The Big Chill: Opportunities for, and Challenges to, Advanced Biopreservation of Organs for Transplantation

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Abstract: The application of advanced biopreservation to organs donated for transplantation may make possible their indefinite storage and thereby improve the utility and equity they provide to patients. The technology is still at a preclinical stage, with many difficult, scientific issues that remain to be answered. At the moment, however, the actual capabilities of the technology are too indefinite to begin formulating the statutes, regulations, and ethical guidance that will be needed to obtain the benefits expected from its use.

Research to develop advanced technologies for preserving biological systems indefinitely has engendered great interest among physicians and scientists in many fields, from aquaculture and conservation to medical therapeutics. Combining biopreservation techniques, such as isochoric freezing, supercooling, and vitrification, with procedures to reanimate the frozen systems, such as nanoparticle infusion and laser rewarming,[1] opens up the prospect that organisms of many types could be stored for long periods, transported near or far, and restored to normal functioning. Some projected uses of these techniques — for example, sending an icy version of Noah's ark, filled with vitrified human beings and domestic animals and plants, off to a distant planet or even another galaxy, should conditions on earth become incompatible with life — may sound like science fiction, but others are much closer to current practices. In the latter category, the possibility that advanced biopreservation could help overcome some of the causes of inequity and inefficiency in the current organ transplantation system[2] has generated considerable interest.[3] Rather than propose firm ethical guidance,

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Table 1

Twenty-Five Year Comparison of Increases in Rates of Deceased and Living Donation, Number of Organs Recovered per Donor, and Number of Recovered Organs Transplanted, Which Shows a Decline in the Percentage of Organs Transplanted*

YEAR	Number of Donors			Organs Recovered (from)			Organs Transplanted (from)			Average number of organs recovered from deceased donors	Percent of organs from deceased donors that were transplanted
	Deceased	Living	Total	Deceased Donors	Living Donors	Total Donors	Deceased Donors	Living Donors	Total Donors		
1999	5,824	5,048	10,872	21,134	5,055	26,189	18,668	5,055	23,723	3.63	88.30%
Increase	*x 2.805*	*x 1.377*	*x 2.142*	*x 2.558*	*x 1.375*	*x 2.329*	*x 2.335*	*x 1.375*	*x 2.131*	*x 0.909*	*x 0.913*
2023	16,335	6,951	23,286	54,050	6,949	60,999	43,594	6,949	50,543	3.30⇩	80.60%⇩

*U.S. Department of Health and Human Services, Organ Procurement and Transplantation Network, National Data: Donors Recovered in the U.S. by Donor Type: January 1, 1988-December 31, 2023 (added fields: Organs Recovered and Organs Transplanted) <https://optn.transplant.hrsa.gov/data/ view-data-reports/national-data/#> (last visited May 5, 2024).

new laws and regulations, or novel institutions to govern the management of advanced biopreservation, the present article provides an anticipatory examination of the ethical, legal, regulatory, and other issues that need to be considered before these still developing techniques are adopted in an attempt to improve organ transplantation.

I. Transplantation from Deceased Donors: A Clinical Success but a Systemic Challenge

Over the past seven decades, organ transplantation has become a highly successful — and, for many patients, the only available — treatment for terminal organ failure. Besides technical expertise and complex systems, which are common elements across modern medicine, organ transplantation is unusual because it depends on a scarce material, donated organs, which mostly come from other patients after their death. In the past 25 years, the annual number of deceased organ donors has nearly tripled,[4] but the need for transplants still greatly exceeds the supply of organs. The several reasons for this gap include the aging of the population, the increased incidence of diseases that lead to end-stage organ (especially kidney[5]) failure, and the increased preference for transplantation over dialysis, since the long-term mortality rate for transplant patients has been shown to be substantially lower.[6] Adding to the problem, many of the organs recovered from deceased donors are not transplanted. In 1999, 88.3% of donated organs ended up being implanted in recipients, but by 2023 that percentage had fallen to 80.6% (**Table 1**).[7] Some organs are discarded because of medical issues with the organ or the donor, but systemic problems with the process for allocating and distributing organs are also major causes of discards.[8]

At the heart of the latter problems lies the limited period of time that donated organs remain viable from the moment that ischemia begins as they cease receiving oxygenated blood in a donor to the moment when an implanted organ begins to receive oxygenated blood within the recipient. Given the many steps that must be completed for a donated organ to reach a recipient — from gathering data and performing laboratory tests to assess organ safety and quality to using national algorithms to rank potential recipients for each organ, and to transplant centers determining whether they find an offered organ to be suitable for their transplant candidates and whether an identified candidate wants to accept the organ and is physically ready at that moment — the ticking clock of ischemia often runs out before an organ can reach the designated transplant center. The resulting loss of organs which had been suitable for transplantation when their donor died could be greatly diminished if better means of preserving organ viability could be found.

II. Safely Extending Organ Viability: The Search for the Holy Grail

The search for means of maintaining organs that are not receiving normal physiologic support began several decades before the first successful kidney transplant in 1954. In the early 1930s, Alexis Carrel and Charles Lindbergh built devices and formulated solutions that were able to perfuse organs removed from animals. When implanted in other animals, the organs regained function. Their experiments demonstrated that organs could be "cultured" for several weeks with oxygenated, normothermic perfusate. Once transplantation became a successful treatment for organ failure — first with kidneys and then livers, hearts, lungs, and other organs — physician-investigators developed

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new, increasingly effective perfusates and established that hypothermia extends the period of organ viability and improves long-term survival of transplanted organs and the patients who received them.[9]

These developments led to the current standard mode for preserving donated organs, static cold storage (SCS), which involves flushing an organ with a protective solution, cooling it to 4 to 8°C, and placing it on ice in a container — typically a picnic cooler, a sight familiar both to transplant professionals and to the public, whether in real life or cinematically — for transfer to its destination. With SCS, metabolism continues, albeit at a reduced rate. Without oxygen, the organ rapidly loses energy stores, and becomes dependent upon less efficient anaerobic metabolism to maintain viability. SCS can prevent the structural and cellular damage caused by energy depletion from becoming irreparable for only a brief period: hearts and lungs can be successfully preserved up to 6 hours and kidneys up to 36 hours, while livers and other abdominal organs remain viable from 8 to 12 hours.[10] Dwindling energy stores, the accumulation of anaerobic metabolites, the diminished function of the homeostatic pathways that preserve cell function, and the associated injuries that worsen, or even become fatal, when reperfusion reinstates oxygenated circulation — a phenomenon known as ischemic reperfusion injury (IRI) — all limit the viability of organs ex vivo, that is, their ability to resume normal functioning once implanted.

The latter concern arises particularly for organs obtained from donation after circulatory determination of death (DCDD), a source that is growing rapidly, having gone from a negligible fraction of all deceased donors to more than a third over the past three decades (**Table 2**).[11] With DCDD, ischemia begins before the circulatory determination of death, unlike in more traditional donation after neurological determination of death (DNDD), where circulation of oxygenated blood can be maintained artificially after death has been declared and until organs are removed. The prompt mechanical perfusion of DCDD organs ex vivo — whether normothermic machine perfusion (NMP) (above 32°C), subnormothermic (15 to 30°C), hypothermic oxygenated perfusion (HOPE) (8 to 12°C), or some combination—reduces the risk of IRI and extends the period of viability, particularly for livers.[12] (The same technology can be used as a supplement or alternative to SCS to extend the viability of DNDD organs that experienced poor perfusion in the donor, a period of hypotension, or warm ischemia.[13])

The technological advance of oxygenated perfusion which has the capacity both to sustain and to resuscitate organs ex vivo is fundamental for effective utilization of available organs, including hearts and lungs.[14] Recent studies have confirmed this with both hypothermic and normothermic perfusion of livers. For example, compared with SCS, HOPE reduced the frequency of symptomatic biliary strictures after transplantation of DCDD livers.[15] In another study, the utilization of blood-based oxygenated normothermic perfusion was tested in livers deemed unsuitable for transplantation.[16] Thirty-one livers (17 DBDD/14 DCDD) that had experienced an average of >7 hours of

Table 2

Twenty-Five Year Growth of Donation after Neurological Determination of Death [DNDD] and Donation after Circulatory Determination of Death [DCDD] *

Type of Deceased Donor (as designated in OPTN data report*)	1995	2023	Percentage Increase/ Decrease 1995-2023
All Donors ("DCD and Non-DCD"*)	5,363 (100.0%)	16,335 (100.0%)	204.59%
DNDD ("Brain Death Donor"*)	5,282 (98.5%)	10,439 (63.9%)	97.63%
DCDD ("DCD Donor"*)	64 (1.2%)	5,895 (36.1%)	9110.94%
Unknown ("Not reported"*)	17 (0.3%)	1 (0.006%)	-94.12%

*U.S. Department of Health and Human Services, Organ Procurement and Transplantation Network, National Data: Deceased Donors Recovered in the U.S. by Circumstance of Death: January 1, 1988-December 31, 2023, <https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#> (last visited May 5, 2024).

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cold ischemia were perfused (>4 hours and <24 hours, averaging about 9 hours), and 71% (12 DBDD/10 DCDD) subsequently met the criteria for transplantation. Recipients of these livers had 100% ninety-day survival. Four recipients developed non-anastomotic biliary strictures, only one of which was associated with hepatic artery thrombosis (>10% NAS). Similarly, in a study conducted at a single center in the U.S., about 70% of rejected livers with cold ischemic time (CIT) under 8 hours were transplantable after NMP.[17] No liver that met the viability criteria resulted in a transplant graft-related death, non-function, or non-anastomotic biliary stricture. Further research is needed to clarify whether normo- or hypothermic delivery is superior for attenuating ischemia and reperfusion liver injury under specific conditions.

Reduced function due to pre-existing organ injury appears to be less amenable to organ resuscitation, especially for kidneys that have reduced function due to advanced donor age.[18] A study of transplantation of paired deceased kidneys, one placed on oxygenated perfusion and the other on standard cold perfusion, demonstrated very similar renal function after a year, although post-transplant complications were reduced using oxygenated perfusion.[19] The extent to which oxygenated perfusion will reduce death-associated injuries in a specific organ requires further study. Improvements in predictive analytics capable of identifying organs that will reliably benefit recipients are needed to reduce system inefficiencies and excessive costs.

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III. Developing Advanced Technologies to Extend Preservation of Organs Indefinitely

Investigators working on advanced biopreservation believe that by manipulating temperature and volume they will be able to go well beyond what can be achieved through hypothermia. Various techniques are being developed to minimize crystalline ice formation which can disrupt organic structures and destroy cells: isochoric (i.e., constricting volume) supercooling (-4 to -6°C); supercooling with the addition of cytoprotective agents (CPAs); partial freezing (-5 to -20°C); and organ vitrification (-120 to -196°C), which involves rapidly cooling a CPA-loaded organ into a glassy state.[20] These techniques are still at a preclinical stage; research is proceeding with animal organs and human organs that will not be transplanted.[21] Scientists are also studying how biopreserved organs can be rewarmed in ways that are uniform throughout, do not cause cellular or tissue destruction, and will not leave anything in the organ that could harm the recipient. The techniques being explored include "nanowarming" (laser photonic or radiofrequency excitation of perfused magnetic nanoparticles) and rewarming techniques that outrun ice recrystallization. The latter have been successful in recovering vitrified rat hearts, livers, and kidneys; after being stored for 100 days and nanowarmed, rat kidneys have resumed functioning following implantation.[22]

Technological innovations in biopreservation may thus remove limits on the time that organs can be maintained ex vivo between donation and successful implantation and reanimation. This would offer many benefits. First, no longer constrained by time or its derivative, distance, the process of locating the optimal candidate for an organ could be both more deliberative and more geographically expansive, thus resulting in greater utility (by better matching of donor and recipient[23]) and equity (by overcoming geographic disparities in organ availability[24]). A second, related benefit would be to reduce the number of organs that are discarded because the viability clock ran out while transplant teams were considering whether to accept them. Third, eliminating time constraints would allow recipients' comorbidities to be optimally assessed and controlled, which should reduce early post-transplant mortality rates by about 50%, to a level comparable to recipients of organs from living donors.[25] Fourth, prolonging ex vivo organ viability could provide the additional days needed to precondition recipients to donor antigens prior to organ transplantation under one of the immunologic tolerance protocols now being developed.[26] Fifth, with added time, donated organs could be more thoroughly tested for malignancies and infectious diseases, which could in some cases be treated, preventing discard of the organ.

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Sixth, removing time constraints would convert organ transplantation from an emergent to an elective procedure. Normal scheduling of the procedure would not only facilitate the improvements in safety that come from following routine surgical practices, but would also be less stressful for transplant teams and avoid disrupting operating room schedules and the resulting pressure on hospitals to create excess capacity to accommodate the unpredictable timing of organ recovery. Finally, many of the difficulties caused by the emergent nature of transplantation are also sources of clinical and logistical expenses that could be avoided if organs were preserved for days or longer;[27] these savings might cover the added costs of biopreservation.

Despite the indisputable benefits that advanced biopreservation might provide, its eventual implementation depends on whether those benefits can be achieved cost-effectively. The technology is still too early in its development to perform actual calculations, absent data about what its clinical application will cost, much less the expense of creating and operating the additional infrastructure that the technology will necessitate. It is not, however, too soon to begin considering the challenges that will need to be addressed before advanced biopreservation can be integrated into our organ transplantation system.

IV. The Challenge of Fairly Allocating Scarce Organs for Preclinical Research

Getting this technology to the point where deceased donor organs can be indefinitely preserved and successfully rewarmed will require extensive basic and applied research, during much of which investigators will also need to use human organs. Given the scarcity of organs for transplantation, where will such organs come from? The 1984 National Organ Transplant Act (NOTA) established the Organ Procurement and Transplantation Network (OPTN) as a public-private partnership between the Department of Health and Human Services (DHHS) and a private entity to maintain a national registry of patients awaiting transplants and match them with available organs. Under a law approved by Congress in 2023,[28] DHHS is now in the process of soliciting bids from organizations — including the United Network for Organ Sharing (UNOS), which has held the OPTN contract for more than 30 years — to fulfill each of the OPTN's various functions, which include conducting the computerized "match runs" that identify suitable recipients of donated organs.[29] Any decision by the OPTN or an Organ Procurement Organization (OPO) to divert to research organs that could instead be transplanted into a waiting recipient must align with the anatomical gift act in the state where the donor died.[30] The criteria and process for making such diversions must also appear in the OPTN's rules (which, like federal regulations, have to be published for public comment before being promulgated). Some investigators do not need viable organs to conduct advanced biopreservation research, such as examining cellular and intercellular changes in organs exposed to different sub-zero preservation and rewarming techniques. Providing them nonviable organs that an OPO plans to discard as unsuitable for therapeutic use would not be inconsistent with the OPTN's organ allocation algorithms. OPOs should, however, have policies and processes for transferring nonviable and viable organs for research that are consistent with their state's anatomical gift act and with OPTN requirements; to provide consistency and to facilitate multi-institutional research, the OPTN should consider establishing such a review process at the national level, on which OPOs could then rely.[31]

A more dramatic departure from normal organ allocation policies would arise if, following success with animal models, the investigators developing techniques of advanced organ biopreservation and rewarming decide that further preclinical research is necessary. Such research could involve implanting the manipulated organs into human bodies which have recently been declared dead by neurological criteria and whose vital functions are being artificially supported. This research would allow the organs' functional capacity to be evaluated in a functioning organism for a period of time, after which artificial support would be withdrawn. Such studies, which are not without controversy, have been proposed for research on bioengineered organs[32] and have actually been used in recent xenotransplantation research.[33] Although the federal rules to which institutions must adhere in carrying out medical research apply only to studies involving living individuals,[34] the OPO having custody of a donated body and all institutions participating in such a study should, as a matter of prudence, subject the research plan to scientific and ethical review.[35] Although dead persons do not have the welfare interests that undergird the ethical guidelines and federal regulations on human subjects research, the dignity and privacy interests of recently deceased patients are legally protected.[36] At a minimum, postmortem maintenance of the body for research should have been explicitly approved in advance by the patient or by their surrogate decisionmaker or legally authorized representative (LAR), and should not interfere with other uses of body parts (e.g., in organ transplantation) that receive priority under the state statutes based on the Uniform Anatomical Gift Act (UAGA).[37]

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The question for the OPTN is whether it could, through its usual processes, adopt a policy that would allow viable organs to be provided for this type of preclinical research without explicit legislative authorization for the organs to be diverted from therapeutic use in waitlisted patients. Two rationales — one practical and the other conceptual — support the OPTN permitting such allocation. The first is that this preclinical research could rely on organs that were viable when procured but have not been accepted by any of the transplant programs to which they have been offered. If such organs underwent experimental biopreservation — that is, preparation, freezing, storage, and rewarming — and were then supported by mechanical perfusion while their viability was assessed, before being implanted in human decedents, patients on the waitlist would be no worse off than if the planned discard of the organs had occurred. Two difficulties may, however, prevent this practical solution from providing many — or any — organs for use in human decedents. First, as oxygenated perfusion comes into wider use, the discard rate of organs that become too marginal for transplantation as their ischemic time accumulates may decline substantially. Second, there is no a priori reason to suppose that an organ that is slated to be discarded because its viability for transplantation cannot be restored before it is frozen and rewarmed would be restorable after it had undergone advanced biopreservation. The researchers are likely to reject organs of questionable viability because of the difficulties they would encounter in interpreting the results — especially negative ones — of the studies using human decedents.

The second, conceptual rationale for allowing the OPTN to allocate viable organs for experimental implantation in human decedents rests on reexamining the OPTN's limits and purposes. As to the former, the argument would be that the policy that donated organs be allocated to patients prioritized by scientific algorithms exists to prevent biased treatment of individual patients or groups with particular characteristics. Since providing some viable organs for preclinical research does not discriminate unfairly among patients on the waiting list, it is not the sort of departure from the usual methodology for allocation that OPTN policies are designed to prevent. The question is thus: does allocating organs to research come within the purposes for which the OPTN was created? In 1984, when NOTA was adopted, it was apparent that more organs were needed to meet demand, that organ procurement agencies (as they were then called) were absent in some locales and overlapped in others, and that lack of coordination led to organ wastage. Promoting fairness meant ensuring that organs were procured and distributed everywhere, while increasing the number of transplants required improving efficiency by knitting OPOs and transplant centers together into a network. And, as the Task Force on Organ Transplantation that was established by NOTA to set up the framework for the U.S. transplant system unanimously concluded in its 1986 report, "future improvements in transplantation depend upon continued and enhanced research and innovation,"[38] and specifically that "research be aggressively pursued in organ preservation,"[39] of which the subzero techniques discussed in this article are the latest example. Thus, the OPTN would be acting within its mandate to support research that can increase the number of organs available for transplantation if, in an orderly and transparent fashion, it adopted a policy under which it could allocate to preclinical trials of advanced biopreservation some organs from deceased donors who had indicated a willingness to have their organs used for research.

V. Challenges Posed by Advanced Biopreservation Clinical Trials

Moving advanced biopreservation of human organs into clinical trials will be more challenging than is typical for novel drugs and medical devices because of two distinctive features of biopreservation. First, the nature of the benefit being sought may affect the permissibility of enrolling any patients in the trial. Second, the OPTN may play a role in selecting subjects that is not typical for an entity that controls access to the thing being studied (in this case, organs that have been through advanced biopreservation).

A. The Risk-Benefit/Equipoise Threshold for Clinical Trials

The first step in moving any medical innovation into clinical use is producing results from laboratory research and animal studies that justify initiating a clinical trial. A prerequisite for conducting such trials is clinical equipoise,[40] that is, genuine uncertainty within the expert medical community about the comparative merits of each arm of the trial, namely, the intervention being studied and an "established effective" or "best proven" intervention (or, when ethically permissible, a placebo).[41] Even though the range of outcomes for patient-subjects is much wider — from markedly more beneficial to lethal — whenever an organ is transplanted than with almost any experimental drug, physician-investigators have been able to carry out trials of various types of oxygenated perfusion ethically because the preclinical results established equipoise between transplanting organs pre-

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served in those novel ways and those preserved in the conventional manner, using SCS.

But the benefit being sought in those trials differs from the benefit expected in advanced biopreservation trials, since the latter aim to improve the organ transplant system rather than improve the outcome for individual organ recipients. The principal benefit of demonstrating the feasibility of prolonged sub-zero storage and rewarming of organs will be to increase the number of deceased donor organs available for future transplants. Of course, it is always true that research is forward-looking: patient-subjects accept risk now so that future patients will have access to better therapies. Yet equipoise means that participating in a trial of a new intervention provides patients at least as good a change of getting a therapeutic benefit as they would have outside the trial, whereas, from what is now known about the effects of advanced biopreservation, patient-subjects in a trial of such a technology are unlikely to benefit individually. Consequently, such trials will probably be designed to show the non-inferiority, rather than the superiority, of transplanting organs that have undergone advanced biopreservation compared to existing preservation techniques. The committees responsible for ethical review of clinical trials (such as a university or hospital Institutional Review Board) would be expected to approve a clinical trial with patients awaiting an organ transplant only if the results of the preclinical studies with human decedents establish comparably successful outcomes for recipients of organs that have undergone advanced biopreservation and rewarming and organs that have been preserved using whatever is then the best available method.

B. External Control over Selection of Research Participants

Conducting clinical trials of transplantation with organs that have undergone advanced biopreservation also entails a second, rather unique challenge. It is always the case that more is involved in enrolling in a clinical trial than one's willingness to participate. In addition to being able to provide informed, voluntary consent, potential participants must meet the study's inclusion criteria (characteristics that define the population to which the study's results should be generalizable and that aim to ensure that the study's endpoints can be measured in each participant) and exclusion criteria (factors, such as comorbidities, that could confound interpretation of the study's results, or characteristics, such as an elevated risk of adverse outcomes, that would make it unethical to enroll a participant). These considerations are "internal" to a study because they follow from the study's scientific design, whereas the unique feature of advanced biopreservation research is the role that an "external" entity, the OPTN, may play in determining patients' eligibility to participate.

In the discussion of preclinical trials of advanced biopreservation above, we focused on the OPTN's legal control over organs for transplantation and concluded that the OPTN would need to promulgate a special policy in order to allocate viable organs to nontherapeutic research.

Once trials begin with actual patients to determine whether organs that have been biopreserved provide comparable benefits to those that have not, the difficulty that arose in using viable organs in preclinical research would be obviated because all the research participants would be potential transplant recipients.

Participants could be selected in a number of ways. For example, a 2017 National Academies report on organ donor intervention research recommended that all potential recipients should be educated about such "research and asked whether, at the time of organ offer, they would potentially consider accepting an organ … that was part of a research study."[42] When prioritized in an OPTN match run, patients who had expressed a possible interest in participating would be provided with specific information about a study of advanced biopreservation that is underway. This has the advantage of preserving the standard method of determining priority for a transplant, but it would be unusual in giving an external entity (the OPTN) a direct role in determining which patients may participate in the trial. Alternatively, information about a trial using advanced biopreservation of organs could be provided to a subgroup of patients on the waitlist (selected based on how long they had been waiting or by some other criterion) and interested patients could volunteer. That method would be feasible only if the OPTN adopted a special policy that allowed it to provide the investigators with sufficient organs, both those that will be subjected to the particular means of biopreservation being studied and then stored and others supplied as needed for participants randomized into the control group.[43] This design raises two issues. The first concerns fairness to the patients who are willing to volunteer for the research. Either volunteers for whom the repository of biopreserved organs cannot supply a good match would have to be declined or the repository could be limited to organs suited to a special, difficult-to-match type of patient, which would require restricting the pool of patients invited to those with particular characteristics. Second, giving volunteers a chance to get a transplant more quickly

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may be problematic. On the one hand, is it fair to other patients on the waitlist who are not given the opportunity to volunteer? And on the other, does the chance to move to the front of the transplant queue constitute an undue inducement to volunteer for the study?

Whatever method is used to select the participants, they should be fully informed about the purpose of the research, about how the organ will be manipulated, about anything that might affect them differently than in an ordinary transplant, and about how participants will be randomized, so that they can make an informed decision about whether they wish to participate in the research or wait until the OPTN assigns them another, non-experimental organ.[44]

VI. A Threshold Challenge: Is Advanced Biopreservation Needed?

If clinical research provides an affirmative answer to one threshold question—are organs that have been biopreserved and stored in a repository a comparably safe and beneficial alternative for transplant patients? — one would need to ask another one — might the significant benefits for which novel biopreservation technologies aim also be achieved, or approximated, in other easier and less problematic ways, such as through further advances in oxygenated machine perfusion?[45] Of course, the maximum amount of preservation time that can be achieved with perfusion remains uncertain. For example, the registration trials that brought current NMP devices to market were designed to demonstrate non-inferiority to conventional SCS, not prolonged preservation. Nor have all the risks associated with extended on-pump time been ascertained. Moreover, oxygenated perfusion is not expected to be able to preserve organs for very long periods of time, much less indefinitely. Nonetheless, the addition of a few days or weeks of viability that improved means of oxygenated perfusion may be capable of delivering over what is provided by prevailing methods such as SCS may be enough to allow transplants to be scheduled on a non-emergency basis and organs to be matched with recipients more precisely and without geographic limitations, all of which would reduce nonuse of viable organs.

Policymakers, both in Congress and in DHHS, may find perfusion technologies more attractive than advanced biopreservation because the former can be used — as they already are — within our existing organ donation and transplantation framework. More than that, they not only prevent viable organs from being lost due to the limited time available to get them accepted by, and implanted into, a recipient, but they can also rehabilitate some organs that were judged not to be usable at the time of donation. Given the organ shortage, this ability — which is not now anticipated to be provided by advanced biopreservation — offers an additional reason to favor perfecting techniques for oxygenated perfusion of organs.

Whatever method is used to select the participants, they should be fully informed about the purpose of the research, about how the organ will be manipulated, about anything that might affect them differently than in an ordinary transplant, and about how participants will be randomized, so that they can make an informed decision about whether they wish to participate in the research or wait until the OPTN assigns them another, non-experimental organ.

Nevertheless, prolonged biopreservation could be of great value in making it possible to create a repository of uncommon organ types, which would otherwise be unlikely to become available for transplantation at the very moment when a patient urgently needs such an organ. For example, even though long-term outcomes of neonatal heart transplants "are better than for any other form of solid organ transplantation,"[46] the highest waiting-list mortality of any age group occurs among infants who require a heart transplantation.[47] Neonates with lethal heart malformations have difficulty obtaining a transplantable heart due to size limitations. As it happens, the number of babies born yearly with anencephaly approximates the number of neonates dying from congenital heart disease, but deaths of anencephalic babies rarely occur close to the time when a heart transplant is needed.[48] If long-term preservation of neonatal hearts were feasible, infants born with otherwise fatal heart diseases could dramatically benefit from the availability of size-

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appropriate, excellent quality hearts that had been donated for transplantation and biopreserved. The same may be true for a small subset of other organs that could be banked to be used in treating adult (and older pediatric) patients with unusual needs or who could benefit from quick treatment for an acute injury.[49] Were that the case, advanced biopreservation might be established in a single repository just for these unusual cases. If, however, this technology is able, at a reasonable cost, to eliminate the pressure of time limits that now hamper the process of allocating organs, and if the problem of removing organs from current use comes to be seen as a temporary, one-time exacerbation of the current shortage of transplantable organs, transplant centers may favor the creation of a national system of "organ banks" for all types of organs, operating under a new means of matching organs to recipients. Furthermore, if the technology of advanced biopreservation provides transplant centers with operational flexibility — or comes to be regarded as a symbol of being a "cutting-edge" program — past experience with other medical innovations suggests that the centers may seek ways of adopting it, even if funding agencies are not convinced that its use is cost-effective compared to alternative methods.[50]

VII. The Challenge of Allocating Organs to and from Advanced Biopreservation Organ Banks

If advanced biopreservation of organs is going to proceed in some form, means will be needed to oversee the safety and efficacy of using the organs in transplants, the operation of the repositories (or "organ banks") where they are stored, and, above all, the processes by which organs move into and out of such banks. While it is admirable that the OPTN's vision for itself includes "balancing competing goals in ways that are transparent, inclusive, and enhance public trust in the national organ donation system,"[51] more than openness will be required and more stakeholders should be involved than those in the OPTN or any inter-agency task force of the sort usually convened to undertake such tasks. Success in formulating and implementing the needed policies will require representation from professional and patient advocacy organizations and from civil society more broadly.

When any new technology is at an early stage in development — as is true for applying various types of advanced biopreservation to organ transplantation — any conclusions about how the technologies should be employed and governed will be based on conjecture rather than evidence. Without knowing what a technology is capable of delivering medically, how can we structure its use in a way that will advance particular values — such as autonomy, equity, efficiency, individual and collective utility — or, indeed, how can we be sure that the technology is even capable of advancing any of those values? While it would thus be premature to prescribe the means of governing advanced biopreservation of organs, it is not too soon to recognize some of the challenges with which policymakers will have to grapple if these technologies are to be well integrated into the organ transplantation system.

A. The Challenges of Establishing and Maintaining Safety and Efficacy

Responsibility for the well-being of organ recipients is spread among several DHHS agencies. The CDC has the lead role in promulgating and revising Public Health Service guidelines to protect organ recipients from being harmed by infected organs. It does this by recommending that OPOs determine, based on medical and behavioral information about the donor, whether any of ten risk criteria are present in a donor; that they test donors with specified laboratory tests for several viruses (HIV and hepatitis B and C); that transplant centers test recipients for infection before and after the procedure; and that these organizations and the OPTN report any infections to public health officials as well as to all transplant centers that received an organ from the donor. When a risk factor or infection is identified, the transplant center should include this information in informed consent discussions with the transplant candidate, along with information about the availability of effective therapies should transmission occur.[52] The OPTN Ad Hoc Disease Transmission Advisory Committee translates CDC guidance into operational policies and procedures for OPOs to detect and communicate risks to patient safety, and also provides ongoing monitoring and investigation of reported potential disease transmissions and educates the transplant community about challenges to patient safety.[53] Separately from the relationship of the OPTN to the OPOs and transplant centers, the guidelines to prevent disease transmission are enforced through the performance criteria established by the Centers for Medicare & Medicaid Services (CMS) for OPOs' accreditation and compensation, and through the Conditions of Participation with which transplant centers must comply to receive payment from Medicare.

The agency principally responsible for the safety and efficacy of drugs, biologics and medical devices is the Food and Drug Administration (FDA) which licenses these products based on satisfactory evidence from laboratory and clinical studies submitted

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by their manufacturers. In organ transplantation, it carries out its assessment and approval functions not only for the drugs used during and after the procedure but also for the devices and perfusion solutions used in organ preservation. But the FDA does not regulate the practice of medicine, and it has treated organ transplantation simply as a surgical procedure, which it excludes from the oversight it exercises over human cells, tissues, and cellular and tissue-based products (HCT/Ps).[54] Given the substantial time gaps and novel manipulation pathways between the retrieval and transplantation of biopreserved organs, the FDA may take a different approach here. If it did, it could limit its involvement to licensing the devices that prepare (such as by adding CPAs or nanoparticles) and preserve the organ, as it now does with the devices for oxygenated perfusion. Or it could set "good manufacturing practice" standards for the entire process, as it can for some HCT/Ps, by assessing all steps along the way (including by monitoring conditions in the organ banks and in the rewarming) and determining that the "products" conform to expectations. The choice about how to proceed may, for example, turn on evidence about the extent of cellular injury or reduced organ function caused by techniques used to achieve deep hypothermia and long-term storage. But it may also depend on how tradeoffs are resolved between the quality of organs and the number of organs available for transplantation, or between spending the available funds on more extensive testing or repairs of organs or on performing more transplants.

Decisions about how extensively to regulate will be greatly influenced by who writes the policy. While the authority to establish the standards of safety and utility ultimately rests with the FDA, the content of the standards will be affected if professional and scientific bodies participate, or even take the lead, in the drafting, or if public representatives are engaged — through hearings or even legislation — because each group may prioritize values and objectives somewhat differently. Whoever is involved, the deliberations will be aided by adequate data not only from clinical trials but also by improving the data reports now produced, which do not include an evaluation of the quality of organs from the time of donation to transplantation. Such data will probably be necessary both for research on, and eventual clinical use of, the organs that undergo advanced biopreservation; it would be very illuminating to have comparable data for organs that are transplanted with and without other forms of preservation.

B. The Challenges of Creating and Managing Organ Repositories

The nature and governance of the repositories for biopreserved organs will depend on the purpose for which they are established. At one extreme, a bank could serve a limited population (such as neonates needing a heart transplant); in that case, a single location might serve the nation. At the opposite extreme, a large percentage of all organs could be biopreserved, in order to be able to have on hand organs that would be suitable for almost any sort of patient. Such facilities could be distributed in regions across the country or in every state or even every designated service area. The question of where banks should be located — does a bank store only organs collected within its jurisdiction or, perhaps more important, distribute organs only within its jurisdiction, or is it a local outpost of a national system that is dispersed across the country to enable most distributions of organs to be handled by ground delivery to a nearby transplant center? — may reflect efficiencies at each of the stages of biopreservation, in terms of dispersed or centralized operations, or may reflect policy preferences of the OPTN, DHHS, Congress, or state officials.

What are appropriate models for the operation and governance of an organ bank? Tissue and bone banks are typically for-profit operations, sometimes run as subsidiaries of non-profit OPOs; eye banks are usually independent. Any of these models would be problematic for organ repositories which are, at least conceptually, simply a holding device for some of the organs that are donated for transplantation (or other purposes). In principle, they should operate in coordination with the organizations that are collecting and distributing "fresh" organs for immediate transplantation. Perhaps OPOs should operate the organ repositories, but this idea may not appeal to Congress at a time when many OPOs have been criticized for inefficiencies. That suggests that they should be under the aegis of some part of the "modernized" OPTN, which will need to develop new education, training, and certification of personnel for the new tasks in which the organ bank(s) will be involved.

C. The Challenge of Allocating Organs to Repositories

As long as a shortage of organs means that thousands of organ-failure patients die each year without a transplant, any policy changes that divert organs from immediate use will be controversial and seem certain to be challenged in court and perhaps in the legislature. Such objections are likely to be more muted if biopreservation is used solely to create a specialized bank for a small number of cases, especially if this

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involves organs that though viable would otherwise be discarded because a recipient-in-need does not exist at the moment of the donor's death. Other limitations have been suggested, such as initially banking "only organs not expected to be transplanted locally," on the grounds that local transplants have "expected excellent outcomes" and that savings in not having to transport an organ to a distant location by air on an emergent basis can offset some of "the extra costs and system complexities" of advanced biopreservation.[55] While this might reduce objections from local transplant centers (and their patients) and perhaps the local OPO and donor families, if the number of organs that are allocated to the organ bank is large, the number of current deaths on the waiting list will also increase in each locality, at least until the organ bank has a sufficient stock on hand that its utility in providing access to well-matched organs becomes apparent.

Many aspects of the technology — how scalable it turns out to be, whether it proves safe and effective in ways that impress the public, and whether any benefits it provides will be sufficient to persuade funders to support it — will shape the policies that are adopted about when and how to assign "fresh" organs for direct use in transplant patients and when to send others to long-term preservation ("frozen organs"). But choices will need to be made and, so long as organ banks function as an extension of the current distribution system, the formulation and application of the policies seem to be encompassed within the OPTN's broad responsibilities for organ allocation. One thing is clear, namely, that it will not be possible to have a worthwhile system of advanced biopreservation if the organs assigned to that use are limited to those that, even with resuscitative efforts, remain marginal for transplantation. Preserving such organs would be a waste of this technology, unless a reasonable likelihood exists that interventions will soon be found to overcome whatever defects currently render these organs unfit.

One unintended consequence of advanced biopreservation may reduce rather than increase the total number of transplants. Several national programs now exist to achieve more living donor transplants by giving "vouchers" either (a) to people who want to donate a kidney to benefit a relative with whom they are "chronologically incompatible" because their relative's need for a transplant will occur sometime in the future (if ever), or (b) to people who are deterred from being altruistic donors because they fear that a relative will later develop a need for a kidney and they will be unable to help because they have already donated one of their kidneys.[56] Since their kidney does not go directly to a relative at the time it is donated, these people serve as "undesignated" donors and their kidney can be used to initiate a kidney chain. If prolonged biopreservation were readily available, these people could place their kidney in a repository where it would remain until a designated voucher-holder needs to claim it, and the many transplants in the chain they would have initiated may never occur. This possible consequence needs careful evaluation if organ banks are going to play a major role in transplantation.

D. The Challenge of Releasing Biopreserved Organs from Repositories

The projected capability of advanced biopreservation to maintain organs indefinitely is a double-edged sword: it cuts through the constraints that time imposes on viability but it also creates the need for new structures. These structures are not just the physical buildings where preserved organs would be processed, stored, and reanimated, but also the governance arrangements needed to address two allocative decisions. Although the first policy — which organs to use now, which to freeze? — is, as we have just seen, difficult to decide, with controversy likely to flow from any policy choice, it may actually be less vexing than a second governance question, which concerns deciding how organs that have been placed in an organ bank should be allocated to a particular patient for transplantation. At present, the allocation process is started by the sudden availability of organs from a deceased donor, which triggers a search for the most suitable patients on the waitlist for each organ.[57] Advanced biopreservation will remove that trigger, which raises the need for deciding on how stored organs would be allocated. Would a request from a transplant center for an organ for a patient be sufficient? Would certain minimum criteria — such as the quality of the match between patient and organ, or the patient's time on the waitlist — be relevant, and if so, who would develop and apply such criteria? The persons who operate the organ repository resemble the surgeons who possess organs after they have removed them from a dead donor; under anatomical gift laws, the surgeons who remove the organs from the donor are regarded solely as custodians of the organs, not decisionmakers about which patients receive them. Again, the OPTN is the designated body for developing and applying the algorithms under which the recipient of an organ is identified, but its existing rules would not be adequate for biopreserved organs.

For example, as a matter of procedural fairness, if the removal of an organ from storage were to be initiated by a request on behalf of a patient, other patients waiting for a transplant would need to be informed

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that a particular organ is about to be removed from the repository. But this raises the question: which patients? When the OPTN does a computer run now, the urgency of identifying a recipient determines which patients are in the group to be ranked to receive the organ: namely, those who are on the waiting list at that moment and who satisfy any specific limitations, in terms of their characteristics and location. Advanced biopreservation changes the role of time: the need for a decision does not arise because of the limits of an organ's viability for transplantation but because of patients who want or need the organ, perhaps because without it they will soon die or suffer in some other way. But if the allocation decision is made at Time_x then other patients whose equally great (or perhaps greater) need for that organ does not arise until Time_{x+y} — which could be the next day, next month, or next year — will lose their opportunity to be in the group of patients among whom the algorithmic priority ranking is made. Fairness requires treating likes alike. But when an organ can be used indefinitely, what is the fair way to decide which present or future patients belong in the pool?[58]

VIII. Challenges to Basic Concepts

Biotechnologies such as isochoric supercooling and vitrification may prompt a conceptual transformation of transplantable organs. No longer just human body parts being quickly rushed from a person who has just died to another person in whom they will resume functioning, organs seem to be transformed by advanced biopreservation into products in warehouses and listed in online catalogues, to be purchased like any other item of commerce.[59] Paying a set price for a particular biopreserved organ when it is distributed from a repository may thus make these organs — and perhaps by extension, all transplantable organs — seem more like market commodities. The charges that now attach to obtaining an organ for transplantation are understood to reflect the professional services of medical and other personnel and institutions in procuring, screening, transporting, and implanting the organ. Patients may first become aware of those charges only after their surgery, when they appear on a hospital bill; other charges only appear in the internal bookkeeping of the institutions involved. In contrast, preserved organs listed on a website with a "price" may seem like merchandise when transferred to recipients. And when that happens, donors may regard them in the same fashion, and ask why they are not also paid for providing the organs in the first place.

A further source of conceptual change may arise from the temporal separation of the donor family and the organ recipient. Even in cases where there is no direct contact, receiving information about how patients benefitted from their gift can provide solace to donor families at what for many is a time of intense loss and grief. That satisfaction and sense of comfort may not be provided by the knowledge that their loved one's organs are being stored indefinitely in a repository so that they may, sometime in the future, help benefit a patient. Again, this is a phenomenon that deserves to be considered and studied.

IX. The Challenge of Ascertaining which Transplants Will Deliver Benefit

New preservation technologies — whether they are used for days at temperatures above 0°C or for much longer periods at temperatures down to -196°C — cannot change the basic fact that transplantation is only beneficial to a recipient when the transplanted organ provides sufficient function to extend the duration and/or to improve the quality of the recipient's life. The deceased donor organs that do that typically come from high quality (that is, young and healthy) donors, while the vast majority of unused organs come from older donors who die with multiple co-morbidities and diminished organ function. Oxygenated perfusion devices have demonstrated that they can make organ transplant procedures safer by restoring metabolic functions and avoiding further harm (such as IRI) in some of the unused organs. But at least at present these devices cannot rescue intrinsically defective organs (e.g., lungs with bullae, kidneys with age-associated loss of renal function, or hearts with prior hypertrophy from hypertension). The value of the devices lies in bringing an organ back to the functional potential it had before the events that led to the donor's death and supporting that functionality until the organ is transplanted, not in making a liver or kidney from the average 70-year-old as functional as one from the average 30-year-old. The key to deriving benefit for transplant recipients thus lies in being able to reliably identify which organs have been sufficiently restored and supported that they will provide their recipients a survival benefit (i.e., more years of life than they would have had without a transplant). Since such predictions are difficult to make at present, research to develop an evidence base for differentiating organs that have sufficient potential function from those that do not is as essential as research on organ preservation techniques if we are going to increase the number of available organs and improve patient outcomes.

The development of means to make reliable predictions would increase utility across all of transplantation. Some clinicians are reluctant to transplant older

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kidneys (donors >65 years) because of uncertainties about the kidneys' quality and the durability of graft function. A study that drew on the U.S. national transplant database for 2000 to 2018 found that the durability of kidney transplants from deceased donors >65 years was similar to younger donor kidneys when stratified by their estimated glomerular filtration rate after one year (eGFR-1). Further, durability decreases as eGFR-1 decreases, such that when an older kidney fails to supply an eGFR-1 >30 ml/min, the recipient loses the survival benefit of having had a transplant.[60] In addition to large retrospective database studies, clinical trials can also be used to generate the information needed to predict which deceased donor organs that have been subjected to which preservation technique will provide sufficient benefit to transplant recipients. For example, kidney pairs from DCDD donors >49 years were randomized either to hypothermic machine perfusion (HMP) or to HMP with oxygenation ($HMPO_2$). Although $HMPO_2$ led to fewer severe postoperative complications, the study's primary outcome (eGFR) did not differ between groups for kidney pairs where both transplanted kidneys were functioning at the end of follow-up. "However, when the beneficial effect of $HMPO_2$ on graft survival was considered, $HMPO_2$ was associated with improved 1-year graft function as measured by eGFR."[61] Besides much more refined criteria for assessing the quality of each type of organ and the results that will occur if it is transplanted into patients with particular characteristics, and improvements in the capacity of artificial intelligence to apply such criteria to the characteristics of candidate recipients with high reliability, the key to providing maximum value to patients and eliminating unjustified discards will rest on the willingness of transplant professionals to accept such findings in place of their individual clinical judgment about a donated organ's suitability for their patient.

X. Conclusion

Advanced biopreservation, although still at a preclinical stage, holds promise for transplant medicine as well as for other fields of science. In addition to the important, and difficult, scientific issues that remain to be answered, major issues of fair allocation, safety, efficacy, payment, and governance will need to be resolved. At the moment, however, the actual capabilities of the technology are too indefinite to know what changes in statutes, regulations, and ethical standards will be needed to obtain the promised benefits. This article has identified a number of challenges that will need to be addressed as the technology advances toward clinical research and possible use in patients, the most basic of which is whether advanced biopreservation is actually needed in light of the benefits that can be provided by other, simpler techniques for preserving organs using oxygenated perfusion, which are already much further along in clinical development and application. It is important that a wide range of stakeholders in addition to the scientists investigating advanced biopreservation begin now to consider the practical and ethical challenges discussed above, even though the formulation of fixed ethical guidance, regulations, or governance structures would be premature and could chill the development of the field.

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Disclosures

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36. "A Framework," *supra* note 31, at 2253–54. The usual gray zone in "donor intervention research" concerns whether novel manipulations of organs (which may still be in, or have just been removed from, a deceased donor's body) fall outside the federal human subjects regulations since the donor is dead. When the organs are going to be implanted in a living patient, however, there is no question that the latter is a human subject of research, like any patient who is given an approved drug as part of a study of, for example, a not-yet-approved indication or mode of administration.
37. See §11(d), UAGA, *supra* note 30.
38. Office of Organ Transplantation, Health Resources and Services Administration, Public Health Service, US Department of Health & Human Services, *Organ Transplantation: Issues and Recommendations — Report of the Task Force on Organ Transplantation* (April 1986) at xxii. The Task Force explained that in "strongly urg[ing] that research on all aspects of transplantation be fostered and encouraged," it had in mind not only basic research but also "laboratory and clinical research of an applied nature." *Id.* at 12.
39. *Id.*
40. B. Freedman, "Equipoise and the Ethics of Clinical Research," *New England Journal of Medicine* 317, no. 3 (1987): 141–145.
41. Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition* (Geneva: CIOMS, 2016), at 15 (Guideline 5: "As a general rule, the research ethics committee must ensure that research participants in the control group of a trial of a diagnostic, therapeutic, or preventive intervention receive an established effective intervention."); World Medical Association, *WMA Declaration of Helsinki–Ethical Principles for Medical Research Involving Human Subjects* (2013) (Sec. 33: "The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s)," except that a placebo or no intervention is acceptable when no proven intervention exists or when necessary "for compelling and scientifically sound methodological reasons … to determine the efficacy or safety of an intervention," provided that doing so will not subject patients to "additional risks of serious or irreversible harm"), *available at* <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/> (last visited August 27, 2024).
42. J.F. Childress, S. Domnitz, and C.T. Liverman, eds., *Opportunities for Organ Donor Intervention Research: Saving Lives by Improving the Quality and Quantity of Organs for Transplantation* (Washington, DC: National Academies Press, 2017), at 12 (Recommendation 4) [hereinafter cited as *Opportunities*].
43. The OPTN might consider adopting such a special policy for allocating some organs to patients participating in a research trial of advanced biopreservation under its authority to approve "Variances," defined by Policy 1.2 (Definitions) as "An experimental policy that tests methods of improving allocation." OPTN Policies Effective as of April 2, 2024, *available at* <https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf>, at 17 (last visited August 27, 2024). However, Policy 1.3.A.1 specifies that variances "must comply with the requirements of NOTA and the Final Rule." *Id.* at 18. Given that placing viable organs into an indefinite period of storage, thereby making them unavailable to patients currently on the waiting lists, would amount to a major departure from normal allocation under the Final Rule, the prudent course for OPTN might be to seek approval from DHHS and perhaps specific legislative authorization from Congress.
44. *Opportunities, supra* note 42, at 92–99.
45. Given the challenges in conducting the preclinical and clinical research needed to get past the first threshold, some might suggest that we should decide whether it is worth proceeding with advance biopreservation of human organs before carrying out such research, but proponents can argue, rather persuasively, that we must do the research to have a full picture of the potential benefits and limits of these technologies.
46. M. John and L.L. Bailey, "Neonatal Heart Transplantation," *Annals of Cardiothoracic Surgery* 7, no. 1 (2018): 118–125, at 124.
47. C.S.D. Almond et al., "Waiting List Mortality Among Children Listed for Heart Transplantation in the United States," *Circulation* 119, no. 5 (2009): 717–727.
48. Anencephalic patients would have to be declared dead based on the medical criteria that are used with other infants who donate after determination of death, rather than on the basis that their neurological deficit provides a ground for declaring them dead even though they are breathing spontaneously. The latter practice, which was followed at some transplant centers from the 1960s to 1980s, was discontinued after being strongly criticized by many medical associations, lawyers, and ethicists. See D.A. Shewmon, A.M. Capron, W.J. Peacock, and B.L. Schulman, "The Use of Anencephalic Infants as Organ Sources: A Critique," *JAMA* 261, no. 12 (1989): 1773–1781. The number of organs derived from this source would certainly be less than the number of anencephalic births both because a majority of these neonates are too small to provide transplantable organs and because of difficulties in determining death in anencephalic neonates who are being managed as potential donors. In July 1988, Loma Linda University Medical Center, the only transplant program in the country that was then attempting to obtain organs from anencephalic infants, announced that it was suspending its protocol following 13 failed attempts to obtain organs in the preceding 7 months. *Id.*
49. R.J. Fontana, "Acute Liver Failure Including Acetaminophen Overdose," *Medical Clinics of North America* 92, no. 4 (2008): 761–794 (early referral of patients with a poor prognosis to a liver transplant center is essential to optimize clinical outcomes).
50. A.D. Maynard et al., "Successfully Bridging Innovation and Application: Exploring the Utility of a Risk Innovation Approach in the NSF Engineering Research Center for Advanced Biopreservation Technologies (ATP-Bio)," *Journal of Law, Medicine & Ethics* 52, no. 3 (2024): 561–567.
51. *Visions and Goals*, Organ Procurement and Transplantation Network, Health Resources and Services Administration, U.S. Department of Health and Human Services, *available at* <https://optn.transplant.hrsa.gov/about/vision-goals/> (last visited August 27, 2024).
52. J.M. Jones et al., "Assessing Solid Organ Donors and Monitoring Transplant Recipients for Human Immunodeficiency Virus, Hepatitis B Virus, and Hepatitis C Virus Infection — U.S. Public Health Service Guideline, 2020," *Morbidity and*

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Mortality Weekly Report 69, no. 4 (June 26, 2020): 1–16, *available at* <https://www.cdc.gov/mmwr/volumes/69/rr/rr6904a1.htm?s_cid=rr6904a1_w#suggestedcitation> (last visited August 27, 2024).

53. *Ad Hoc Disease Transmission Advisory Committee*, Organ Procurement and Transplantation Network, Health Resources and Services Administration, U.S. Department of Health and Human Services, *available at* <https://optn.transplant.hrsa.gov/about/committees/ad-hoc-disease-transmission-advisory-committee/> (last visited August 27, 2024).
54. "Vascularized human organs for transplantation" are explicitly excluded from the FDA's definition of HCT/Ps. Food and Drug Administration, "Human Cells, Tissues, and Cellular and Tissue-Based Products," 21 C.F.R. § 1271.3(d)(1) (2023).
55. Ward et al., *supra* note 27, at 343.
56. J.L. Veale et al., "Voucher-Based Kidney Donation and Redemption for Future Transplant," *JAMA Surgery* 156, no. 9 (2021): 812–817; J.L. Veale, "Vouchers for Future Kidney Transplants to Overcome 'Chronological Incompatibility' Between Living Donors and Recipients," *Transplantation* 101, no. 9 (2017): 2115–2119.
57. Although recipients are usually identified before organs are removed from the donor, the use of oxygenated perfusion devices may delay selection while the organ's functioning is evaluated on the device. The portable metra device from OrganOx has been shown to be superior to SCS for livers, both when use is initiated immediately at the donor site and when the livers are transported in SCS to a transplant center and then placed on the device. Another company, Lung Bioengineering, is running a clinical trial on its Centralized Lung Evaluation System, in which lungs are sent to one of its two facilities, where they undergo rehabilitation and assessment on XPS, an FDA-approved ex vivo lung perfusion device manufactured by a Swedish company, XVIVO; if the lung is deemed acceptable, it is sent to the transplant center to be implanted in the pre-identified recipient. XVIVO also sells Organ Assist perfusion devices for livers, lungs, and kidneys. The Organ Care System (OCS) from Trans Medics, Inc. is a transportable NMP device to which the FDA has given premarketing approval (PMA) for standard and expanded criteria lungs (those initially deemed unacceptable for procurement); the device is in clinical trials under investigational device exemptions (IDE) for expanded criteria hearts and for DCDD and DNDD livers. Organs can be treated, assessed for suitability, and transported to the patient identified by the OPTN on the OCS device.
58. J.F. Childress et al., "Ethical Issues in Emerging Technologies to Extend the Viability of Biological Materials across Time and Space," *Journal of Law, Medicine & Ethics* 52, no. 3 (2024): 568–582.
59. The historical reality of bodies being treated as articles of commerce is described in M.B. Goodwin, "An 'Amazon of Living Things'? The History & Horror of Commodifying Life," *Journal of Law, Medicine & Ethics* 52, no. 3 (2024): 609–621.
60. T.L. Pruett, G.R. Vece, R.J. Carrico, and D.K. Klassen, "US Deceased Kidney Transplantation: Estimated GFR, Donor Age and KDPI Association with Graft Survival," *EClinicalMedicine* 37 (2021): 100980, doi: https://doi.org/10.1016/j.eclinm.2021.100980.
61. COMPARE, *supra* note 19, at 1654.

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