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Personal Viewpoint

Honoring the gift: The transformative potential of transplant-declined human organs

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ABSTRACT

For decades, transplantation has been a life-saving treatment for those fortunate enough to gain access. Nevertheless, many patients die waiting for an organ and countless more never make it onto the waitlist because of a shortage of donor organs. Concurrently, thousands of donated organs are declined for transplant each year because of concerns about poor outcomes post-transplant. The decline of any donated organ—even if medically justified—is tragic for both the donor family and potential recipients. In this Personal Viewpoint, we discuss the need for a new mindset in how we honor the gift of organ donation. We believe that the use of transplant-declined human organs in translational research has the potential to hasten breakthrough discoveries in a multitude of scientific and medical areas. More importantly, such breakthroughs will allow us to properly value every donated organ. We further discuss the many practical challenges that such research presents and offer some possible solutions based on experiences in our own research laboratories. Finally, we share our perspective on what we believe are the necessary next steps to ensure a future where every donated organ realizes its full potential to impact the lives of current and future patients.

1. Summary sentence

We believe that the use of transplant-declined human organs in translational research has the potential to hasten breakthrough discoveries in a multitude of scientific and medical areas, allowing every donated organ to be properly valued. We offer here our perspective on how to conduct such complex research and how to overcome the severe logistical challenges associated.

2. Embracing our past to forge our future

The history of solid organ transplantation is rich with stories of intrepid pioneers pushing the boundaries of what was possible.[1] A commitment to evidence-based research allowed the field to progress through the decades despite countless setbacks and lives lost. These efforts were ethically justified at the time by the absence of alternative treatments for patients facing certain death from end-stage organ failure. Our current circumstances are starkly different. In the modern era, transplantation has become a remarkably safe and effective therapy. One-year patient survival in the United States has reached 97.1% for kidney, 91.8% for liver, 90.9% for heart, and 87.9% for lung recipients.[2] As a result, there is little regulatory tolerance for the inherent risks associated with innovation. However, these statistics only include patients fortunate enough to receive a transplant and overlook the vast numbers of patients who die on the waitlist or never make it on to the waitlist. Thus, the central challenge facing transplant has fundamentally

Abbreviation: NMP, normothermic machine perfusion.

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changed. Where our forbearers were tasked with making transplant safe and reliable, we must now determine how to make such procedures broadly accessible without compromising the well-established standards of safety.

The difficulty of this new task is exacerbated by the fact that our current donor population is considerably older and less healthy than in previous generations.[3-5] Consequently, thousands of organs from higher risk donors go untransplanted each year so as not to compromise post-transplant outcomes.[6] The missed opportunity represented by a non-transplanted donor organ is a tragic loss at multiple levels. For the potential recipient, it means that they will remain on the waitlist and face the reality that death may come before the next organ offer. Equally heartbreaking, the donor's family is denied the solace of knowing that their loved one's gift saved a life and thereby prevented another family from experiencing the same grief. Lastly, the clinicians and organ procurement professionals—who have spent significant time and resources on the potential of that organ—experience the frustration of being unable to help a patient in need. Statistical analyses suggest that many discarded organs could be used to benefit some patient.[7-9] However, the severe logistic and regulatory pressures we face in transplant can strip these statistics of their power in the middle of the night when one surgeon considers one "suboptimal" organ offer for one very sick patient.

In this viewpoint, we propose a new perspective on the potential impact of transplant-declined human organs. We believe that a human organ does not need to be transplanted to have a profound impact. In transplant—unlike few (if any) other areas of medicine—we have the capacity to perform pre-clinical studies on the exact specimens we aim to use in a clinical setting. Moreover, these investigations can be conducted in a near-physiologic manner thanks to new technologies, such as *ex situ* normothermic machine perfusion (NMP). We thus believe that a well-supported pre-clinical infrastructure utilizing transplant-declined human organs has the potential to be transformative. Such research could catalyze the translation of new diagnostic and therapeutic strategies that dramatically expand access to transplant. Moreover, pre-clinical research on transplant-declined human organs holds the potential to revolutionize our understanding of human biology, enabling breakthrough discoveries in wide ranging areas of medicine. Most importantly, these efforts could ensure that every donated organ has a profound impact, regardless of whether it is considered safe to transplant by current standards.

3. Maximizing impact with a little help from our nontransplant friends

Animal models of disease remain the gold standard of both mechanistic research and therapeutic development. Although these models have utility to evaluate hypotheses in a reproducible model, they also have significant limitations. Rodents, dogs, pigs, and humans are evolutionarily distinct organisms. Each developed unique strategies to cope with the physiologic stressors and resulting injuries. The only way to truly understand human mechanisms of pathophysiology—and ultimately create effective treatments for human disease—is by studying human samples. This realization has led to an increased emphasis on enabling research with patient samples or even with complete donors. Recent studies used donors after brainstem death as short-term recipients of porcine organs demonstrating that transplant donors can make unique contribution to biomedical research.[10] However, access to human samples often presents a major bottleneck, particularly with respect to tissue-based research that typically requires invasive means of sample collection.[11] Moreover, it is increasingly recognized that a single biopsy collected at a single time point may not be representative of a whole dynamic organ.[12] Human organ-based research overcomes these hurdles by providing an entire organ's worth of tissues that can be leveraged for an effectively limitless variety of investigations.

Tissues gifted by transplant organ donors have already contributed to several seminal advances in our understanding of human biology and pathophysiology. For example, single cell ribonucleic acid sequencing of transplant-declined organs has led to the discovery of new cell types and cellular processes as part of the international Human Cell Atlas initiative.[13-16] Cells isolated from transplant-declined organs have also generated important insights into the development of cancer via whole genome sequencing.[17-20] Metabolomic studies of these tissues have also uncovered fundamental mechanisms that propagate ischemia-reperfusion injury.[21] In each of these examples, the researchers developed cutting edge "omic" technologies with human tissues to address scientific questions beyond the traditional scope of organ transplantation. Nevertheless, the large "unbiased" data sets generated can be readily used to answer subsequent research questions with direct clinical impact in transplant. For example, we leveraged access to transplant-declined human hearts to confirm succinate as a key mediator of reperfusion injury.[21] In addition to revealing a new fundamental aspect of human pathophysiology, this study generated a comparative metabolomics methodology—in collaboration with a leader in that field—to validate our previous findings in animals.[22] We subsequently applied the same approach to human kidneys, which showed that the inhibition of succinate accumulation can prevent the disruption of the electron transport chain on reperfusion.[23] These findings have led to the development of novel therapeutic interventions that have the potential to reduce organ injury and increase utilization of marginal organs.

As the preceding example demonstrates, NMP is particularly beneficial for evaluation and optimization of drug delivery. In another recent example, we utilized NMP to evaluate the efficacy of delivering vascular-targeted nanomedicines in transplant-declined human kidneys.[24] This work revealed the challenge of translating drug delivery strategies from a petri dish into complex human settings. It also led to the discovery of a novel mechanism of injury—accumulation of renal-derived fibrinogen and subsequent formation of microvascular obstructions[25]—and development of an *ex situ* therapeutic intervention that will be the subject of an upcoming first-in-human pilot clinical trial. Several other groups have also leveraged NMP as a platform for pre-clinical development and evaluation of new strategies to expand access to transplant, including: gene therapy in lungs,[26] cellular therapy in kidneys,[27] and organ supercooling in livers.[28] Recent advances in the length of time human organs can be stably maintained on NMP[29,30] will further expand the utility of this approach for accelerating translation by allowing researchers to better assess safety/efficacy in a human context without putting patients at risk.

None of the preceding advances would have been possible without the precious gift of transplant-declined human organs. These examples also demonstrate that access to these tissues is not enough to generate transformative scientific advances. It is essential to assemble diverse cohorts of experts from many different fields who each bring with them highly specialized tools and techniques. Partnerships outside the field of organ transplantation can be particularly fruitful. These researchers often have expertise with and/or are developing the latest in cutting edge experimental tools. However, they often lack the access to human tissues necessary to realize the full biomedical potential of their novel tools. We in transplant have an opposite (and complementary) problem. We have abundant access to human tissues and the ability to study these organs under dynamic conditions with organ perfusion, but we often lack the deep expertise with cutting edge assays like single cell ribonucleic acid sequencing or comparative metabolomics. Thus, if we want to ensure that every donated organ has a profound impact, it is essential for all parties to join forces and work together as collaborative teams. We must acknowledge that this collaborative approach is easier said than done because of the severe logistical challenges that arise when working with organs that can be received with little to no advanced notice.

4. Tackling the logistics of "emergency" science

Pre-clinical research on nontransplanted human organs mimics the clinical practice of transplant in many ways. Transplant-declined organs may be offered for research at any time of day or night, requiring an on-

call staff with a diverse array of expertise ready to go at a moment's notice. Additionally, research laboratories can go days or weeks with no suitable organ offers and then suddenly be inundated with multiple offers in quick succession. Once an organ is accepted for research, there can be major delays in recovery and/or transport of the organ to the research site, which makes coordinating the members of the research team difficult. Just as in the clinical setting, overcoming these logistical challenges requires a highly dedicated team and a substantial financial commitment.

Unlike the clinical setting, pre-clinical research does not have the benefit of shared hospital infrastructure, nor does it generate clinical revenue that can offset the significant costs. Instead, each laboratory typically relies on grants or other institutional support to build its own ad hoc infrastructure, including training programs to teach personnel the wide array of necessary skills. Another key difference between clinical and pre-clinical research settings is the definition of a "good outcome." In a clinical scenario, a good outcome is easy to define; the patient leaves the hospital healthy and with a well-functioning graft in a timely manner. In pre-clinical research, the definition of a "good outcome" is not as obvious or consistent. The experimental goal typically varies with each study, meaning that the marker of success can also vary case by case and may not be reached until months or even years later when the whole study is completed.

Nevertheless, we believe that a good outcome in this context can be defined as that which maximizes the biomedical impact of each individual organ. Our experience in this research suggests that—much like the clinical setting—the key to consistently achieving this optimal outcome is a highly disciplined and systematized set of processes that ensures each organ receives the highest possible "standard of research care." The specific details of how to best define and implement these processes will likely be dependent on the specific circumstances associated with each research center (eg, space, personnel, and resources available; specific focus of the research). However, based on our experiences across different research centers, we believe that there are 3 core values that can serve as a foundation for any well-run research program that utilizes transplant-declined human organs: trust, rigor, and sustainability (Fig. 1).

5. Embracing the inherent variability of human organs (handling N of 1)

A frequent criticism of pre-clinical research with declined human organs is the unavoidable and significant donor-to-donor variability (Fig. 2). Studies utilizing declined human organs typically have large variance in critical variables, such as preservation time, donor age, and donor comorbidities. A standard critique will argue that the lack of control over these variables prevents any definitive conclusions. Therefore—this line of reasoning would argue—animal models are superior by virtue of the ability to control such variables more tightly. There is no

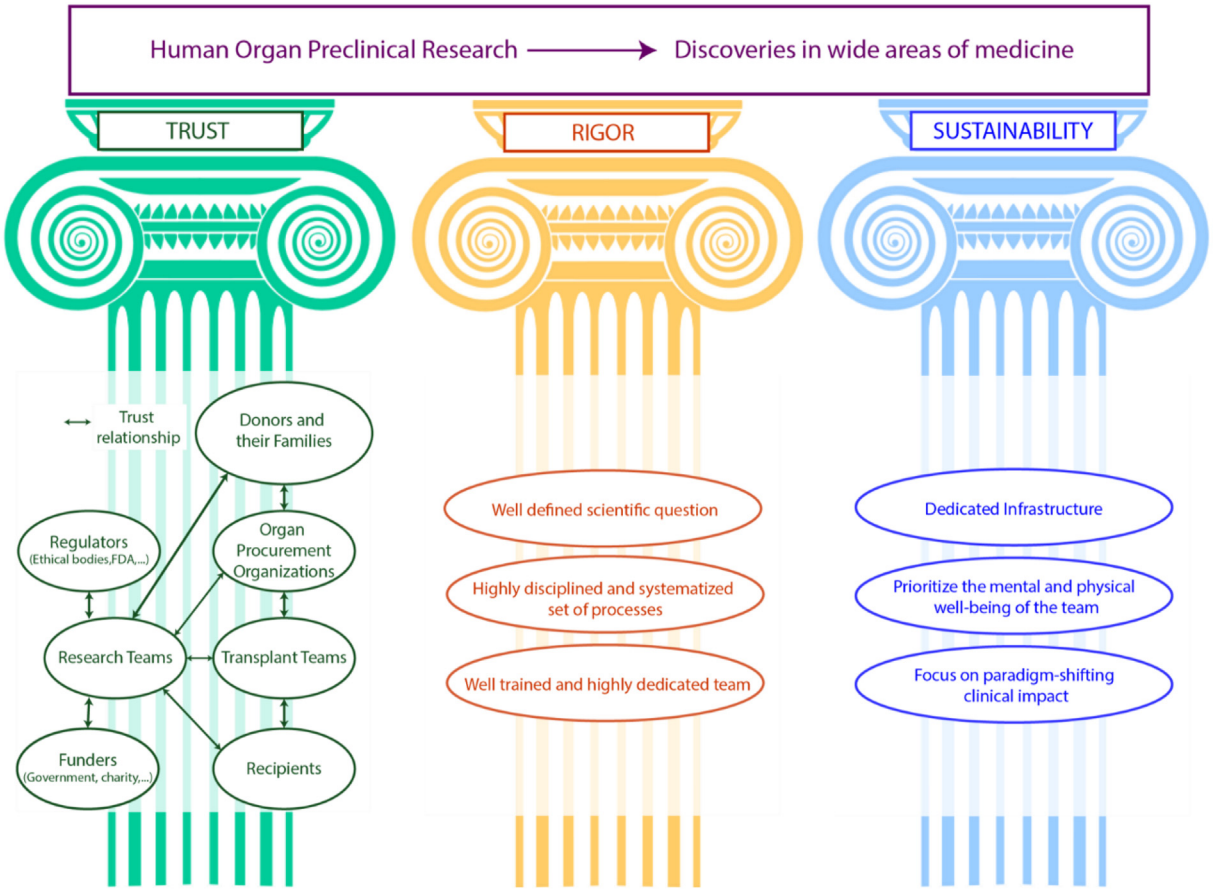

Figure 1. Trust, sustainability, and rigor, the 3 pillars of a well-run human organ pre-clinical research program that can lead to discoveries in wide areas of medicine. A steadfast dedication to building and maintaining trust must be at the center of any human organ research program. These bonds of trust must extend between all stakeholders, including the donor families, the research team, supporting clinical colleagues, and organ procurement organizations. All members of the research team must never lose sight of their solemn responsibility as stewards of each donor organ; every single organ must be treated with the same care and deference as if it were going for clinical transplant. We must never sacrifice the rigor of our scientific design and execution if we are to properly value each organ. Rigorous design and execution are particularly essential to capitalize on the one aspect of human organ research that can likely never be replicated in animal models: natural human variability. Finally, to ensure the research team can consistently maintain this highest level of "research care" for each organ, we must also acknowledge and account for the tremendous demands that emergency science places on the research staff. The physical and mental well-being of all members of the research team must therefore be a top priority to ensure the long-term Sustainability of the research program.

question that the use of animal models to constrain variability can make it easier to achieve statistical significance. Unfortunately, this statistical significance often comes at the expense of clinical relevance.

The human population that biomedical research intends to benefit is highly variable. "Personalized" medicine has arisen as a direct result of the need to consider this variability to identify an effective treatment.[31] It can be difficult, or even impossible, to study relevant human variability in pre-clinical animal models. When we exclude such variability in the pre-clinical phase of research—as is typical in current practice—it is then left to clinical research to address this omission. However, clinical research is, by design, slow and difficult to adapt once initiated. Moreover, the consequence for having an incorrect hypothesis in the clinical phase can be severe.

In contrast, the pre-clinical study of transplant-declined human organs provides an opportunity to transform this inherent variability into an advantage by allowing us to identify critical variables before patient's lives are at stake. Although capturing human variability within a pre-clinical research population presents a powerful opportunity, realizing the benefits requires grappling with statistical reality. In human organ research, these challenges are compounded by constraints on the number of experiments that can reasonably be performed. So, if the variability is large and the N is constrained, how can we properly power such studies to avoid inconclusive and unreproducible science? First and foremost, we need to restrict our focus to large effect sizes.

In typical pre-clinical research—for example, with cell culture or animal models—researchers often seek to minimize variability in their experimental groups in order to resolve differences in experimental endpoints that are as small as 10% to 20%. Such small differences can be biologically relevant and thus this degree of resolving power may be essential to tease out nuanced biologic mechanisms. However, a drug treatment that only yields a 10% to 20% improvement in a tightly constrained animal model is unlikely to produce meaningful benefit in a highly variable human population; the high rate of failure in first-in-human clinical trials supports this conclusion. If we instead hold ourselves to a higher threshold of effect size (eg, at least 100%), we will dramatically increase the likelihood that our results will be robust against natural human variability.

In addition to focusing on large effects, we need to acknowledge and embrace that every human organ—like every patient—is an N of 1. The setting of isolated human organ research can help us circumvent this challenge. An entire human organ has a massive amount of tissue allowing for repeat sampling that would not be possible in a clinical setting. Additionally, *ex situ* perfusion allows real-time dynamic monitoring before, during and after interventions.[32] This can allow us to establish internal controls using a baseline prior to intervention followed by longitudinal tracking. Although the organs may have large initial variability, evaluating trends can significantly reduce the negative statistical impact of this variation. This combination of large effects size and internal controls can enable robust statistical analysis even with a relatively small number of organs.

Finally, although every organ is an N of 1, there are nevertheless commonalities among organs from different donors that can allow us to define specific cohorts for comparison. Most commonly, such cohorts are defined on the basis of individual donor demographics (eg, donation after brainstem or circulatory death) under the presumption that these variables are the key differentiators in how a specific organ responds to stress or intervention. It is also possible to group organs according to functional and/or molecular phenotypes. Molecular phenotyping via multiomic analysis is a particularly promising strategy because this approach can allow us to leverage "big data" techniques (eg, principle component analysis) to reveal hidden cohorts in an unbiased manner.[33] Moreover, identification of the molecular signatures associated with response to

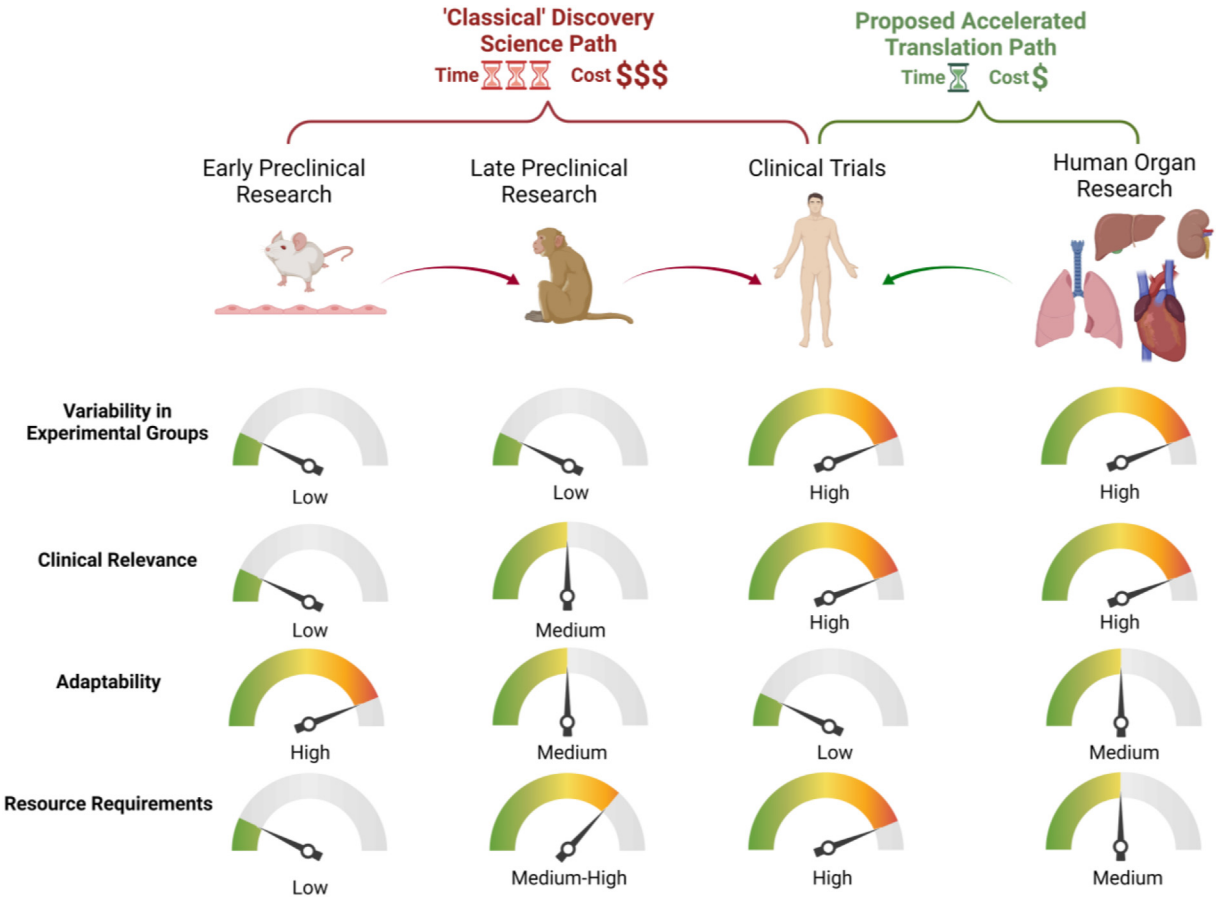

Figure 2. Comparison of the "classical" discovery science path and the proposed accelerated translational path based on transplant-declined human organs.

stress or therapeutic intervention represents the essential first step toward a future where we can apply a personalized medicine approach to *ex situ* revitalization of injured organs. Regardless of the approach used, it is critical to understand that the high variability of transplant-declined human organs is a feature—not a shortcoming—of this research.

6. A next step to realizing the transformative potential of every donor organ

We believe strongly that a deceased donor organ does not need to be transplantable to be transformative. Realizing this potential will require an unwavering commitment to a new paradigm of pre-clinical research. This new paradigm is motivated by the fundamental belief that the most efficient way to understand human pathophysiology, and thereby develop effective therapies for humans, is to study isolated human organs recovered from deceased donors. Pre-clinical animal studies can of course still complement work in human organs, particularly if we first confirm in human organs that a given pathway is pathologically relevant and that a similar phenotype is recapitulated in the animal model. If these two conditions are met, we can then leverage the unique advantages of animal models (eg, greater control over variability, ability to perform genetic manipulations, etc) to gain deeper biologic insights. These biologic insights can also still be leveraged for evaluation of therapies relevant to humans in animal models, provided we hold ourselves to a higher threshold of effect size and if we resist the temptation of artificially reducing variance, for example by using a range of strains, sexes, and ages of animals.

There are clearly many challenges and constraints associated with research on transplant-declined human organs, many of which we have highlighted above. The critical point we hope to convey is that these challenges are not insurmountable if we as a transplant community adopt the mindset that pre-clinical research on transplant-declined human organs is fully within the spirit of honoring the gift of organ donation. We suggest the transplant community should commit to the philosophy that a donated organ does not have to be transplantable to be transformative. To create maximum impact, the following steps could be actioned:

1. Communicate the importance and the potential of research use of organs and tissues to donor families and obtain informed consent for that purpose.
2. Always recover organs as if they were used for transplant to ensure their optimal condition for research use.
3. Invest in infrastructure at transplant centers and organ procurement organizations to support this research.
4. Support policy that will ensure broad access to research organs.

It is our hope that this viewpoint will initiate a coordinated discussion at the national and international level among all stakeholders in our community to systematically address the many ethical, logistical, and scientific questions that remain.

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Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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