A Roadmap for Innovation to Advance Transplant Access and Outcomes: A Position Statement From the National Kidney Foundation

Krista L. Lentine, Stephen Pastan, Sumit Mohan, Peter P. Reese, Alan Leichtman, Francis L. Delmonico, Gabriel M. Danovitch, Christian P. Larsen, Lyndsay Harshman, Alexander Wiseman, Holly J. Kramer, Joseph Vassalotti, Jessica Joseph, Kevin Longino, Matthew Cooper,* and David A. Axelrod,* on behalf of the National Kidney Foundation

Over the past 65 years, kidney transplantation has evolved into the optimal treatment for patients with kidney failure, dramatically reducing suffering through improved survival and quality of life. However, access to transplant is still limited by organ supply, opportunities for transplant are inequitably distributed, and lifelong transplant survival remains elusive. To address these persistent needs, the National Kidney Foundation convened an expert panel to define an agenda for future research. The key priorities identified by the panel center on the needs to develop and evaluate strategies to expand living donation, improve waitlist management and transplant readiness, maximize use of available deceased donor organs, and extend allograft longevity. Strategies targeting the critical goal of decreasing organ discard that warrant research investment include educating patients and clinicians about potential benefits of accepting nonstandard organs, use of novel organ assessment technologies and real-time decision support, and approaches to preserve and resuscitate allografts before implantation. The development of personalized strategies to reduce the burden of lifelong immunosuppression and support “one transplant for life” was also identified as a vital priority. The panel noted the specific goal of improving transplant access and graft survival for children with kidney failure. This ambitious agenda will focus research investment to promote greater equity and efficiency in access to transplantation, and help sustain long-term benefits of the gift of life for more patients in need.

As this article reflects the official position of the National Kidney Foundation (NKF) and because it was reviewed and approved by NKF, it was not peer reviewed by AJKD. This article was prepared by a work group comprising the authors and chaired by Dr Krista Lentine. It was reviewed and approved by the NKF Scientific Advisory Board and the NKF Executive Committee.

Introduction

Kidney transplantation—and especially living-donor kidney transplantation (LDKT)—offers patients with kidney failure the best chance for long-term survival and improved quality of life, at the lowest costs to the health care system.1,2 There have been many positive trends in kidney transplantation in recent years, including a progressive rise in rates of deceased donor kidney transplantation and improvements in short- and longer-term allograft survival.3 However, the field continues to face important challenges. The vast majority of the more than 700,000 persons in the United States with kidney failure will not have an opportunity to receive a transplant due to limitations in organ supply. Those who receive a transplant often ultimately return to dialysis due to limited long-term graft survival resulting from chronic allograft nephropathy, recurrence of native disease, medication nonadherence, or other causes.4,5 Efforts to expand the deceased donor organ supply have increased the use of kidneys from older and other nonstandard donors to some extent, yet many potentially transplantable organs continue to go unused. Decisions not to use recovered organs are generally attributed to kidney quality, but are, in fact, multifactorial, reflecting opinions about transplant benefit, cost, program regulatory risk, and logistical complexity, not all of which are supported by evidence-based assessments.

The population in need of transplant is increasingly complex and diverse, including a higher prevalence of older patients, as well as individuals with comorbidities (eg, obesity, diabetes mellitus, cardiac disease) and of non-White race or ethnicity (Fig 1).7 Furthermore, rates of LDKT in adults and children have generally stagnated while racial disparities in LDKT access persist or worsen.5 The need to increase access to kidney transplantation received unprecedented support from the federal government in the July 2019 Advancing American Kidney Health executive order, which articulated goals for increasing the initiation of kidney replacement therapy through transplant and substantially increasing the number of kidneys available for transplant by 2030.6 These efforts were initially hampered by the global novel coronavirus disease 2019 (COVID-19) pandemic, although rates of both deceased donor transplantation and LDKT subsequently recovered to prepandemic levels.7,8,9

To assess the knowledge gaps amenable to research support aimed at advancing the practice and outcomes of kidney transplantation, the National Kidney Foundation (NKF) convened an expert panel. The panel was charged with developing a research agenda to facilitate access to kidney transplantation for all patients who can benefit,
support the goal of “one transplant for life” for organ recipients, and reduce/eliminate racial and ethnic disparities in transplant access and outcomes. Participants included nephrologists, surgeons, organ procurement organization (OPO) leaders, NKF leadership, patients, and other interested parties. Consensus-building was conducted through email, conference calls, and an in-person roundtable meeting December 13, 2019, in New York City. Through facilitated discussions, the panel developed 7 priorities for research innovations. The in-person meeting occurred shortly before the COVID-19 pandemic, and recommendations have been updated in the context of the latest challenges facing the field.

Priorities for Research Innovation

**Priority 1: Expand Opportunities for Safe Living Donation and Access to LDKT**

Living kidney donors can be related, unrelated, nondirected, or participants in donor exchange (kidney paired donation [KPD]) programs. Benefits of LDKT over deceased donor kidney transplantation include faster access to transplant and superior patient and allograft survival at the lowest cost to the health care system. In the United States, the number of LDKT declined from 6,000 in 2004 to approximately 5,500 per year through 2017; 2018-2019 showed a promising trend of
an increase to nearly 6,900 LDKT, although growth was stalled in 2020 by the temporary disruption of nearly all LDKT activity at the start of the COVID-19 pandemic.9 Barriers to LDKT include the transplant candidate’s ability to identify a willing and appropriate donor, concerns for donor health and follow-up, and economic barriers to donation including out-of-pocket expenses and lost wages.10

Development of KPD programs for patients with willing but biologically incompatible donors has been an important advance in expanding opportunities for LDKT.11 Using algorithms to exchange kidneys among 2 or more donor–recipient pairs, KPD programs create compatible combinations that address blood group and donor-specific alloreactivity incompatibilities. Nondirected donors (ie, donors who do not have an identified recipient) provide the unique potential to expand the donor pool through chains of kidney exchanges.12 KPD is the fastest growing LDKT modality and currently comprises approximately 16% of LDKT per year (Fig 2).3 However, KPD is underused due to cost, complexity, patient and physician acceptance, and degree of allosensitization. If all centers used KPD at the rate of high-performing centers, it is estimated that another 1,000 transplants could be performed annually.13 Entering compatible pairs into KPD is another suggestion to further increase the pool of potential matches and provide benefits such as better balance in kidney mass/function of exchanged donors, and improved degree of tissue matching (ie, reduced eplet mismatches) to lower long-term rejection risk.14 Additional innovations in some KPD programs include “advanced donation,” wherein a donor gives to the KPD pool in exchange for a voucher for a donation to their intended recipient at a later time if and when needed, designed to overcome “chronological incompatibility.”15

Other strategies for increasing LDKT include educational interventions, public campaigns, evaluation efficiencies, and donor cost mitigation efforts.16 In a scoping review, Barnieh et al identified 26 studies reporting strategies to increase LDKT.17 Patient education was the only strategy empirically assessed by randomized clinical trials, and only 2 (involving home-based education of transplant candidates and members of their social network) found significant increases in LDKT and living donor evaluations.18,19 Despite the urgent need to increase access to LDKT, only 6 quasi-experimental and 13 observational studies assessed diverse strategies such as education, organ donation awareness campaigns, advocacy (training a donor champion), efficiency (web-based screening, creation of interdisciplinary teams), removal of disincentives (leave policies, tax benefits), and institution of KPD programs. The only quasi-experimental study in the systematic review that identified an increase in LDKT was a structured educational program for potential recipients and their families.20 Further, well-designed evaluation trials are needed to identify successful interventions for increasing LDKT, especially for populations with reduced LDKT access.

Recently, a growing body of evidence has quantified and continues to improve estimates of the potential risks of living donation for donors, such as a tool using donor candidate demographic and health characteristics to estimate (in the absence of donation) the 15-year and lifetime risk of kidney failure (https://www.ckdpc.org/tools.html).21 Additional research is required to validate and increase the precision of such tools22 and to incorporate emerging risk factors (eg, apolipoprotein L1 [APOL1] as a genetic risk marker).23 Unfortunately, methods for effectively communicating risk information to potential donors have been poorly studied. Even though interventions to
improve transparent communication of risks and long-term donor safety are not primarily directed at increasing LDKT, these efforts are critical to sustaining trust in LDKT and for informing evidence-based education and donor selection practices.24 Efforts to develop registries tracking long-term living donor outcomes in diverse populations are also needed.25,26

Attention to improving equity in LDKT access for Black, Hispanic, and other non-White patients, as well as those with lower levels of socioeconomic status and health literacy, is a vital priority.27 Although removing financial disincentives is broadly accepted as necessary to improve equity in donation and access to LDKT, evidence demonstrating the impact of programs targeting financial neutrality on donation rates has been limited to date.28 Addressing financial burdens to donors is particularly vital, as a pandemic-related recession may challenge opportunities for living donation beyond the end of the public health emergency. Technology may enable efficient education delivery, but evidence is needed to determine if e-learning, telehealth, or telephone-based LDKT education programs are as effective as in-person education. Further research is also needed to improve the efficiency of donor evaluations and to generate evidence-based standards to address modifiable process delays.29,30 Dissemination studies are also necessary to assess whether effects persist when programs are scaled and to identify unexpected barriers that may arise with wider implementation.

**Recommendations**

The panel agreed with recent suggestions that high-priority research to increase access to LDKT should include developing, accessing and expanding strategies (Fig 3)10 to:

• Improve education and outreach to kidney patients about effective strategies for potential donor identification;
• Reduce financial disincentives to donation;
• Improve the efficiency of donor evaluations and predonation processes, with particular attention to removing disincentives and logistical barriers to KPD participation for programs and patients;
• Optimize donor risk assessment and long-term follow-up; and
• Identify and implement methods to improve risk communication, transparency, and shared decision-making in the donor candidate evaluation.

**Priority 2: Improve Waitlist Access, Management, and Pretransplant Readiness**

Among the nearly 95,000 patients waiting for kidney or combined kidney/pancreas transplant in March 2021, 43% had an inactive status.31 Thus, despite being approved for,
and presumably in need of, a kidney transplant, these patients will not appear on a match run for organ offers. Patients are inactive for a variety of reasons (eg, current medical illness, psychosocial barriers, preserved kidney function that meets listing criteria but does not warrant kidney replacement therapy). Patients who are initially listed as inactive have twice the risk of waitlist mortality and 32% lower rates of eventual transplantation than patients initially listed as active. The prevalence of inactive status on the waiting list is higher among racial and ethnic minority populations. One study of national US waitlist records found that, among patients who were inactive, Black patients were 19% less likely to convert to active status and Hispanic patients were 27% less likely than their White counterparts. This disparity directly impacts access to transplantation and overall mortality.

The process of referral and evaluation for transplant is complex and often difficult to navigate. Patients must complete rigorous testing and examinations to ensure that there are no medical or surgical contraindications to transplantation. Racial and socioeconomic disparities in completing the evaluation are well documented and persist even after controlling for other social determinants of health. Time- and resource-intensive interventions (eg, patient navigators, individually tailored educational programs, coaching) have increased the proportion of patients who are successfully waitlisted in single-center trials.

The panel agreed that there is an urgent need to develop and disseminate best practices for transplant centers to reduce inactivation status on their waiting lists. Kataria et al reported that frequent programmatic review allowed 18% of inactive patients to be made active, although this also led to delisting of 40% of inactive patients at their center. The panel considered research opportunities that target specific barriers with effective interventions. For example, patients with a body mass index exceeding center acceptance thresholds can be referred for nutritional interventions and possible bariatric surgery. Bariatric procedures have been shown to achieve durable weight loss and increase transplant access for appropriate candidates. A systematic review/meta-analysis including 288 patients with advanced kidney disease demonstrated that 50% lost sufficient weight for transplant listing. However, access to bariatric surgery remains limited for the population with advanced kidney disease.

Frailty is another frequent barrier to kidney transplantation, such that frail patients are half as likely as nonfrail counterparts to be listed for transplant. Among those who are listed and receive transplants, the approximately 20% of recipients who are determined to be frail at transplant are twice as likely to die after transplant as nonfrail recipients. Current data suggest that objective frailty scoring systems, rather than subjective physician assessments, are more accurate and should be used at the time of evaluation. For frail patients, a structured program of “prehabilitation” and physical therapy may help improve physical functioning sufficiently to allow transplant. Further work is needed to identify the best assessment tools and successful interventions to facilitate access to transplantation and improve posttransplant outcomes for frail kidney patients. The COVID-19 pandemic created a new emphasis on remote assessments, including of candidate physical functioning at evaluation and while awaiting a transplant offer.

**Recommendations**

- Optimize strategies to eliminate barriers to waitlist acceptance, including management of obesity, frailty, and deficiencies in adequate psychosocial support, grounded in transparent communication of eligibility criteria to patients and referring clinicians.
- Develop and implement educational interventions that assist all patients, particularly members of racial and ethnic minorities, to successfully reach the waitlist expeditiously.
- Implement scalable and generalizable information technology solutions to support waitlist access and maintenance of transplant readiness.

**Priority 3: Decrease Organ Discard by Expanding Clinician and Patient Organ Acceptance**

Long waiting times for kidney transplantation create a strong imperative to make the best use of donated organs. Nearly 10% of individuals with a previously declined organ offer die on the waitlist without a transplant, and another 20% are removed from the waitlist without a transplant. The United States has the highest rate of organ recovery without transplantation (nonutilization or “discard”), at nearly 20%. The federal government has focused national attention on increased organ recovery and reduced organ discard rates as the first objective of the Advancing American Kidney Health executive order’s increasing kidney transplant goal. There are opportunities to increase the number of deceased donor kidney transplants by measuring and maximizing the potential pool of deceased donor kidneys and minimizing the number of organ nonutilizations. Expanding the pool of accepted organs will likely require multifaceted efforts that address barriers at the levels of patients, transplant centers, and OPOs. Furthermore, researchers and funding organizations should invest in developing new technologies to optimize early organ function, assess transplantability of higher-risk or damaged organs, and foster the potential to repair injured kidneys prior to transplant.

There is abundant evidence that many deceased donor kidneys that could benefit some patients are not utilized or never recovered. For example, although the number of patients aged 65 years and older continues to rise (20.5% of additions to the waiting list in 2020), the average age of deceased kidney donors has not increased in parallel. A study comparing deceased donor transplant practices in the
United States versus France in 2004-2014 found that the mean donor age of kidneys transplanted in the United States was substantially lower, 36.2 versus 50.9 years. Donor age and mean Kidney Donor Risk Index (KDRI) steadily rose over time in France, while donor age and KDRI of kidneys transplanted in the United States showed little change, suggesting significant untapped donor potential. Studies of US registry data demonstrate a strong relationship between organ quality scores and discard rates, such that more than 45% of kidneys with Kidney Donor Profile Index (KPDI) scores > 80% are discarded (Fig 4). Despite higher rates of graft failure, high-KDPI organs can provide survival and quality-of-life benefits over maintenance dialysis in appropriate patients. A national registry study found that transplant with high-KDPI kidneys (defined as KDPI > 70) was associated with increased short-term death risk compared to remaining on dialysis for 6 additional months. However, these organs improved long-term survival compared to waiting on dialysis for a higher-quality organ among those who were older, had diabetes, or were living in areas with prolonged waiting times. The highest-risk organs (KDPI 91-100) appeared to benefit patients older than age 50 years at centers with median waiting times longer than 33 months.

As another example, unilateral discard (in which only 1 of 2 recovered kidneys is transplanted) is a relatively common occurrence that calls into question the reliability of organ evaluation. While some discordant discard is expected (eg, in the presence of significant nephrolithiasis or surgical injury), many of these decisions appear to be based on inaccurate data, including procurement biopsies. Evidence shows that kidneys are more likely be discarded on the weekend and that organs that are accepted and successfully transplanted on the weekend are declined many more times before eventually being accepted. Differences in organ acceptance on a weekend versus a weekday suggests that factors beyond organ quality and patient issues influence the willingness of transplant centers to accept an organ. Frequently cited reasons for organ offer declines include the desire to wait for a “better organ offer” for patients at the top of the waitlist, as well as concerns about program outcomes. Taken together, these findings imply a substantial opportunity to transplant many currently discarded kidneys, particularly if the offers are targeted to willing patients and centers.

Many programs report kidney nonutilization due to concerns for posttransplant outcomes that, if markedly worse than those at peer centers, may lead to censure by the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS), loss of private payer contracts, and decreased transplant volume. Additionally, managing delayed graft function (DGF; typically defined as need for dialysis in the first week after transplant) creates additional burdens and costs for programs. These costs pose a significant financial disincentive for accepting lower-quality kidneys. Care of transplant recipients who need dialysis during weeks 2-12.

**Figure 4.** Deceased donor kidneys: use and outcomes. The discard rate rises more rapidly with higher Kidney Donor Profile Index compared to the graft failure and delayed graft function (DGF) rates. Prepared from Scientific Registry of Transplant Recipients data, 2010-2020.
posttransplant requires increased resources and costs. Yet, over the life of the organ, there are significant clinical and economic benefits of transplantation with nonstandard, higher-risk organs. Developing alternative payment methodologies to eliminate financial barriers to nonstandard organ acceptance is vital to achieve the goal of increasing organ acceptance.

Patients and some clinicians may also be dissuaded from accepting kidneys due to perceived stigma associated with donors with a history of injection drug use or sex work, despite the very small probabilistic estimates of viral transmission to recipients. Kidneys from infection risk donors (IRDs) defined by US Public Health Services (PHS) criteria continue to be discarded at elevated rates, but provide significant benefit over dialysis. IRD kidneys are often high-quality organs from young donors with excellent long-term survival, which confer minimal infection transmission risk in the era of universal nucleic acid testing. In December 2020, the OPTN revised policy related to IRD organs to align with the 2020 updated US PHS Guideline, including replacing the requirement to obtain specific “informed consent” with a requirement that transplant clinicians inform intended recipients when the donor has any risk criteria, combined with increased posttransplant monitoring of all recipients. The impact of this policy change on acceptance of organs from IRD donors by patients and clinicians, and on posttransplant outcomes, should be closely monitored.

The introduction of direct-acting antiviral (DAA) medications that achieve sustained viral response (cure) rates above 95% with few side effects has expanded opportunities to safely use organs from donors with hepatitis C viremia (HCV) in uninfected recipients, which, when coupled with DAA posttransplant therapy, results in excellent outcomes. Nonetheless, up to 40% of US transplant programs remain reluctant to incorporate transplants from donors with HCV into their practice due to barriers including insurance coverage concerns, cost, and perceived risk of transmitting resistant infection. The COVID-19 pandemic created an urgent need to develop tools for rapid and reliable screening of donors for a new viral infection. As the prevalence of individuals with recovered COVID-19 increases in the population, determining if and when organs from donors with recovered COVID-19 can be safely used is a critical research priority.

Importantly, metrics of transplant success have focused largely on patient and graft survival. However, for some patients—especially the elderly—the most important benefits of transplantation may relate to other domains such as quality of life or greater social participation. Freedom from dialysis, even for a shorter period, may be highly valuable for patients and families.

**Recommendations**

- Develop and evaluate patient- and clinician-facing educational materials to foster understanding of the potential benefits of accepting kidneys at risk for discard (KARD), including organs from donors with older age, lower quality scores, acute kidney injury, behaviors associated with viral infections, or certain known viral infections.
- Create and evaluate communication strategies to effectively educate patients and clinicians about organ offers and promote shared decision-making at listing and throughout the experience on the waiting list.
- Incorporate additional definitions of success (incremental survival, quality of life improvement) into models of transplant acceptance.

**Priority 4: Decrease Organ Discard With Use of Novel Assessment Technologies and Real-Time Decision Support**

Given the growing complexity of organ acceptance to optimize competing concerns for graft failure versus death on the waiting list, logistical complexity exacerbated by geographically broader organ sharing, and clinician concerns for patient and program outcomes, decision support systems may promote KARD acceptance. Despite widespread use and integration into organ allocation, the KDPI is a first-generation tool to assess kidney quality that has modest ability to predict graft survival and carries a significant chance of misclassifying risk, which may increase the likelihood of organ discard. Investigators should seek to develop tools for transplant clinicians to objectively assess the benefits of specific kidney offers for individual patients, accounting for logistical realities during time-sensitive and complex decision-making. These tools might incorporate machine learning, artificial intelligence (AI), and other advanced analytics to integrate the complex clinical information available about donors and candidates to match organs to appropriate recipients. Efficient interfaces are needed with OPTN/UNOS systems to provide data in real time without additional data entry. For example, integrated interpretation of complex serum creatinine trajectories, renal pathology images, or machine perfusion parameters such as resistance and flow patterns could be facilitated by AI or advanced modeling tools.

Clinicians and scientists have proposed multiple explanations for high kidney discard rates in the United States; however, the primary code used for organ decline is organ quality, often related to biopsy results. Nearly half of deceased donor kidneys in the United States undergo post-recovery biopsy to evaluate “quality,” despite nearly uniform evidence refuting the benefit of these biopsies, which add to cost and cold ischemia time. A study comparing allocation in the United States versus France and Belgium—where kidneys are not routinely biopsied during allocation—reported no predictive value of biopsies over what is routinely available from donor medical records. The reliability of kidney biopsy is further complicated by the limited availability of trained renal pathologists and the difficulty of interpreting frozen sections due to artifact.
Telepathology allows remote review and image interpretation, while whole-slide interpretation using AI systems appears promising to improve reliability of biopsy reports. Accurate biopsy data utilizing AI solutions could facilitate more rapid placement of organs, as the community appears not yet ready to significantly limit biopsies, as some have proposed. A pilot trial to assess the feasibility of surgeon willingness to defer access to biopsy information at the time of offer acceptance is under way.

**Recommendations**
- Identify tissue, urine, or circulating biomarker tools to better predict kidney graft survival, and inform organ acceptance decisions.
- Define appropriate use of and approach to procurement biopsies by:
  - Assessing the impact of organ selection without biopsy on patient-centered outcomes (discard, renal function, graft survival, patient survival).
  - Evaluating the accuracy of whole-slide/multilevel biopsy review including AI-supported reading.
- Develop AI systems to integrate complex, multifaceted information including kidney biopsy data, novel biomarkers, and other donor risk information to:
  - Generate graft survival predictions tailored for patient clinical profiles.
  - Reduce inter-clinician variability in organ acceptance.

**Priority 5: Develop and Implement Strategies to Preserve, Resuscitate, or Evaluate Kidney Allografts Before Implantation**

Technology for preservation of kidney allografts has not advanced substantially over the past 2 decades. Static cold storage in electrolyte-rich preservation solutions can allow successful transplantation of kidneys with prolonged cold ischemic times (CITs) even exceeding 36 hours. However, organs preserved with static cold storage alone for extended periods have high rates of DGF. Hypothermic pulsatile machine perfusion has been demonstrated to reduce the incidence of DGF and costs of the transplant hospitalization. In a randomized trial of 752 paired kidneys, machine perfusion resulted in significantly reduced DGF in transplants with CIT less than 10 hours (6% vs 28%; P < 0.002) but did not significantly decrease DGF in the context of longer CIT. Pulsatile perfusion appears to have benefits for both standard-criteria and higher-risk kidneys. A retrospective analysis of US registry data found reduced DGF rates after pulsatile perfusion of kidneys from both standard and higher-risk donors.

Innovations have extended the benefits of perfusion technology from preservation alone to organ assessment, improvement, and resuscitation. While standard hypothermic pulsatile perfusion flow and resistance parameters have been correlated with graft outcomes, innovations in perfusion technology promise greater information about the organ and, potentially, the opportunity to improve its quality. Normothermic perfusion of kidney allografts can permit assessment of graft function in an ex vivo setting. Successful transplant of a kidney with severe acute kidney injury from rhabdomyolysis following effective warm perfusion has been reported. A prospective trial of normothermic perfusion is currently under way to assess impacts on graft utilization and outcome.

Alternatively, hypothermic oxygenated perfusion can be performed. A small cohort study comparing extended-criteria donor kidneys with matched historical controls (15 perfused kidneys vs 30 controls) failed to demonstrate significant benefits in rates of DGF or graft failure. Ongoing trials in Europe are underway to assess the value of hypothermic oxygenated perfusion in kidney allografts from extended-criteria donors. However, more work is needed to determine which perfusion techniques lead to optimal outcomes in different clinical contexts.

Finally, novel methods to improve marginal kidney function during ex vivo perfusion using pharmacologic, cellular, and genetic therapies are currently being explored. These therapies are designed to mitigate ischemic reperfusion injury and diminish alloimmune activation and organ damage. Ex vivo treatment offers significant potential advantages. First, the therapy can be targeted directly to the organ without impacting the potential recipient. Second, the intervention is limited to the kidney and will not impact other organs recovered from the same donor. The infusion of mesenchymal stromal cells has been evaluated as a method to decrease alloreactivity and induce tolerance. Mesenchymal stromal cells can home in on injured cells and promote recovery through the release of growth factors and cytokines. Preclinical studies suggest that mesenchymal stromal cell infusion during normothermic perfusion results in decreased inflammatory cytokines and markers of ischemia-reperfusion injury. Gene therapy, such as methods that have been widely used in altering T-cell receptor specificity, has been suggested as a method to promote tolerance, limit the detrimental effects of ischemic reperfusion, and modify host–organ interaction in xenotransplantation. The only clinical trials to date of therapy administration during kidney perfusion have utilized pharmacologic agents, and did not yield significant reductions in DGF rates.

**Recommendations**
- Investigate optimal preservation strategies (including innovative perfusion technologies) to decrease DGF rates and improve organ utilization.
- Evaluate novel techniques to monitor transplants during preservation, improve the accuracy of quality assessments, and optimize utilization.
- Examine ex vivo interventions directed at improving allograft function, reducing ischemia-reperfusion injury, and extending the life of donor allografts through immune regulation.
### Priority 1: Expand Opportunities for Safe Living Donation and Access to LDKT

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<tr>
<th>Challenges</th>
<th>Recommended Research Targets</th>
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<tbody>
<tr>
<td>• Transplant candidates have varying abilities to share their need and identify potential living donors</td>
<td>• Improve education and outreach to kidney patients about effective strategies for potential donor identification</td>
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<td>• Lack of information and disincentives may deter willing, healthy persons from donation:</td>
<td>• Reduce financial disincentives to donation</td>
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<td>• Gaps in ensuring donor follow-up and complete risk assessment</td>
<td>• Improve the efficiency of donor evaluations and predonation processes, with particular attention to removing disincentives and logistical barriers to KPD participation for programs and patients</td>
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<td>• Economic barriers, including out-of-pocket expenses and lost wages</td>
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<td>• Identify and implement methods to improve risk communication, transparency, and shared decision-making in the donor candidate evaluation</td>
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### Priority 2: Improve Waitlist Access, Management, and Pretransplant Readiness

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<tr>
<td>• Racial and ethnic minority populations face disparities in access to transplantation and overall waitlist mortality</td>
<td>• Optimize strategies to eliminate barriers to waitlist acceptance including management of obesity, frailty, and deficiencies in adequate psychosocial support, grounded in transparent communication of eligibility criteria to patients and referring clinicians</td>
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<td>• Weight-loss methods to improve BMI, like nutritional interventions and bariatric surgery, are not accessible for many obese patients</td>
<td>• Develop and implement educational interventions that assist all patients, particularly members of racial and ethnic minorities, to successfully reach the waitlist expeditiously</td>
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<td>• Structured or standardized “prehabilitation” and physical therapy programs to improve physical function prior to transplant are not accessible for many frail patients</td>
<td>• Implement scalable and generalizable information technology solutions to support waitlist access and maintenance of transplant readiness</td>
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<td>• Referral and evaluation are complex, multi-step processes</td>
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### Priority 3: Decrease Organ Discard by Expanding Clinician and Patient Organ Acceptance

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<td>• On average, 20% of kidneys are discarded after recovery, and this proportion rises sharply for nonstandard organs</td>
<td>• Develop and evaluate patient- and clinician-facing educational materials to foster understanding of the potential benefits of accepting a KARD, including organs from donors with older age, lower quality scores, AKI, behaviors associated with viral infections, or certain known viral infections</td>
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<td>• Patient and clinician perceptions and education limit acceptance of organs from donors with high KDPI, increased risk of viral infection, or some known viral infections</td>
<td>• Create and evaluate communication strategies to effectively educate patients and clinicians about organ offers and promote shared decision-making at listing and throughout the experience on the waiting list</td>
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<td>• Metrics of transplant success have focused largely on patient and graft survival, and not incorporated QoL</td>
<td>• Incorporate additional definitions of success (QoL improvement) into models of transplant acceptance</td>
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### Priority 4: Decrease Organ Discard Through Use of Novel Assessment Technologies and Real-Time Decision Support

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<td>• Despite integration into organ allocation, the KDPI has modest ability to predict graft survival and may misclassify true organ quality</td>
<td>• Identify tissue, urine, or circulating biomarkers tools to better predict kidney graft survival and inform organ acceptance decisions</td>
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<td>• Biopsied kidneys are 3-times more likely to be discarded despite:</td>
<td>• Define appropriate use of and approach to procurement biopsies by:</td>
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<td>• Marked variation in indications for biopsy, technique, and expertise in interpretation</td>
<td>◦ Assessing the impact of organ selection without biopsy on patient-centered outcomes (discard, kidney function, graft survival, patient survival)</td>
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<td>• Limited reliability of standard frozen section biopsy and uncertain prognostic value</td>
<td>◦ Evaluating the accuracy of whole slide/multilevel review including AI-supported reading</td>
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Priority 6: Sustain One Transplant for Life

Although contemporary tissue-typing techniques have essentially eliminated hyperacute rejection, and potent immunosuppression has substantially reduced acute cellular and humoral rejection, long-term graft survival remains limited. Furthermore, immunosuppression is associated with complications including infection, malignancy, glucose intolerance, and decreased quality of life. Personalization of maintenance immunosuppression with appropriate applications of steroid-sparing regimens, alternative pharmacologic agents (e.g., extended-release tacrolimus), and judicious use of mammalian target of rapamycin inhibitors (mTORis) may limit immunosuppression-associated toxicities. However, novel strategies are needed to achieve the goal of one transplant for life.

The development of personalized and effective immunosuppression strategies requires a shift from phenotypic (e.g., demographics-based) assessments to genotypic assessment of patient characteristics. Accurate models require the collection and analysis of biobanks from large and diverse patient populations. In the DeKAF and GEN03 cohort studies, investigators utilized genome-wide

Abbreviations: AI, artificial intelligence; AKI, acute kidney injury; BMI, body mass index; GFR, glomerular filtration rate; GWAS, genome-wide association study; KARD, kidney at risk for discard; KDPI, kidney donor profile index; KPD, kidney paired donation; IRI, ischemic reperfusion injury; IS, immunosuppression; LDKT, living-donor kidney transplantation; QoL, quality of life.
association studies (GWAS) to detect clinically significant differences in calcineurin inhibitor metabolism on the basis of a complex interaction of multiple genetic polymorphisms. These data demonstrate that the impact of recipient genetic variation is complex, differs by patient characteristics, and extends beyond well-characterized genomic variation (eg, CYP34). Developing clinical application of genotypic data will benefit from systematic collection and analysis of donor and recipient genetic variations through GWAS, linked directly with baseline clinical and outcomes information.

Belatacept, a soluble fusion protein comprising the modified extracellular domain of CTLA-4 fused to a portion (hinge-CH2-CH3 domains) of the Fc domain of a human immunoglobulin G1 antibody, has been evaluated in 2 prospective clinical trials as a novel alternative to oral immunosuppression. While initial studies suggested high rates of rejection, pilot studies combining belatacept, alemtuzumab induction, and slow tapering of calcineurin inhibitors have facilitated successful belatacept monotherapy in some patients. Alternative strategies under investigation include use of combined cellular and kidney transplantation to induce a state of “tolerance” through chimerism, allowing tapering and elimination of maintenance immunosuppression. Incorporation of novel biomarkers into posttransplant surveillance may help identify which patients have lower immunologic risk and could benefit from immunosuppression minimization to reduce complications without increasing risk of rejection.

**Recommendations**

- Develop personalized strategies for posttransplant immunosuppression management, incorporating novel assessment tools such as GWAS data for donors and recipients and novel posttransplant monitoring tools.
- Assess the impact of tolerance induction strategies on patient and graft survival, quality of life, and development of immunosuppression complications.

**Priority 7: Optimize Kidney Transplantation for Pediatric Patients**

Although patients younger than 20 years of age account for less than 2% of the total North American patient population treated by kidney replacement therapy, the prevalence of pediatric kidney failure has increased by 32% since 1990. Approximately 50% of all pediatric kidney failure diagnoses are due to congenital, nonglomerular anomalies, and half of all pediatric patients with congenital kidney disease will progress to a need for transplantation during their lifetime. Pediatric kidney failure is associated with an array of multisystemic sequelae, and the impact of kidney failure on cognition has important implications for optimizing outcomes of transplantation in the pediatric population. Pediatric kidney failure is associated with risk for academic underachievement and executive function deficits. Furthermore, both the duration and severity of kidney disease in pediatric patients may lead to structural brain abnormalities. While significant cognitive impairment may not be present in most children with chronic kidney disease, even subtle cognitive impairments can pose barriers to understanding of and adherence to complex medication regimens required as part of caring for a transplant. The impact of these subtle cognitive deficits cannot be overemphasized given that the highest-risk period for graft loss among pediatric transplant patients occurs in late teenage/early adulthood years when critical periods of neurodevelopment are not yet complete, in parallel with periods of transition from pediatric to adult care teams. Children also face high risk of viral-driven malignancy from donor-derived viral infections.

**Conclusions**

Kidney transplantation offers hope to thousands of patients each year, but the goal of universal access to this treatment remains elusive. Addressing the priorities outlined in this research agenda has the potential to transform kidney patient care by expanding opportunities for safe living donation, improving waitlist access and transplant readiness, maximizing use of available deceased donor organs, and extending graft longevity. These priorities will frame research and funding initiatives for the NKF and assist patients with chronic kidney disease in receiving and nurturing the gift of transplant (Box 1).

**Article Information**

**Authors’ Full Names and Academic Degrees:** Krista L. Lentine, MD, PhD, Stephen Pastan, MD, Sumit Mohan, MD, MPH, Peter P. Reese, MD, MSCE, Alan Leichtman, MD, Francis L. Delmonico, MD, Gabriel M. Danovitch, MD, Christian P. Larsen, MD, PhD, Lyndsay Harashman, MD, MS, Alexander Wiseman, MD, Holly J. Kramer, MD, MPH, Joseph Vassalotti, MD, Jessica Joseph, MBA, Kevin Longino, MBA, Matthew Cooper, MD, and David A. Axelrod, MD, MBA.

**Authors’ Affiliations:** Saint Louis University Center for Abdominal Transplantation, St Louis, MO (KLL); Department of Medicine, Emory Transplant Center, Atlanta, GA (SP); Department of Medicine, Columbia University Medical Center (SM); National Kidney Foundation (JV, JJ, KL); Department of Medicine, Icahn School of Medicine at Mount Sinai (JV, New York, NY); Renal-Electrolyte and Hypertension Division, University of Pennsylvania, Philadelphia, PA (HPC); Department of Medicine, Icahn School of Medicine at Mount Sinai (JJ, New York, NY); National England Organ Bank, Wellesley Hills, MA (FLD); University of California, Los Angeles, Los Angeles, CA (GMD); Department of Pediatrics (LH), Department of Surgery (DAA), University of Iowa Transplant...
Institute, Iowa City, IA (LH); Department of Medicine, Centura Health-Porter Adventist Hospital, Aurora, CO (AW); Department of Medicine, Loyola University, Chicago, IL (HJK); Department of Surgery, Medstar Georgetown Transplant Institute, Washington, DC (MC) and Department of Surgery, Emory Transplant Center, Atlanta, GA (CPL).

**Address for Correspondence:** Krista L. Lentine, MD, PhD, Saint Louis University Center for Abdominal Transplantation, 1201 S Grand Blvd, St Louis, MO, 63104. Email: krista.lentine@health.slu.edu

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