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Personal Viewpoint

Governing new technologies that stop biological time: Preparing for prolonged biopreservation of human organs in transplantation☆

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Abbreviations: ATP-Bio, Advanced technologies for the preservation of biological systems; CMS, Centers for Medicare and Medicaid Services; CPA, cryoprotective agent; DHHS, Department of Health and Human Services; FDA, Food and Drug Administration; HCT/P, human cells, tissues, and cellular-based and tissue-based products; HRSA, Health Resources and Services Administration; NASEM, National Academies of Sciences, Engineering, and Medicine; OPO, organ procurement organization; OPTN, Organ Procurement and Transplantation Network; PHSA, Public Health Service Act.

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ABSTRACT

Time limits on organ viability from retrieval to implantation shape the US system for human organ transplantation. Preclinical research has demonstrated that emerging biopreservation technologies can prolong organ viability, perhaps indefinitely. These technologies could transform transplantation into a scheduled procedure without geographic or time constraints, permitting organ assessment and potential preconditioning of the recipients. However, the safety and efficacy of advanced biopreservation with prolonged storage of vascularized organs followed by reanimation will require new regulatory oversight, as clinicians and transplant centers are not trained in the engineering techniques involved or equipped to assess the manipulated organs. Although the Food and Drug Administration is best situated to provide that process oversight, the agency has until now declined to oversee organ quality and has excluded vascularized organs from the oversight framework of human cells, tissues, and cellular-based and tissue-based products. Integration of advanced biopreservation technologies will require new facilities for organ preservation, storage, and reanimation plus ethical guidance on immediate organ use versus preservation, national allocation, and governance of centralized organ banks. Realization of the long-term benefit of advanced biopreservation requires anticipation of the necessary legal and ethical oversight tools and that process should begin now.

1. Introduction

Organ transplantation was one of the 20th century's major medical advances. Nevertheless, a 2022 report from the National Academies of Sciences, Engineering, and Medicine (NASEM) found that the US transplantation system is "inefficient and inequitable" and that a person's "chance of being referred for a transplant evaluation, being added to the waiting list, and receiving a transplant varies greatly based on race and ethnicity, gender, geographic location, socioeconomic status" and other factors.[1] In September 2023, Congress enacted P.L.118-14 to address these and other problems in the system. The network modernization initiative recently launched by the Health Resources and Services Administration (HRSA) to implement the statute[2] should also study the potential effects of new means of organ preservation. Time limits on organ viability constrain deceased donor organ availability[3] and contribute to inequitable distribution of organs and other problems identified by NASEM. Technologies now being developed may allow extended storage of organs, which could alter the transplant system in major ways, from reducing nonuse of donated organs to improving recipient outcomes.

Cooling organs with cold solutions—conventional static cold storage or machine perfusion—has been the foundation for reliable ex vivo organ preservation. However, reliable return of function of static cold storage preserved organs is time constrained, typically less than 24 hours. The US transplant system has evolved to accommodate short times of organ viability, typically offering available organs to rank-ordered candidates either immediately before or, in the case of kidneys, immediately after surgical recovery of the organ. Oxygenated machine perfusion is beginning to challenge this model.[4] Hypothermic or normothermic oxygenated machine perfusion not only extends the time of ex vivo organs viability but also expands the ability to resuscitate and assess metabolic function, reduce ischemia/reperfusion injury, and determine suitability for use.[5]

Multiple technologies involving a gradient of subzero preservation temperatures (isochoric cooling, perfusion-based supercooling, and vitrification) (Table 1)[4,6-8] have significantly extended organ viability time in animal and preclinical organs.[7,9,10] However, some techniques require very sophisticated engineering, nonmedical procedures—including loading cryoprotective agents (CPAs) and nanoparticles, controlled cooling and vitrification, rapid rewarming technologies, and unloading CPAs and nanoparticles.

Recognizing the transformative potential of advanced biopreservation technologies, the National Science Foundation funded an Engineering Research Center on "Advanced Technologies for the Preservation of Biological Systems" (ATP-Bio) starting in 2020.[11] ATP-Bio includes an Ethics and Public Policy component.[12] Through literature review, consultation with multidisciplinary experts, and structured dialog, the Ethics and Public Policy group and key ATP-Bio researchers analyzed the steps needed to build responsible governance for advanced biopreservation in organ transplantation (Table 2).

Integrating prolonged organ biopreservation into the US transplantation system will have significant impacts (Tables 3 and 4). Accommodating these will require at least 4 key tasks: (1) instituting oversight authority and standards for manipulated organs, (2) establishing new facilities governed by appropriate processes and principles, (3) creating policies for immediate

Table 1
Preservation methods for human solid organs and ex vivo preservation time limits.

Current preservation methods (approximate temperature range)	Current ex vivo organ preservation time limits
Hypothermia (4-8 °C)	Heart, lung: ~6 h Liver, intestine, pancreas: ~8-12 h Kidney: up to 36 h
Hypothermic oxygentated machine perfusion (2-10 °C)	FDA approved for up to 24 h in kidney[6]
Subnormothermic oxygenated machine perfusion (15-30 °C)	Up to 24 h in liver[7]; potentially up to days
Normothermic oxygenated machine perfusion (above 32 °C)	68 h reported in liver[4] but upper limits ill-defined
Advanced biopreservation methods in development (approximate temperature range)	Potential ex vivo organ preservation time limits
Supercooling (−4 to −6 °C)	Days to weeks
Partial freezing (−5 to −20 °C)	Days to months
Vitrification (−120 to −196 °C)	Years to decades

FDA, Food and Drug Administration.

organ use vs biopreservation for future use, and (4) addressing equity and fairness in advanced biopreservation.

2. Establishing oversight authority and standards

Oversight of the US transplantation system is distributed across multiple agencies in the Department of Health and Human Services (DHHS), but current regulations protect the authority of transplant programs to determine the suitability of an offered organ for a specific candidate.[8] Advanced biopreserved organs will challenge clinicians' ability to assess organ suitability. Not only are the technical details associated with most subzero biopreservation beyond usual clinical knowledge, but also the transplant center clinicians will be temporally distant from the events of donor management, organ preparation, preservation, and reanimation at multiple facilities over extended periods. Advanced biopreservation promises to lengthen the time from organ retrieval and preservation until reanimation and transplantation, potentially by years. Clinicians will require sufficient information to assess the likelihood of organ function for a recipient after transplantation. New regulatory oversight processes and informatics should be crafted to fill this gap and provide clinicians and patients clarity and assurance of advanced biopreserved organs' suitability for transplantation.

However, the first challenge will be to establish the authority of a regulator to oversee the steps of advanced biopreservation and reanimation of transplantable organs, both to ensure the organs' basic safety and effectiveness and to require labeling disclosures to guide clinicians in assessing organ suitability for specific patients. Of the DHHS agencies involved in national donation and transplantation processes, the Food and Drug Administration (FDA) is the only 1 with appropriate staffing and experience to oversee technical and manufacturing practices. The FDA already plays a role in organ preservation and transplantation, overseeing organ preservation solutions and perfusion devices, as well as immunosuppressive drugs.[13] However, the FDA has historically declined to assert jurisdiction over transplantable organs.[14] The FDA is responsible for regulatory oversight of human cells, tissues, and cellular-based and tissue-based products (HCT/Ps), but its current regulations explicitly exclude "vascularized human organs for transplantation" from the definition of HCT/Ps.[15]

The policy of excluding transplant organs from the FDA oversight was made before the possibility of advanced biopreservation. This policy can, and should be, revisited now. The FDA conducted its first examination of its legal authority to regulate transplant organs in 1983.[14] The agency noted that a "human organ transplant could be regarded as within the literal language" of the statutory definitions of drugs and devices that Congress authorizes the FDA to regulate. The device definition seemed particularly apt because it includes implants intended for therapeutic use that do not achieve their primary intended purpose through chemical action or by being metabolized.[16] The transplanted organ is clearly not metabolized, rather it provides either a mechanical or filtering function or intact cellular functions for homeostasis (synthetic, detoxifying, or hormonal). Nevertheless, the FDA stressed that Congress "understood the term 'device' to refer to the product of human artifice."[14] The human organs transplanted in the 1980s were not, in the FDA's view, manmade products of the sort Congress authorized the FDA to regulate.

However, advanced biopreservation requires sophisticated engineering processes (including CPA and nanoparticle loading, supercooling or vitrification, and rapid rewarming) and, in effect, transforms an organ into a new, manufactured product not found in nature. Advanced biopreserved organs are a "product of human artifice"[14] meriting safety and effectiveness oversight by the FDA. The FDA could assert its authority to provide this oversight by clarifying that the past exclusion of vascularized organs from its HCT/P framework pertains only to conventionally preserved organs and not those processed via advanced biopreservation techniques. If necessary, Congress could resolve any doubts through legislation that clarified FDA's authority to regulate advanced biopreserved organs as HCT/Ps under the Public Health Service Act (PHSA)[17] and Food, Drug, and Cosmetic Act.[18]

Regulation under the FDA's existing HCT/P framework would address clinicians' concerns without unduly intruding on the physician-patient relationships in which physicians remain ultimate arbiters of organ suitability for specific patients. All HCT/Ps receive basic safety oversight under Section 361 of the PHSA[19] and FDA regulations at 21 Code of Federal Regulations Section 1271. Facilities involved in manufacturing biopreserved organs

Table 2
Governance changes needed to integrate advanced biopreservation into U.S. organ transplantation.

Needed governance changes	
1. Establish oversight authority and set substantive standards for biopreserved organ quality and safety	• FDA should assert jurisdiction over the safety and quality of biopreserved organs. • FDA may elect to use the HCT/P framework, and regard significantly manipulated organs as custom devices. • FDA should set safety and quality standards for biopreserved organs and preservation processes • A DHHS multiagency task force, in conjunction with professional societies, engineering experts and public stakeholders should collaborate to formulate system modifications, quality metrics, and predictive analytics required for identification and equitable, efficient use of biopreserved organs.
2. Establish new facilities for organ biopreservation, storage, and reanimation	• Industry and federal agencies should collaborate to build supply chain infrastructure for organ preservation, storage, and reanimation. • Federal agencies and industry should engage with stakeholders (including transplant centers, clinicians, and patient advocacy groups) to establish standard operating procedures for organ preservation, storage, reanimation, and transportation.
3. Create policy for immediate organ use vs biopreservation	• OPTN and transplant system stakeholders should create guidance on the assignment of retrieved organs for immediate transplantation vs biopreservation. • Given the current shortage of organs for transplantation, organs reserved for biopreservation should be reliable, high-quality organs without a recipient, but with significant need (infant/neonatal organs); an available organ for a recipient who requires additional time until transplantation (eg, immunologic preconditioning); potential use as a bridge to an available fresh organ; or to accommodate the needs of an available live organ donor. • If (when) predictive analytics can reliably identify available organs with suitable function, then unused organs with acceptable function should be biopreserved.
4. Advance equity and fairness through biopreservation	• OPTN and transplant system stakeholders should use the relief from time and geographic constraints provided by advanced biopreservation to advance equity and fairness in transplantation. • OPTN and transplant system stakeholders should use the centralization of biopreservation facilities and organ repositories to reduce unjustified variation by organ transplant region and center. • Development of biopreservation should prioritize promoting access and avoiding exacerbation of inequities.

DHHS: Department of Health and Human Services; FDA, Food and Drug Administration; HCT/P, human cells, tissues, and cellular-based and tissue-based products; OPTN, Organ Procurement and Transplantation Network.

are required to register with the FDA, submit lists of their products, undergo inspections, and implement quality programs addressing basic safety issues like sample mix-ups, labeling errors, and contamination with disease-causing pathogens. Beyond this, organs that are more than minimally manipulated (eg, advanced biopreserved organs) would receive additional review under Section 351 of the PHSA[20] and, when applicable, FDA's device or drug regulations. This second level of review considers safety and effectiveness of the advanced biopreserved organ itself, in terms of its expected functionality, durability, and other parameters affecting its suitability for transplantation.

Although the agency historically declined to oversee safety and effectiveness of transplantable organs, this policy arose at a time when organs required immediate transplantation, precluding detailed regulatory review. Advanced biopreservation will extend the time between organ procurement and transplantation, but

Table 3
Overview of processes in the current time-constrained organ transplant system.

Procurement	• Organ procurement with limited testing
Organ preparation	• OPTN listing (note that HRSA/OPTN are now accepting proposals from multiple potential contractors in modernization)[3]
Allocation	Allocation affected by the following: • Patient referral and listing • OPTN criteria • Donor/organ specifics • Transplant center policy • Patient and surgeon availability • Transplant program and surgeon discretion
Transport	• Organ transport under severe time constraints • Recipient travel and preparation for procedure
Transplant procedure	• Organ transplant, often performed emergently • Follow-up care

HRSA, Health Resources and Services Administration; OPTN, Organ Procurement and Transplantation Network.

traditional premarket clinical studies of product safety and effectiveness will remain infeasible because each organ is unique. In its 1983 jurisdictional analysis,[14] the FDA noted that transplant organs technically fit within Congress's definition of an FDA-regulable medical device, offering a promising oversight pathway for advanced biopreserved organs. The FDA already oversees safety and effectiveness of "custom devices"[21] for which manufacturers produce no more than "5 units per year of a particular device type." The FDA exempts custom devices from its premarket approval requirements, recognizing that clinical trials of efficacy are infeasible for n-of-1 custom devices, and from mandatory performance standards. Instead, the agency looks to the treating physician to determine whether a custom device offers a satisfactory risk/benefit ratio for the individual patient. However, custom devices remain subject to FDA's Quality System Regulation, including design controls, adverse event reporting, labeling requirements, registration and listing requirements, and other provisions allowing close FDA oversight of the manufacturing processes, along with transparent labeling and adverse event information to guide physicians when assessing organ suitability for specific patients.[21]

Advanced biopreservation will modify the physician ascertainment of an appropriate risk-to-benefit ratio. Today, deceased organs are offered to rank-ordered candidates and accepted/declined for transplantation based on *clinical data*.[8] Scrutiny of the donor/organ data often results in requests for additional testing and information after the initial organ offer but before its acceptance. A sizable percentage of offered organs are rejected because clinical judgment assessed the offered organ possesses

Table 4
Overview of anticipated processes with changes needed to integrate advanced biopreservation.

Procurement and identification of organs for biopreservation	• Identify donor • Determine which organs to transplant immediately vs biopreserve • Procure organs • Perform assessment and potential rehabilitation of organs for biopreservation • Recipients requiring immunologic or other preconditioning regimens before transplantation
Organ biopreservation and storage	• Transport organ to biopreservation facility • Biopreserve organ • Transport to storage facility • Store organs for extended or unlimited time (depending on biopreservation technique); ensure adequate accompanying data
Allocation	• List biopreserved organs for transplant, with extensive evaluation data • Increase consideration of equity in organ matching • Decrease role of geography in allocation • Identify recipient with immunologic matching, prepare recipient, and time transplantation to optimize recipient health
Transport and organ reanimation	• Transport organs across greater geographic distances • Organ reanimation
Transplant procedure	• Time transplant to allow recipient travel and optimize recipient condition • Perform organ transplant as a scheduled procedure • Follow-up care

insufficient (or uncertain) quality for recipient benefit.[22] Further separating the time of organ donation from the time of transplantation will leave transplant centers (clinicians) incapable of gaining further clinical information to assess organ suitability. Effective organ use will require improved predictive analytics for biopreserved organ function and community agreement about which donor organs to biopreserve. However, gaining regulatory and community agreement will require a DDHS Secretary-level coordination between agencies with existing oversight/involvement in the donation/transplantation system. This includes donor selection, assessment, and organ recovery and use (Centers for Medicare and Medicaid Services [CMS], with organ procurement organization [OPO] Conditions for Coverage and transplant center Conditions of Participation)[23]; adherence to good manufacturing processes (FDA)[24]; assessment of organ function (predictive analytics/AI, currently unavailable but could be created by HRSA or separate contractor); appropriate organ matching with candidates (allocation, HRSA/Organ Procurement and Transplantation Network [OPTN] contract)[8]; avoidance of disease transmission (Centers for Disease Control and Prevention), integration within payment structures of national healthcare system (CMS and insurers); and long-term assessment of outcomes and system impact and policy modifications (HRSA/OPTN and CMS). Maintenance of public trust and addressing unanticipated consequences will also require input from organ donors/families, organ candidates/families, transplant recipients and providers, and the health care systems. This broad task should be addressed either through rejuvenation of the Secretary's Advisory Committee on Organ Transplantation or a request from stakeholders or Congress that NASEM provide the Secretary guidance for optimization of the donation/transplantation systems in anticipation of oversight impact from rapidly evolving technologies.

3. Establishing facilities for organ biopreservation, storage, and reanimation

Immediate organ use requires transportation methods to move organs rapidly from the site of organ retrieval to the recipient centers, but little else. In contrast, technologies permitting significant ex vivo preservation times will require specialized facilities for biopreservation, prolonged storage, reanimation, and transport, with standards and processes to ensure organ quality.[1,25] Rigorous adherence to standards and protocols will be necessary to avoid damaging organs. This can be encouraged by adopting best practices for organ biorepositories, building on established principles for responsible stewardship and governance, and potentially through accreditation.[26] Ongoing oversight will be required to address deviations, support continuous improvement, and maintain public trust.

A challenging issue will be recommendations to the Secretary and Congress about how advanced biopreservation should be funded, whether through additional appropriations that support the multiple steps involved or through adding the costs of the new modalities as charges for each organ provided. Federal law prohibits the purchase or sale of human organs but allows reasonable reimbursement not only for the expense of removing, transporting, and implanting organs but also for their processing, preservation, quality control, and storage.[27] Thus, the additional costs of the facilities, equipment, supplies, and staff necessary for a biopreserved organ may legitimately be added to the amount billed for the organ, subject to the statutory requirement that such amounts are reasonable.

The existence of biopreserved organs held in repositories and made available to transplant patients at specified prices could result in organs not being regarded as a voluntarily donated community resource but rather as articles of commerce, available for a price. In recommendations to the Secretary, Advisory Committee on Organ Transplantation or a NASEM panel should address the likelihood that leaving the creation, storage, and distribution of biopreserved organs to the private sector means that the price of organs will include some amount (large or small) of profit for the company involved, which may raise the question whether it is fair to compensate everyone involved except the donor or the donor's family.[28]

Commercialization may also raise global ethical concerns. Well-regulated jurisdictions (such as the US, Europe, Australia, South Korea, and Japan) should be able to accommodate advanced biopreservation within existing ethical and legal norms. In jurisdictions with less effective oversight, the option of extended biopreservation may increase the incidence of organs purchased—or coerced—from poor and otherwise vulnerable persons. Global standards and intensified efforts will be needed to combat the exploitation, coercion, and organ trafficking.[29]

4. Creating policy for immediate organ use vs biopreservation

Advanced biopreservation technologies could make suitable organs available on demand, permitting elective organ transplantation without prolonged waiting. Policies on selecting an organ for immediate use vs prolonged storage, a decision that will need to occur rapidly upon organ retrieval, should remain an OPTN responsibility. Yet policymakers and the public may be unwilling to allocate organ for future use, when many candidates are dying for lack of an organ.[30]

While rejected deceased donor organs may seem optimal for advanced biopreservation, the organ quality is quite uncertain.[22] It may be more prudent to restrict the initial organs for biopreservation to those with a high potential for excellent transplant function. For example, a recipient may not be identified for an available, deceased infant organ, and it would become an ideal organ for advanced biopreservation. Another opportunity may be to biopreserve an available, accepted deceased organ for a recipient requiring additional time to complete preconditioning protocols for tolerance or desensitization. It may also be possible to biopreserve donated organs from live donors at a time than minimizes life disruptions.

If biopreserved organs are shown to be noninferior to immediately transplanted organs or even superior after manipulation or resuscitation, a new calculus will be needed to determine which organs should be biopreserved. Even if biopreserved organs are less efficacious, policymakers may propose allocation of some

organs as a temporary bridge, until a suitable organ becomes available. Ultimately, biopreservation may promote expansion of successful transplants by allowing for organ rehabilitation and recipient preconditioning, while extending indefinitely the time available to identify an appropriate recipient.

5. Addressing equity and fairness in biopreservation

The NASEM report found the current transplant system inequitable and unfair. "[P]atients of color, lower socioeconomic status, [and] female gender," for example, get "transplants at a disproportionately lower rate and after longer waiting times than other patients with comparable need."[2] The report also found unwarranted variation in organ availability among OPOs and transplant rates among transplant centers. The changes recently mandated by Congress and initiated by DHHS are intended to address the financial disparities, implicit biases of providers and health care facilities, nonuse of viable organs, and underperformance of some OPOs by uprooting the causes of these inequities.[3]

The NASEM report also concluded, "The organ transplantation system could save additional lives and be more equitable if its component parts functioned in a more cohesive fashion and were overseen by a single entity, or by several entities operating in a coordinated fashion."[2] This vision should guide the creation of new institutions to preserve, store, and release organs in conformity with established principles. Moreover, the increased time that advanced biopreservation builds into transplant processes can be used to promote more equitable access to, and fairer distribution of, transplantable organs, including reduction of geographic disparities. Patients can be considered for preconditioning protocols and treatment of comorbidities to optimize transplant outcomes, allowing those with greater disease burden a better chance to receive transplanted organs and experience positive transplant outcomes.

Although integrating organ biopreservation into the transplant system will not eliminate longstanding problems of inequitable access, the new technologies can be introduced in ways that advance equity. For example, policymakers can make sure that biopreserved organs are financially accessible to all (through insurance, public subsidies, and reasonable pricing), and can support efforts to familiarize patients and clinicians with the new technologies and to engage them in meaningful and sustained ways.

6. Conclusion

Advanced organ biopreservation will disrupt the existing organ transplantation system. Realizing optimal safety and efficacy of this technology will require clarification of oversight authority and FDA jurisdiction, creating substantive standards, creation of facilities for the multi-step biopreservation process, and developing policy and ethics guidance. Additionally, predictive analytics to identify organs with suitable function for recipients must continue to evolve in parallel with biopreservation technologies. These emerging technologies will require early consultation with affected stakeholders to ensure successful integration.

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Declaration of competing interests

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*: J. Bischof is co-founder of Vitristor and discloses "Cryopreservation compositions and methods" pending U.S. Patent Applications 14/775,998 and 17/579,369. K. Uygun is co-founder of Organ Solutions LLC. He and M. Toner are co-founders of Sylvatica Biotech Inc. All other authors have no disclosures.

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