Purpose of review
Despite over 60 years of progress in the field of since the first organ transplant, insufficient organ preservation capabilities still place profound constraints on transplantation. These constraints play multiple and compounding roles in the predominant limitations of the field: the severe shortages of transplant organs, short-term and long-term posttransplant outcomes and complications, the unmet global need for development of transplant infrastructures, and economic burdens that limit patient access to transplantation and contribute to increasing global healthcare costs. This review surveys ways that advancing preservation technologies can play a role in each of these areas, ultimately benefiting thousands if not millions of patients worldwide.

Recent findings
Preservation advances can create a wide range of benefits across many facets of organ transplantation, as well as related areas of transplant research. As these technologies mature, so will the policies around their use to maximize the benefits offered by organ preservation.

Summary
Organ preservation advances stand to increase local and global access to transplantation, improve transplant outcomes, and accelerate progress in related areas such as immune tolerance induction and xenotransplantation. This area holds the potential to save the healthcare system many billions of dollars and reduce costs across many aspects of transplantation. Novel preservation technologies, along with other technologies facilitated by preservation advances, could potentially save millions of lives in the coming years.

Keywords
cryopreservation, organ banking, perfusion, tissue preservation

INTRODUCTION: REALIZING THE FULL POTENTIAL OF ORGAN PRESERVATION
The goal of organ preservation is to maintain an organ outside the body in a state that is ideal for its intended application. For decades, the field of transplantation has focused on a relatively simplistic version of this goal: moving a deceased donor organ from the site of procurement to the site of transplantation with tolerable levels of ischemic injury. But the organ preservation concept itself is far more expansive, entailing many different conditions under which an organ must be maintained for various durations depending on the individual circumstances. The impact of organ preservation on transplantation can be equally expansive, if the full scope of the field is realized.

Beyond simply transporting organs from point A to point B, diverse goals within the field of transplantation can be accomplished by preservation technologies. First, transplantation can be profoundly improved by active intervention during and after organ recovery, such as assessment of organ function, rehabilitation of marginal transplant organs, organ immunomodulation, and treatment for a variety of transplant contraindications. Second, organs from deceased donors that are not...
KEY POINTS
- Organ preservation technologies would be game-changers, enabling true solutions to the growing organ shortage.
- Current evidence suggests that preserved organs could improve short-term and long-term outcomes and reduce patient complications.
- These technologies could increase global access to transplantation by lowering the infrastructure requirements.
- In addition to saving lives, preservation technology would reduce the costs of transplantation and the financial burden of end-stage organ failure.
- As these technologies mature, so will the policies surrounding their use and best practices.

This attention has been spurred by the increasing recognition that if pursued together and at scale, organ preservation technologies hold promise to dramatically improve organ transplantation and human health [29**]. The social, economic, and policy implications are discussed in the following.

ADDRESSING THE ORGAN SHORTAGE
Although the US transplant waitlist numbers roughly 115 000 people [30], this represents only a fraction of the true need for organ replacement. Only approximately 50 000 people are added to the US transplant waitlist each year, yet over 700 000 US deaths per year are attributable to end-stage organ disease [31,32]. Some estimates suggest that as many as 30% of deaths in the United States could be prevented by organ replacement with supply and technology constraints removed [33–35]. The unmet need is far greater worldwide; globally, deaths from organ impairment or from other causes theoretically addressable by organ transplantation number above 15 million per year [36].

Increasing organ utilization and expanding the donor pool
In the United States, only 0.3% of deaths result in organ donation [31,37]. Each of these donors can theoretically provide eight lifesaving organs, yet on average only two to three of these are currently transplanted [31]. Short preservation windows heavily constrain organ use, resulting directly in the discard of thousands of organs [31], placing constraints on transplant centers’ ability to respond to an organ offer [38], and impeding optimal donor–recipient matching [39] and organ assessment [40**,41*] (Table 1). Additionally, perfusion-based preservation platforms have enabled the rehabilitation of otherwise unsuitable organs by repairing a great variety of defects [10,42,43*,44–52], even resulting in the successful transplantation of donor hearts after circulatory death [48,53,54,55*,56**]. This offers the promise of increasing organ utilization and dramatically widening the pool of organ donors, ameliorating the organ shortage. Although roughly 70% of hearts from organ donors in the United States currently go untransplanted [57,58], studies suggest that often a heart turned down in its allocation region would be accepted by a transplant center elsewhere [38,59]. Successfully transplanting just 10% of those hearts would provide organs for all of the current heart waitlist patients who do not receive a new organ in time [60].

transplanted could be efficiently used for other lifesaving purposes such as cell transplantation, biomedical research, and preclinical drug testing, each of which can require optimization of a variety of unique preservation considerations. Third, many new opportunities to expand access to transplantation or improve transplant outcomes can be created by organ banking, a sub-field of organ preservation that aims to achieve preservation durations constituting a true ‘shelf life’.

To achieve these goals, a family of organ preservation approaches should be pursued that encompasses ex-vivo perfusion at a variety of temperatures [1–3,4*,5–10], cryopreservation [11–15], ‘high-subzero’ preservation regimes such as supercooling [16,17], pharmacological induction of a hypometabolic tissue state [17–20], and related innovations. These preservation regimes can be readily combined with each other and with other cytoprotective strategies [21–23] applied before and after organ recovery.

Historically, financial support for these preservation approaches has been fragmented and relatively modest. But a wave of interest in advancing organ preservation has begun to develop in recent years, with targeted funding and support from White House Office of Science and Technology Policy [24], US Department of Defense [25], US Multi-Agency Tissue Engineering working group [26], the Canadian Institutes of Health Research [27], and others. Growing recognition of the importance of preservation to transplantation is also reflected by the recent launch of the American Society for Transplantation’s Organ and Tissue Preservation Community of Practice in partnership with the Organ Preservation Alliance [28].
Reducing disparities in access to transplantation

By greatly increasing opportunities for donor–recipient matching, preservation advances can help level the playing field for historically hard-to-match populations: children, ethnic minorities, and patients in areas with the worst organ shortages who do not have the financial means to relocate. These disparities are often stark. For example, while 84% of the adults who die on the liver waitlist are offered at least one organ, only 45% of the children that die or are delisted receive such offers [61]. Similarly, ethnic minorities receive fewer transplants than their white counterparts despite making up a majority of the transplant waitlist [30,62]. Geographic differences in organ availability and need can result in three times more deaths on the liver waitlist in organ-poor areas, compared with organ-rich regions [63].

Expanding limb, face, and other vascularized tissue transplantation

Approximately 185,000 people per year undergo amputation [64], and an estimated two million people are living with limb loss (approximately half from traumatic injury) [65]. Vascularized composite allograft (VCA) transplantation can restore function [66] and self-image [67] after amputation, and a large fraction of amputees have expressed a desire for both upper limb and lower limb transplantation [68,69]. However, access to these procedures is bottlenecked by the immunogenicity of VCA and difficulty to find adequately matching donors and recipients within the short (ideally 4-h) window to transport tissue from the procurement site to the patient’s transplant center [70]. Extending preservation times would dramatically expand options for donor–recipient matching, and, importantly, preservation advances could also enable immune

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**Table 1. Impacts on organ transplantation**

| Impact on transplantation                  | Perfusion | High subzero | Cryobanking |
|-------------------------------------------|-----------|--------------|-------------|
| Expanding the donor pool                  | x         |              |             |
| Ex-vivo functional assessment             | x         |              |             |
| Ex-vivo immunomodulation                  | x         |              |             |
| Ex-vivo functional enhancement            | x         |              |             |
| Increasing organ utilization              | x         | x            |             |
| Improving transplant outcomes             | x         | x            |             |
| Immune tolerance induction                | x         | x            |             |
| Disease screening                         | x         | x            |             |
| Reduced procurement costs                 | x         | x            |             |
| Reduced postoperative complications       | x         | x            |             |
| Increased use of marginal organs          | x         | x            |             |
| Improved matching for disadvantaged patients | x     | x            | x           |
| Geographic constraints                    | x         | x            |             |
| Increased hand, limb transplant           | x         | x            |             |
| Donor–recipient matching                  | x         | x            |             |
| Increased organ quality                   | x         | x            |             |
| Reduced postoperative costs               | x         | x            |             |
| Elective scheduling of surgery            | x         |             |             |
| On-demand for acute conditions            |           | x            |             |
| Backup transplant organs                  |           |             |             |
| Fertility protection for recipients with cancer |       |             | x           |
| Off-the-shelf research organs and tissues |           |             | x           |
| Future transplant of today’s marginal organs |         |             | x           |
| Global organ matching                     |           |             | x           |
| Xenotransplantation supply chain          |           |             | x           |

Some impact, including indirect, exists for almost all relationships between the aspects of transplantation shown and each preservation modality; however, the most direct and dramatic impacts are indicated with an ‘x.’

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tolerance induction approaches that have been successful in the context of live kidney donation [71–73] to be adapted to VCA transplantation [74,75].

Creating new organ supplies
Addressing the true need for transplantation necessitates development of organ sources beyond donation to increase the number of organs available. There have been significant investments in optimizing humanized animal (xenogeneic) [76–79] and bioengineered [80,81] organs for transplantation. In particular, because of advances in immune tolerance induction and gene editing [78,82], xenotransplantation has made a resurgence in recent years and is now showing success in primate studies [83*] with clinical trials beginning as early as 2018 [78]. Many groups, such as the White House Office of Science and Technology Policy [24], Department of Defense [25], and US Multi-Agency Tissue Engineering working group [26] have noted that preservation constraints have already slowed progress toward nondonor sources of transplant organs, while also creating looming concerns for future patient access to life-saving transplants.

Enabling off-the-shelf transplantation for acute conditions
The prospect of organ banking offers the novel opportunity to treat patients with acute conditions, organ injury, or rapidly deteriorating health. Trauma, including motor vehicle accidents, represents the largest cause of early death in the United States and over 50,000 of these deaths per year are because of organ damage that might be treatable with on-demand organ transplantation [84,85]. In cases of acute liver failure, 20% of patients die waiting for a life-saving liver transplant [86]. Similarly, in 2016, over 100,000 people died from a heart attack [87], and the International Society for Heart and Lung Transplantation has speculated that many of these deaths could be prevented if a replacement heart were immediately available [88]. Even a product that provides limited graft lifespan could act as a first-of-its-kind bridge therapy for patients with no other option.

IMPROVING TRANSPLANT OUTCOMES
Over the past 25 years, US patients have gained over two million life-years because of organ transplantation [89], and organ transplant has become the gold-standard treatment for an extensive range of conditions [90–95]. Yet the success of transplantation is still limited by significant morbidity and mortality because of primary graft dysfunction and chronic rejection [96]. Roughly half of all hearts, kidneys, and livers are rejected within 10 years of transplantation, and as few as 25% of transplant lungs and intestines survive a decade after transplant [97]. This makes the long-term success of transplant operations a central concern for achieving this field’s potential for addressing organ impairment. Many benefits for transplant efficacy can be created by preservation advances, outlined in the following.

Delaying and preventing graft rejection
Constraints on immunological matching contribute heavily to both acute and chronic graft rejection, limiting both immediate transplant success and long-term outcomes [98,99]. For example, even a single human leukocyte antigen (HLA) mismatch is associated with a 44% higher chance of kidney graft failure [62*]. Increases in preservation time would enable national or world-wide matching, which could eliminate the need to accept a suboptimally matched organ while also enabling efficient HLA matching for all organs (rather than kidney only) [100].

Immune tolerance induction
Inducing donor-specific immune tolerance has the potential to increase postoperative survival for transplant patients from the current typical gain of 4.3 life-years [89] to decades [101], making organ transplantation a cure rather than a lifelong condition. It could also decrease or even eliminate the need to take immunosuppressive drugs, which are associated with cancer, infections, and other complications that can limit the length and quality of a transplant recipient’s life [102]. For instance, heart transplant patients on high levels of immunosuppressive drugs develop non-Hodgkin’s lymphoma at rates 120 times higher than the general population [103]. Significant progress is being made in tolerance induction through stem cell transplantation, but the approaches that have been developed require days to weeks, and the protocols that have shown clinical success at MGH, Stanford, and Northwestern are restricted to transplantation from living donors [71,73,104]. With increased organ preservation times, new possibilities would be created for recipients of organs from deceased donors (80% of organ transplants today) to undergo immune tolerance protocols, by beginning protocols before transplantation.

Providing flexibility for transplant procedures
Outcomes for the same procedure are typically better for elective surgeries than urgent ones.
[105,106*,107], and even extending preservation times to days could provide tremendous flexibility in scheduling transplant operations. This can have compounding effects, for instance, reducing the need for transplant surgeons to remain on call day or night and allowing more freedom to train younger transplant surgeons and other personnel.

Increasing donor organ quality
Given that increases in ischemic time – even during organ recovery – increase the risk of graft loss [108,109], preservation protocols that minimize ischemic time and allow rehabilitation of allografts should improve patient outcomes. Recent advances in machine perfusion [6,110–115] have also opened the door to active intervention after organ recovery to improve organ function prior to implantation: there has already been success integrating perfusion platforms and gene editing techniques to enhance organs in animal transplant models [116*,117] and in human lungs [118] that were not transplanted. Other perfusion-based approaches have included ‘immunocloaking’ [119], RNAi [120], and reversal of liver steatosis (‘de-fatting’) [121].

Preventing infection and malignancy
Although transmission of infectious diseases and malignancies to organ recipients remains an extremely rare event (<1% of all transplants) [122], minimizing this risk remains a significant concern. Similarly, transmission of cancer from donor to recipient is uncommon, but occurs before cancer has been detected in the donor [123]. Increasing organ preservation time could enable more comprehensive testing for infections, better informing transplant decisions. Protocols could be expanded to include nucleic acid testing in combination with serologic tests and testing of organ preservation fluids, which under current time constraints have unclear efficacy [122]. With increased preservation times, positive results could be confirmed by subsequent testing, preventing deaths that occur when false positives prevent safe organs from reaching recipients in need. Preservation technologies could also provide a platform to resolve infections or administer prophylactic treatment in donated organs, avoiding complications and preventing otherwise healthy organs from being discarded. Early successes using this approach have recently been reported, where ex-vivo lung perfusion of antibiotics and antifungals decreased the microbial load of lungs [124,125**].

Assessment of organ quality
Perfusion allows clinicians ample time to assess organ function and to determine suitability for transplantation [126,127**,128,129]. For instance, metabolic profiling to predict the likelihood of primary graft dysfunction [40*,130] could enable more informed decisions about an organ’s suitability for transplant and its potential longevity.

FACILITATING GLOBAL ACCESS TO TRANSPLANTATION
Dramatic disparities currently exist in worldwide access to transplantation. For instance, although approximately 16% of the world’s population resides in Africa, under 0.5% of the world’s transplants are performed on the continent (Fig. 1) [131,132]. As of 2011, deceased donor transplantation was limited to roughly 40% of the World Health Organization’s member countries with low-income countries performing less than 1% of all transplants [133]. And of the countries with transplantation capabilities, 28% perform limited or no deceased donor transplantation. This suggests that surgical skill and patient care infrastructure are not the principal bottlenecks in a country’s ability to develop transplant infrastructure; rather, the logistics of organ procurement and transport play a major role. Without robust organ procurement organization and the rapid transport capabilities of jets and helicopters, many areas lack the time to get usable organs to patients in need. In addition to overcoming these barriers and lowering transplant costs, extension of organ preservation times could allow the intimidating requirements of transplantation to be addressed individually rather than developing colocalized infrastructure, while facilitating involvement of countries with developed transplant systems. Barriers are expected to be further lowered as tolerance induction protocols [71,73,104] making the need for lifelong immunosuppression unnecessary in many cases.

Overcoming initial low-transplant infrastructure density
The sites of organ recovery and implantation must be relatively colocalized, preventing transplants in areas where few such sites exist. Organ sharing across long distances and even across borders could ameliorate or eliminate these issues, creating tremendous synergy between countries’ parallel efforts to develop transplantation. For instance, cross border sharing may be especially valuable in sub-Saharan Africa, where countries with nascent transplant programs (e.g. Ghana, Nigeria, Kenya, and Zambia) do not often border each other [134–137].
Global propagation of transplant expertise
The project ‘Transplants Without Borders’ has provided proof-of-principal for bringing abdominal transplantation to developing regions through dedicated training programs, while maintaining success rates comparable with the United States (>90%) [138]. Currently programs of this nature require long-term deployment of transplant surgeons to other countries, limiting scalability and increasing costs. Saving organs after procurement would allow transplantation in batches with ‘tutor’ surgeons who only need to commit to days or weeks of service – greatly accelerating training and propagation of transplantation in areas wherever surgical expertise is needed.

Centralized testing and organ recovery
As noted above, organ preservation advances can facilitate access to donor–recipient matching assays, testing for transmissible diseases and malignancies, assessment of organ function, and emerging technologies such as siRNA treatment or gene editing for immunomodulation. With extended preservation windows, these methods could be centralized and scaled, greatly lowering costs and providing opportunities to bring cutting-edge advances to faraway, developing transplant infrastructures.

DELIVERING HEALTHCARE SAVINGS
The economic toll of organ impairment is immense, and diseases treatable by organ replacement disproportionately strain healthcare infrastructures. In 2014, more was spent by Medicare on renal disease treatment than all cancer treatments combined, despite cancer claiming 12 times as many lives as renal disease. The cost of end-stage organ disease is also tremendous at the global level, with more than $1 trillion spent over a decade globally on renal disease treatment alone [139]. In 2013, the two costliest diseases in the United States were diabetes and heart disease [140], both diseases for which transplantation is often the gold standard treatment.

Organ preservation advances can reduce the cost of transplantation itself as well as costs incurred by the treatment of posttransplant complications, and Table 2 provides examples of cost changes in heart transplantation that could be created by improved heart preservation technologies.

Reducing organ procurement costs
Organ procurement and transport averages around $100 000 [141], with costs exacerbated by the need for round-the-clock ‘on call’ jet or helicopter transport. By increasing safe preservation durations from hours to days or longer, we can enable ground transport of organs in almost all cases and provide much needed flexibility for organ procurement organizations.

Reducing transplant and postoperative care costs
Approximately half of the costs associated with transplantation are incurred during hospital admission, including extended postoperative care [141].
Even short-term organ preservation would reduce the reliance on last-minute operating room bookings and on-call surgical staff, decreasing the currently high costs of transplant admission. Admissions costs are additionally increased by transplant complications and even characteristics of the donor organ [142]. Current preservation technologies have already made progress towards improved transplant outcomes, including a promising trend towards lower rates of primary graft dysfunction in recipients of perfused lungs [128,143,144]. Continued advances in preservation can further reduce complications and thus the need for expensive extended postoperative care.

### Reducing lifelong complications

To prevent rejection, patients typically must begin immunosuppressant regimens after transplant. Immunosuppression leads to a number of serious complications including increased risk of cancer and viral infections, which requires long-term monitoring and drug prophylaxis to prevent [102]. Currently, the first 6 months of immunosuppression and additional prophylactic drugs average $22,000–$71,000 (depending on the organ) [141]. However, organ banking would enable immune tolerance induction and better donor–recipient matching, decreasing the need for immunosuppression and thus, lowering the costs of immunosuppression and monitoring while preventing cost of subsequent complications.

### Transplantation as a cost-saver

For some organs, simply expanding access to transplantation can create substantial cost savings as well. For instance, the net savings of kidney transplantation as an alternative to dialysis has been estimated at nearly $500,000 per patient [145**] while dramatically increasing quality of life [146,147]. The average lifetime costs for bilateral upper extremity prosthetics are about $1.5 million, with historical increases as technology advances, whereas bilateral transplant is currently under $500,000 for the first year, with costs likely to decrease as preservation technologies mature [148].

### DESIGNING POLICIES FOR A CHANGING TRANSPLANT LANDSCAPE

Current allocation policies are, in large part, based on geographic structures designed to meet time limitations and specific logistical requirements of various organ types. Following donation, the allocation of organs usually proceeds in a sequential fashion to patients at programs in a defined local area surrounding the donor hospital to patients in a larger regional distribution, and then to patients nationally, if required. As distances and time increase, the potential for successful organ allocation decreases.

This necessary but artificial allocation hierarchy creates substantial logistical and medical complexities, resulting in a complex allocation policy. Current organ allocation policies are heavily time-dependent. For example, transplant centers have 1 h to acknowledge an organ offer and then one additional hour to accept or decline the offer before it goes to the next patient on the list. Policies governing these system operational issues will need to evolve to address new realities that result from enhanced organ preservation.

| Stage of Tx                                      | Average cost | Examples of cost changes |
|--------------------------------------------------|--------------|---------------------------|
| Pretransplant, procurement and transport         | $145,300     | Eliminate the need for costly jet and helicopter flights to immediately transport organs |
|                                                 |              | Additional testing (serology, HLA matching) enabled. Some testing can be centralized, lowering costs [121] |
|                                                 |              | Preservation technology itself will impose costs, varying widely according to model used |
|                                                 |              | Fewer cases where heart transplant surgeons and procurement teams are sent for organs that are subsequently turned down [37,58] |
| Hospital transplant admission                    | $979,700     | Elective scheduling, reducing the need for on-call surgical staff and operating rooms |
|                                                 |              | Admission costs are a function of donor organ quality [141]; preservation technologies have already improved transplant outcomes, for example, lowering rates of primary graft dysfunction [127**, 142, 143]. |
|                                                 |              | Fewer complications should decrease the length of admission and decrease the costs of immediate postoperative care [127**, 142,143] |
|                                                 |              | Reduced need for retransplant in the case of graft failure |
| Posttransplant care                               | $257,300     | Reduce readmission for complications by increasing transplant efficacy [101] |
| (for first 6 months)                             |              | Reduce lifelong cancer incidence by facilitating immune tolerance induction and transmissible malignancy screening |
|                                                 |              | Reduce lifelong complications, for example, CMV, PTLD |
|                                                 |              | Reduce need for immunosuppression and drugs for complications (e.g. $34,500 for first 6 months) [140] |

Current estimated heart transplant costs are discussed in [140].
As new preservation technologies are incorporated into the donation and transplantation system, policy must be developed to guide selection of organs from the existing organ pool for enhanced preservation or for banking. Perhaps only organs not expected to be transplanted locally will be initially chosen for extended preservation or banking. The extra costs and system complexities of advanced technologies may not be appropriate, at least initially, for organs that are destined for local transplantation with current expected excellent outcomes. The present kidney allocation algorithm incorporates a measure of organ quality that drives distribution. Policies that incorporate an accurate assessment of the expected outcomes from a wide range of organ preservation technologies or organ modifications will add complexity into allocation decisions and into the modeling of expected outcomes.

System transparency and patient consent issues addressed by current policy will have to evolve to address the changing clinical environment. Allocation policy development will need to ensure that equitable access by all patient populations to an expanded pool of transplantable organs is maintained. Immunologic modification of organs must provide benefits broadly to the pool of potential recipients and not solely to a subgroup of patients.

To capture the potential benefits of enhanced preservation, Organ Procurement and Transplantation Network (OPTN) policies will need to address a wider spectrum of donor organ and recipient characteristics. Careful oversight will be critical, and this must be guided by appropriate policy that addresses organ modification procedures to ensure patient safety. The removal of time constraints from organ donation will allow a more thorough assessment of the risks of donor disease transmission and also enhance patient safety. Policy around living donation can change to decouple donation from the transplant operation. The living donor procedure can be scheduled to suit the donor’s needs and not the immediate medical needs of the recipient.

Geographic access inequities, one of the biggest challenges facing the OPTN, will improve with adoption of new preservation and banking technologies. An enhanced supply of transplantable organs matched effectively to recipient-specific needs should more effectively address the disparity between the demand for organ transplantation and the number of available donor organs. As organ preservation and modification technologies mature, allocation policies focusing on recipient equity and outcomes and less on logistical considerations driven by specific organ needs will be possible.

**CONCLUSION**

In the last decade, a new generation of organ preservation technologies have shown promise to deliver a striking array of new capabilities for transplantation. There is reason for optimism that a family of synergistic research areas can deliver dramatic advances in preservation capabilities, with the potential to help address organ shortages, improve transplant outcomes, increase graft longevity, reduce long-term posttransplant complications, facilitate global proliferation of transplantation, reduce costs across many aspects of transplantation, and decrease the burden of end-stage organ disease on the economy. Ultimately, many aspects of organ allocation policy must evolve over the coming years and decades to keep pace with this progress.

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found that there was a linear relationship between mismatches and the probability
There has been disagreement about the importance of HLA matching in deceased
matched DBD hearts, opening up an important new supply of organs.
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