely because* they lack therapeutic alternatives—their lack of a therapeutic alternative is what makes them the target of these trials. Again, the research promises to benefit many individuals, not only those who are severely ill, and yet, research participation is open only to individuals who lack therapeutic alternatives and are at risk of dying. Their medical vulnerability is causally linked to their inclusion in the trials.

The fact that such medically vulnerable individuals are targeted for inclusion in initial phase 1 XTx clinical trials gives reason to doubt the legitimacy of their consent—they are given the choice of enrolling in the clinical trial or likely dying. The Nuffield Council on Bioethics notes the cruelty of offering a possible lifesaving option that results in a painful, drawn-out death rather than palliative care: "The offer of such a procedure in itself puts pressure on patients to accept—and may distort judgment."[48] Appelbaum et al. agree that patients who otherwise lack medical care should not be recruited to studies that promise to treat their illness, for that would render the decision to participate involuntarily.[49] Of course, the choice is never presented thus, but there are compelling reasons to think medically vulnerable individuals interpret it as such—evidence suggests that the terminally ill participate in clinical trials from desperation and a mistaken belief in therapeutic benefit.[50] In other words, severely ill individuals interpret the offer to participate as a viable option to avoid death. So, the concern about the voluntariness of consent to XTx clinical trials remains.

## Societal Values Underpinning XTx Guidelines

So far, we have been critical of current XTx guidelines, and it might be believed at this point that the societal values underpinning XTx guidelines manifest a bias against medically vulnerable individuals. Medical research, as W. M. Kong observes, is a social undertaking that is pursued for the benefit of society, and it thus reflects social values with those engaged in such research operating as societal agents.[51] Part of what this entails is that research proposals reflect certain values and can be evaluated accordingly. Current guidelines suggest that XTx research is ethically defensible on the seriously ill but not defensible on the non-seriously ill, and it could be inferred that this manifests an assumption that the seriously ill have less value than the non-seriously ill, as Kong explains: "It does not follow that research which is unethical in a fit young adult is suddenly ethical because the patient is dying…The dying have as much right to not be harmed or used as the healthy."[52] If XTx trials are ethically permissible, then they should be open to everyone who may benefit from participating in them, not just a vulnerable subset of people.

However, we cannot so easily dismiss current guidelines, because they are grounded in the principle of beneficence: Researchers should do no harm and seek to maximize benefits and minimize harms. Consider phase 1 experimental cancer therapies for those patients who have exhausted all other options. Clinicians first provide standard care, and then, after those modes are exhausted, a last-ditch effort via risky therapy is permissible in that population. Whereas a patient who has not yet received standard treatment could consent to a phase 1 experimental cancer treatment, clinicians should not enroll them in the trial on the grounds that doing so promises more risk and uncertain benefit compared with proven therapeutic alternatives. Similarly, offering allotransplant candidates a place in a risky and invasive XTx clinical trial would present them with an opportunity that promises few, if any, benefits but likely involves significant harm. The principle of beneficence cuts against the idea of broadening XTx inclusion criteria to all who may benefit.

We suggest that current XTx guidelines reveal a significant tension between ethical principles. On the one hand, patient selection should be equitable, and the case has been made here that current XTx guidelines are not so: The risk–benefit ratio is unfavorable; the selection criteria are unfair; and there is concern about whether consent can be voluntary. On the other hand, patient selection should guard patients from excessive risk of harm, especially when therapeutic alternatives exist. Enrolling someone who has proven therapeutic alternatives in a risky XTx clinical trial is wrong because it promises excessive harm and minimal, if any, benefit.

What, then, should be done? Should researchers cease XTx clinical trials altogether on the grounds that they are just too risky for participants and that the risk–benefit ratio is unfavorable? Or should researchers continue with existing XTx guidelines on the grounds that the research promises immense benefit to future people?

These are not easy questions to answer, and we think scholars can defend either position. In other words, each position is ethically defensible depending on which moral values are emphasized or

prioritized. Proponents of XTx may argue that because XTx is likely to have a significant role in addressing the organ shortage and bringing about the associated societal benefits, it is necessary to assess its safety and efficacy. Moreover, the informed consent procedures can be revised to mitigate concerns of voluntariness, and although concerns over infectious disease should be taken seriously, they should not be seen as an obstacle to initiating clinical trials—providing the appropriate methods for detection and elimination are implemented. Therefore, the emphasis on beneficence outweighs the concerns around justice and its potential risks. Conversely, critics of XTx may argue that the risk of zoonotic disease is too great and that other options are worth exhausting first, not to mention the ethical tension of targeting a vulnerable population for a risky and experimental procedure. For critics, justice and what are perceived to be its intrinsic risks outweigh beneficence in this case.

## Conclusion

If XTx trials continue—which we assume will be the case—the upshot of our argument is that researchers ought to take steps to mitigate charges of injustice. According to existing XTx guidelines, would-be participants are—plausibly—being selected in an inequitable manner, and although expanding participation to include allotransplant candidates who are low on the transplant waiting list is advisable, ethical tensions remain. To mitigate charges of inequity, clarity, communication, and transparency are essential. Clarity about the risks involved for the individual, their loved ones, and society writ large, along with transparency about recent XTx research, would place the subject in a position to voluntarily join otherwise ethically problematic research. One goal of the informed consent process should be to guard against misunderstanding and false hope. Discussion about revising the XTx informed consent process is ongoing and, in light of our argument, necessary.

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**Competing Interest.** The author declares none.

## Notes

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