Meeting Report

Solid-Organ Transplantation in Older Adults: Current Status and Future Research

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**An increasing number of patients older than 65 years
are referred for and have access to organ transplan-
tation, and an increasing number of older adults are
donating organs. Although short-term outcomes are
similar in older versus younger transplant recipients,
older donor or recipient age is associated with inferior
long-term outcomes. However, age is often a proxy for
other factors that might predict poor outcomes more
strongly and better identify patients at risk for ad-
verse events. Approaches to transplantation in older
adults vary across programs, but despite recent gains
in access and the increased use of marginal organs,
older patients remain less likely than other groups
to receive a transplant, and those who do are highly
selected. Moreover, few studies have addressed geri-
atric issues in transplant patient selection or manage-
ment, or the implications on health span and disability
when patients age to late life *with* a transplanted or-
gan. This paper summarizes a recent trans-disciplinary
workshop held by ASP, in collaboration with NHLBI,**

NIA, NIAID, NIDDK and AGS, to address issues related to kidney, liver, lung, or heart transplantation in older adults and to propose a research agenda in these areas.

Introduction

The patient population on organ transplant waiting lists is growing older, particularly as the number of patients aged 65 years and older increases (1) (Figure 1). Older adults have gained more access to transplantation over time (2), but transplantation rates among these patients still vary across organs (Figure 2). For kidney, the proportion of older patients placed on the waiting list is lower than that of other age groups, even though older patients represent about half of all patients with end-stage renal disease (ESRD). However, of the older patients listed for kidney transplant, the proportion who receive transplants is similar to that in younger age groups. For lung, transplantation rates increase with age because of the high rate of transplantation for idiopathic pulmonary fibrosis, a disorder primarily affecting older adults (3).

The average age of donor organs is also increasing, but the impact of older donor age on transplantation varies by organ. On the basis of data from old studies, the clinical decision to use 'older' hearts for transplantation is rare. The number of heart donations remains flat overall, and the number of older donors remains small. In contrast, the number of lung and kidney donations is increasing (4), even as the proportion of donors older than 65 years remains flat. Lung transplant data suggest that donor organ age has minimal impact on short-term survival and that a combination of age and longer ischemic time (5), not donor age alone, is associated with inferior outcomes. Similarly, the outcomes for patients receiving older kidneys or livers are only slightly worse than those for patients receiving younger organs. Yet many transplantation centers still ex-

clude donors aged 55 years and older, and particularly for kidney, organs from older donors are more likely to be discarded (Figure 3) (1) when their inclusion could expand the donor pool.

The likelihood of receiving organs from expanded criteria donors (ECD) increases with recipient age (6,7). In addition, older donor age increases the likelihood that an organ will be classified as ECD (8), but for heart and lung donations, there are no common accepted definitions for ECD organs. Thus classification of ECD organs often depends on expert opinion and, in the case of the lung, on criteria unrelated to risk factors that affect posttransplantation outcomes. Moreover, despite evidence that some patients will benefit from ECD organs (9), and even though patients' willingness to receive these organs can be influenced by careful presentation of evidence (10), the proportion of those patients who are willing to receive such organs is low, even among centers with longer waiting times (11).

Donor Organ Quality

Large studies, the majority of which have focused on kidney transplantation, have shown that organ quality declines with older donor age. The quantity and quality of nephrons in the donor kidney, and particularly the initial number of healthy glomeruli, are more important determinants of allograft survival than donor age. Techniques to accurately quantify the number of functioning glomeruli have not yet been established, and surrogate measures, such as body surface area (12) or kidney weight, are not useful or practical in the existing allocation system (13). Estimates from autopsy studies in individuals without known kidney disease suggest that on average, glomerular filtration rate and the number of functioning glomeruli decline with age (14). Estimates based on renal physiology and morphometry show similar numbers and trends for functioning glomeruli in living donors (15) but a significantly lower number in older deceased donors (16,17) (Figure 3). Consistent with these observations, allograft survival is considerably better for living donor kidneys, even those from older donors (18). However, the rate of allograft failure is still excessive for older donor kidneys, compared with younger ones.

Injury to renal tubular epithelial cells following procurement and implantation (19,20) might also affect donor kidney quality. The risk for ESRD following postischemic acute renal failure is substantial among older adults, particularly those with preexisting chronic kidney disease, compared with younger patients (21). The mechanism of this injury is unknown, but evidence suggests that repair of epithelial cells is limited by cellular senescence, and atubular glomeruli have been observed in kidneys from older adults and in renal allografts with chronic allograft nephropathy
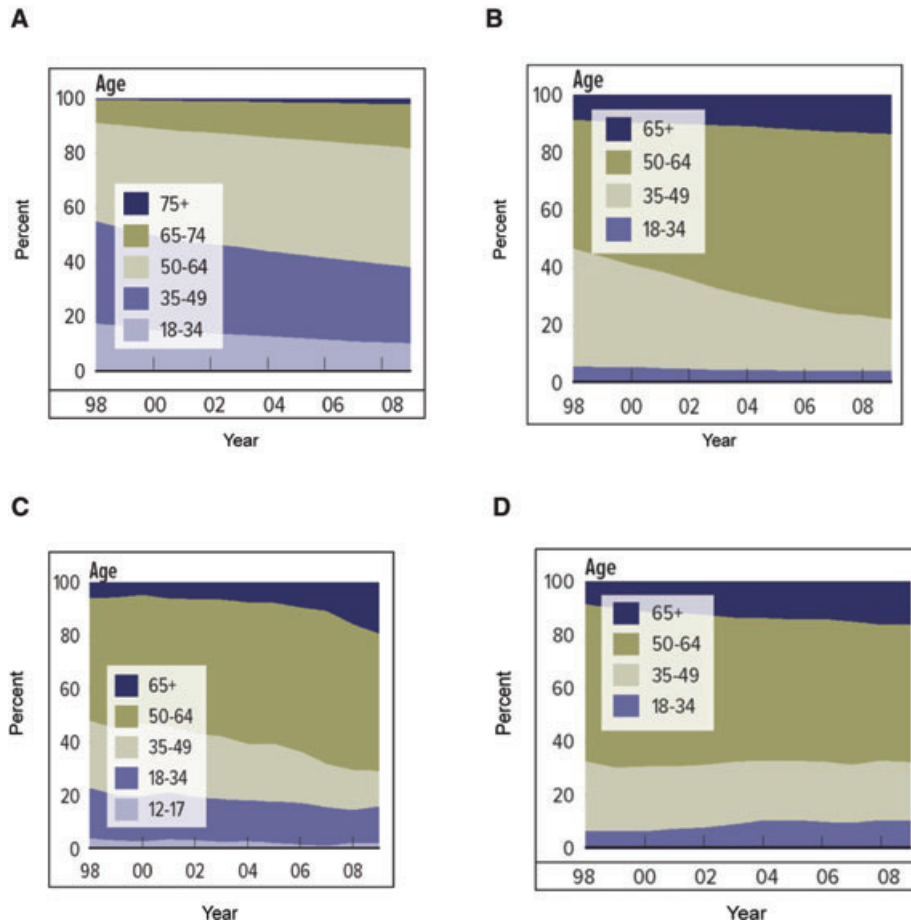
Figure 1: Proportion of patients on transplant waiting lists, by age (1), for (A) kidney, (B) liver, (C) lung and (D) heart.

(22). Thus in deceased donor allografts, the reduction of the number of nephrons below a critical threshold could render the allograft more susceptible to accelerated decline, and subsequent injury from rejection or drug toxicity could hasten complete allograft failure. Further study on the mechanism and prevention of such injuries could guide interventions to increase the longevity of allografts from older donors.

Organ Allocation

Organ allocation systems vary by specific organ and by programmatic tendencies. The Lung Allocation Score, which includes age as a variable, grades disease severity and physiologic reserve. The Model for End-Stage Liver Disease (MELD) predicts waitlist mortality but predicts posttransplant outcomes only at scores above 35. The likelihood of patients dying while waiting for a liver depends on the donor service area in which they reside. A regional sharing and prioritization system for MELD scores of 15 or more has received widespread support, and recent evidence (23) supports a similar system for MELD scores higher than 35. An allocation system that accounts for several predictors of posttransplant mortality and considers

posttransplant lifetime relative to lifetime on the waitlist has also been proposed. However, this system is seen as too complicated and thus has mixed support.

Kidney allocation policy is based primarily on waiting time and local organ distribution, and it only minimally addresses potential outcomes and immunologic matching. Thus the potential survival of the donor organ and that of the recipient are often mismatched, increasing the need for retransplant and decreasing the number of potential life-years realized from a transplant. Moreover, current kidney allocation does not consider recipient age, except for pediatric patients. Efforts to improve kidney allocation by age-matching donors and recipients have been controversial because of perceptions of age discrimination, and there is no evidence that age matching improves outcomes (24). A newer model incorporates longevity matching, which includes age and other metrics for prediction, and replaces the current ECD system with a Kidney Donor Profile Index score (25), which accounts for several clinical and demographic factors, including donor age. With this model, calculation of waiting time includes the amount of time a patient has lived with ESRD. Simulations suggest that the number of older patients receiving kidneys will decrease by approximately 5%, based on a difference in average age between donors
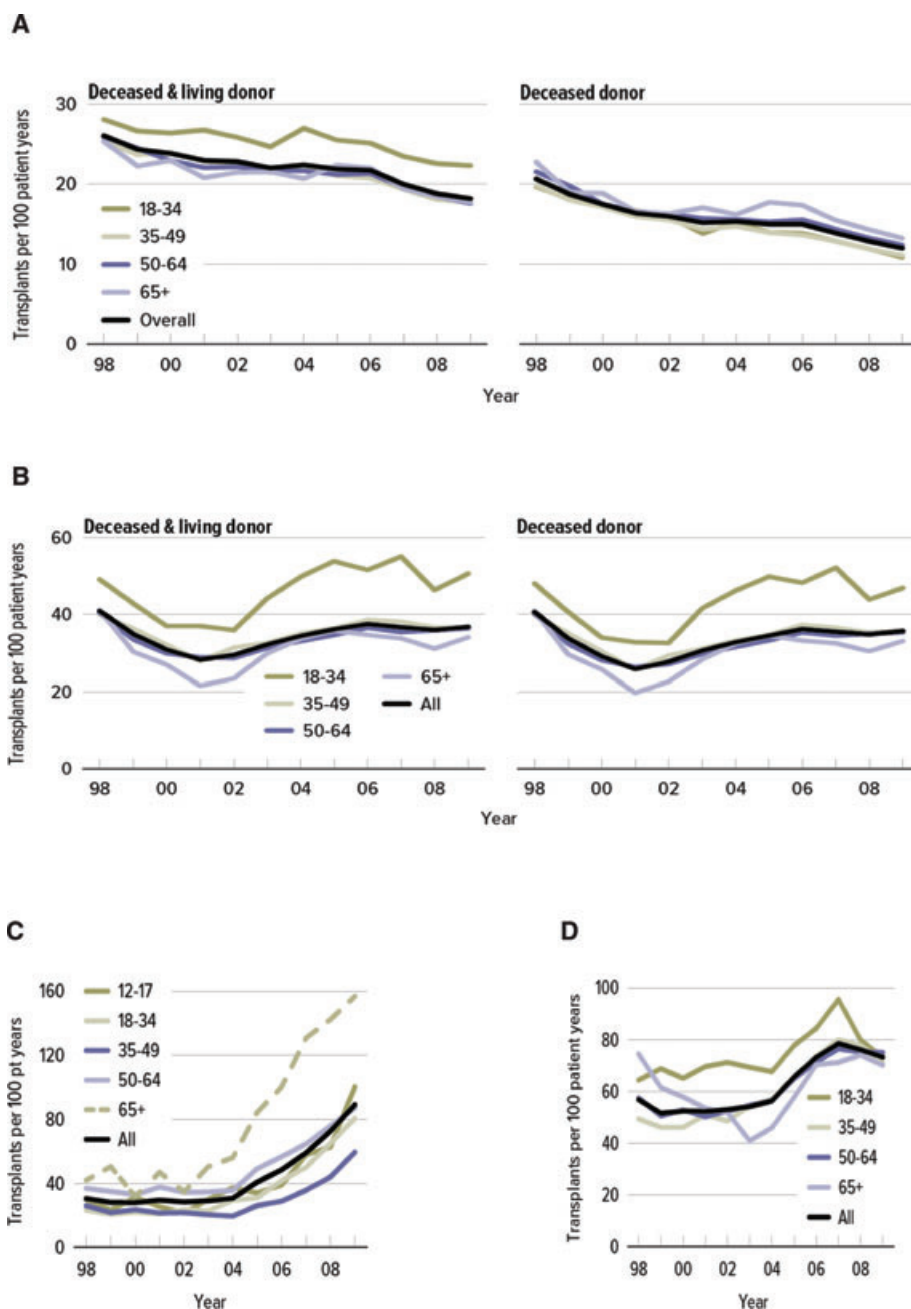
A

B

C

D

Figure 2: Transplant rates for adults on the waiting list, by age (1), for (A) kidney, (B) liver, (C) lung and (D) heart.

and recipients. However, allocation systems based more heavily on recipient functional status and prognostic variables, rather than age alone, are more likely to be acceptable to the public.

Recipient Selection and Management

Illness severity is often better than age in predicting postoperative complications. However, despite recent gains in access for older patients on the waiting list and evidence that older patients benefit from transplantation if their wait-

ing time is shorter (26–29), older patients still have less access to transplantation than other age groups because they are not placed on the waiting list (30). Moreover, older patients who are referred for transplant often are highly selected, and they are less likely to receive an organ from a living donor (31). Comprehensive risk assessments, based on stronger predictors than age and accounting for end points such as independence and quality of life, might be needed to evaluate risk versus benefit for older recipients.

Transplant recipients are selected based on the likelihood of successful outcomes, and age is often used as a
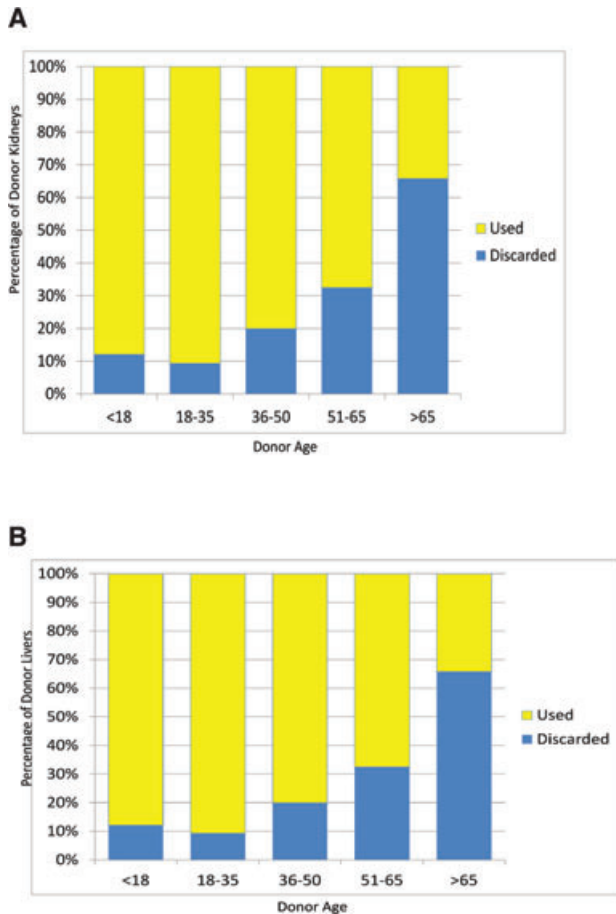
A

B

Figure 3: Proportion of donor organs discarded, by age. (A) Kidney, (B) liver. (Based on data from the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research (STAR)).

determinant. However, age is a surrogate for many other health and functional issues, and there is no specific predictive rule that examines most age-related variables to determine which patients will do well after a transplant. Thus, transplant physicians judge candidate suitability based on their clinical experience and a subjective assessment of physical fitness, or the so-called eyeball test. More objective measures of fitness have focused on lean trunk muscle size for liver transplantation and a 6-minute walk test for lung transplantation, and both of these factors correlate with posttransplant survival (32,33). Among older patients undergoing elective surgery, an American Society of Anesthesiologists (ASA) risk score combined with a frailty assessment is more predictive of outcomes than the ASA score alone (34). In kidney transplant recipients, frailty is strongly associated with early allograft dysfunction (35). Thus evaluations of physical performance, which might better represent a patient's physiologic age, might prove a more objective approach to recipient selection.

While physical function can be affected by organ failure and transplantation (36–39), it might also play a role in a recipient's posttransplantation recovery time, risk for disability, cardiovascular health, and health-related quality of life (HRQOL). Dialysis patients reporting a higher level of physical function are at lower risk for posttransplantation hospitalizations and death (40), and posttransplantation gains in exercise capacity and muscle strength are higher with exercise than with usual care (41). To date, no exercise intervention trials have examined the potential benefits of pretransplant exercise on posttransplant outcomes in ESRD patients.

For most solid organs, organ failure has been associated with cognitive impairment (42–47), and several potential mechanisms are supported by modest data (42,48–54). Chronic organ failure has been associated with encephalopathy and dementia, especially in renal disease, and acute insult to the organ can cause delirium that, when recurrent, can lead to chronic encephalopathy and dementia. In addition, the risk for cognitive impairment increases with age. Cognitive impairment leads to medical nonadherence and thus to higher rejection rates (55–57). However, the use of cognitive impairment as an exclusion criterion for transplant varies by organ (58–61), and assessments are usually done only if dementia is suspected, rather than by formal, standard evaluation.

Psychosocial well-being improves after transplantation in most patients, but not to normative levels. For example, rates of emotional distress and psychiatric disorders are higher, and the rate of gainful employment lower, among transplant recipients, compared with the general population (62–65). Psychosocial well-being is routinely assessed to aid in decisions to list patients for transplants and to guide interventions to ameliorate psychosocial contraindications to transplant (59,60,66). Posttransplant medical adherence, mental health outcomes and quality of life for older recipients are similar to, and occasionally better than, those for younger recipients (67–71). Nevertheless, little evidence suggests that age is a major predictor of posttransplant psychosocial outcomes, and few analyses of psychosocial well-being in transplant recipients have been stratified by age. A more complete understanding of age effects on psychosocial outcomes could aid the development of interventions tailored to recipient age.

Comorbidities might also influence outcomes. For example, postoperative survival is shorter among cancer patients who have two or more comorbidities when undergoing tumor resection (72). However, few data address the impact of comorbidities on posttransplantation outcomes, particularly in older patients. Thus preoperative assessments of comorbidities vary across centers, and patients older than 70 with multiple serious comorbidities are unlikely to receive transplants unless their functional status is exceptional. Risk assessments based on comorbidities may be confounded by the primary organ failure that can

Figure 4: Changes in glomerular filtration rate (GFR) and glomerluar number, by age. (A) Changes in GFR (17). (B) Changes in glomerular number, estimated from autopsy studies (14). (C) Changes in glomerular number from deceased donors, estimated by combining renal physiology with morphometry from kidney biopsies, compared with estimates from autopsy studies (16). (D) Changes in glomerular number from living donors, estimated by combining renal physiology with morphometry from kidney biopsies (15). Reprinted with permission.
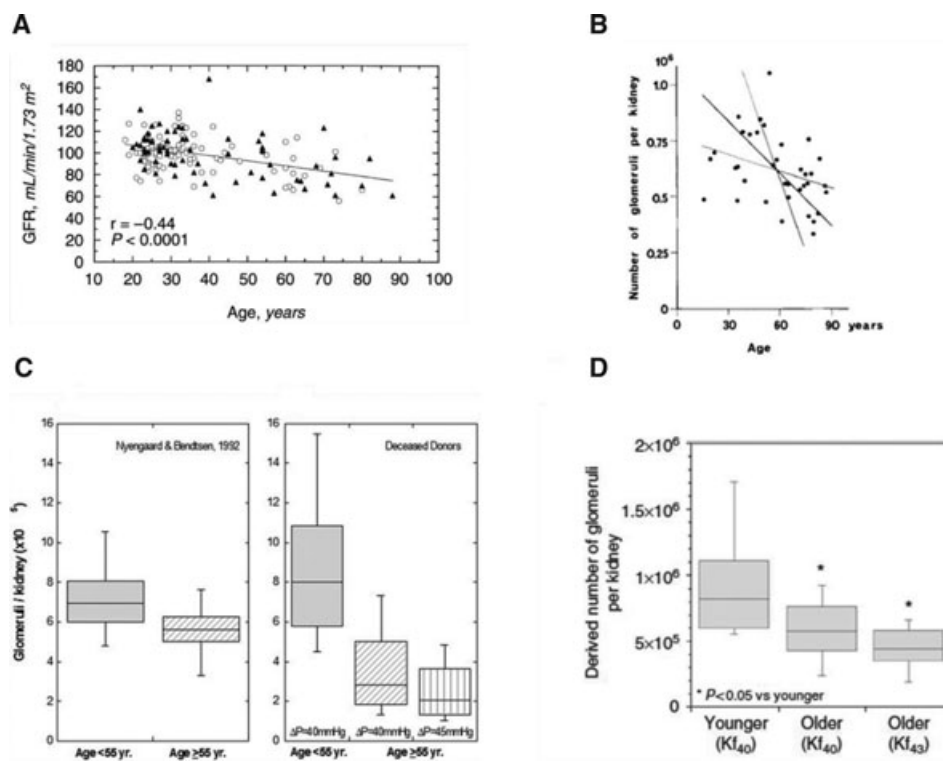
be reversed with transplantation, but few studies have addressed reversibility by age.

Immunosuppression in the Older Transplant Recipient

Aging broadly influences diverse affects of immunity including exaggerated inflammation and altered innate immunity important in host defense (73,74), but cell-mediated immunity is most clearly affected. A precipitous decline in the production of naïve T cells and a resulting decline in T cell diversity have been observed in the older immune system. In addition, clonally expanded T cells, particularly in the CD8 T cell compartment, lead to a narrower repertoire and accumulation of 'exhausted' and 'senescent' T cells (75–77). These changes can be exacerbated by persistent viral infections such as cytomegalovirus, which restimulates memory T cells over a lifetime (78–80). Senescent T cells are marked by absent CD28 expression, increased CD2 expression, altered dependence on costimulation versus adhesion ligand-receptor interactions, and overproduction of proinflammatory cytokines (81). As a result, mechanisms underlying organ rejection likely differ between younger and older transplant recipients.

Consistent with this hypothesis, mouse studies suggest that costimulation blockade is less effective in older indi-

viduals (82). Further, while immune senescence generally impairs immune responses, the impact of acute rejection is more profound in older recipients (83,84). In addition, the risk for delayed graft function associated with acute rejection (85–87) is higher for older donor organs. Thus, the impact of the immunobiology of aging on transplantation deserves investigation, and immunosuppression protocols for older transplant recipients must balance the risk for acute rejection with the risk for poor cardiovascular, infectious and/or metabolic outcomes.

Immunosuppression protocols also must account for age-related physiological changes that alter the pharmacokinetics, pharmacodynamics, and potential toxicity of immunosuppressive drugs (88). Therapeutic blood target ranges associated with efficacy and toxicity might be different in older recipients. In addition, because older recipients are more likely to have comorbidities and thus take multiple medications, they are at higher risk for adverse drug interactions. Studies exploring immunosuppressant pharmacokinetic disposition among older kidney recipients have yielded mixed results (89–91), and their sample sizes are too small for interpretation. Few studies have assessed antibody therapy in the older recipient. Biologic assays that measure overall immunosuppression would be useful.

Despite possible age-related immunologic and pharmacologic changes, immunosuppression protocols are typically

similar regardless of age (92). However, risk stratification data suggest there is a link between IL-2RA and risk for cardiovascular death and that the impact of acute rejection is most profound when both donor and recipient are classified as high risk (92). Tailored immunosuppression strategies such as calcineurin inhibitor avoidance (93,94) and mycophenolic acid withdrawal (95) are designed to reduce morbidity and might improve patient and graft survival. There are also likely to be important effects of age on autonomic disturbances (e.g. postural hypotension) and neuropsychiatric issues that could influence drug choices. The benefit of steroid avoidance is less clear (96) but perhaps more important in seniors in whom age-related bone loss, glucose intolerance and other metabolic effects complicate steroid therapy. Moreover, previous studies are largely retrospective, single-center studies without controls, and they have not collected data on older patients.

Long-Term Outcomes

Although short-term outcomes are acceptable for older transplant recipients across organs, long-term outcomes differ by age (6,97). Older donor organs also have been associated with inferior long-term outcomes (98), for example increased risk for graft loss.

Older adults are more susceptible than young adults to infections that are often more severe and arise from a wider range of pathogens. Among waitlisted patients, the risk for infection-related death increases with age (99). It is not clear which changes in immunity contribute to these risks, but immunosuppressive drugs further impair host defenses. Risk for death from infection increases exponentially with age among kidney transplant recipients (99), and among kidney and lung recipients older than 60 years, infection is the leading cause of increased mortality seen in the first postoperative year (100,101). Yet no guidance exists to help clinicians prevent or manage infections in older transplant patients. Multiple factors reduce host defense in senior transplant recipients; vaccine efficacy decreases markedly with age (102), antibiotic prophylaxis in older patients likely leads to complications such as *C. difficile* infection or antimicrobial resistance in specific pathogens, and less virulent pathogens (e.g. nonvaccine serotypes of *S. pneumoniae*) cause disease more frequently in old than young adults (103).

Cardiovascular disease (CVD) is an important predictor of mortality in transplant recipients (104–106). Among kidney recipients, even in those screened for CVD before transplantation, left ventricular dysfunction and a patient's Framingham Risk Score can predict cardiac events (105,106). In nontransplant patients, traditional risk factors such as hyperlipidemia or smoking can predict postoperative cardiac risk, but coronary artery disease revealed by coronary imaging further increases that risk,

even if the disease is not hemodynamically significant (107). However, cardiac assessments of transplant candidates focus only on their ability to survive the surgery itself. How best to predict long-term cardiac risk, particularly among patients with coronary disease, is not clear.

Cancer incidence increases with age in the general population. Overall, transplant recipients are at twice the age-adjusted risk for cancers; the risk is elevated for non-Hodgkin lymphoma and cancers of the lung and kidney, but not for breast or prostate cancer (108). Because the spectrum of cancers and the underlying pathways to cancer differ between transplant recipients and the general population (109), it is unlikely that transplantation simply accelerates age-related processes leading to cancer. It is unclear whether immunosuppression regimens affect the biology of a cancer, although some evidence suggests that cancers behave more aggressively in immunosuppressed patients. Immunosuppression could reduce the ability to clear early cancer precursors (109).

Although data on quality of life following transplantation are few, the quality-of-life benefit does not appear to differ between older and younger recipients (110,111). In some cases, reported life satisfaction among recipients older than 60 years is actually higher (112,113). Across organs, the most important aspects of HRQOL differ between older and younger recipients (114,112,115). However, the effects of age on posttransplant HRQOL are complex, whether in older patients receiving a transplant or in patients aging after a transplant. One study suggests an immediate drop, then rebound, in quality of life for donors (116), but more data are needed.

Health Disparities in Transplantation

Across all ages, ESRD incidence of end-stage renal disease is four times greater among racial and ethnic minorities (117), but Hispanics are less likely to receive preemptive transplants, and African Americans are less likely to be waitlisted and transplanted in general (118,119). Compromised health literacy (120), increased likelihood of higher disease severity requiring emergency treatment (121), variable or suboptimal discussions of transplantation and living organ donations (122,123) and an apparent hesitation on the part of minorities to donate organs (124–127) all contribute to this disparity. Racial and ethnic disparities in access to transplantation have improved somewhat with the aid of home-based educational approaches (128), changes in donor kidney allocation policy (129,130), amended Medicare coverage rules, the establishment of the National Living Donor Assistance Center and changes in provider reimbursements for patient education.

Little is known about racial and ethnic differences in long-term posttransplant outcomes (131). Across organs, graft

and patient survival rates are highest for Asian and Hispanic recipients and lowest for African American recipients, with Non-Hispanic Whites in the middle. Among kidney recipients, the benefits of preemptive transplantation are observed predominantly among White recipients. Hepatitis C infection, a risk factor for graft failure, is seen at higher rates among African American recipients, and disparities in outcomes are confounded by issues of access to transplantation. However, adjustment for these factors does not completely explain the worse outcomes in African Americans. More work is needed to identify factors underlying disparities in outcome, and no specific data address age or functional status issues in minority versus nonminority transplant recipients.

Health Care Utilization and Cost

The full cost implications of transplanting older recipients or using organs from older donors are poorly defined. The financial impact of elderly candidates includes the incremental costs of additional evaluation, age-specific costs incurred in the short term following transplant, and longer-term costs that are related but more difficult to attribute to the transplant procedure. The financial impact of older donor organs includes costs related to discarded organs, longer-term organ nonfunction and dysfunction and shorter graft survival. Cost-effectiveness analyses often emphasize quality-adjusted life years saved (QALYS), but it is not clear whether the comparator in such analyses is the younger donor or recipient or a therapeutic alternative to transplantation. Moreover, cost variations between centers for otherwise comparable patient populations arise from variations in practice, which are more likely to reflect institutional culture than patient needs. Selection biases against transplantation in older adults might reflect providers' risk aversion rather than empirical evidence, which might become more important as regulators and payers focus more on patient outcomes. Moreover, analyses of cost- and comparative-effectiveness must also address the moral and ethical appropriateness of therapeutic decisions, especially as patient-centeredness and shared decision making become more prevalent in health care delivery.

Despite these difficulties in analyzing cost-effectiveness data, a decision analysis of kidney transplantation in older adults (113) suggests that the incremental cost of a QALYS is sensitive to older age, length of time on the waitlist, and potential for resource utilization associated with comorbidities and posttransplant complications. However, resource utilization among older donors and recipients is difficult to predict, and the few studies that have addressed it (132–135) have produced conflicting results or failed to compare predictors in older versus younger patients. As suggested by data from other high-intensity care scenarios (136,137), the inclusion of geriatric assessments (138) can prove useful in decisions about transplantation in older adults, but

whether these assessments can predict resource utilization among older recipients is not yet clear.

Future Research Directions

Although advanced age has been associated with compromised posttransplant outcomes, it is likely a proxy for stronger predictors, such as functional status, physiologic organ reserve, or comorbidity. There is a critical need to address basic science issues of aging in transplantation with the potential to shape clinical investigations and protocols, but rodent models of aging may not closely mimic human aging (139). Further, few clinical studies have directly explored transplantation in older patients, but further research in this population could guide the education, selection and management of appropriate candidates.

Critical areas of research need are comprehensively listed in Table 1, but can be summarized into several broad themes:

1. What critical immune mechanisms that change with age and life-long viral infections (e.g. CMV, hepatitis C) differentially affect transplant outcomes, and how should these influence patient management?
2. Age serves as a surrogate for many other factors, such as functional status, body composition, or comorbidity. What is the contribution of each, and how can that better guide selection of donors and recipients, organ allocation systems and clinical management of transplant recipients?
3. What is the impact of transplantation and chronic immune suppression on the aging process in various organ systems? Does that alter prevention and treatment strategies?
4. How can functional outcomes, comorbidity, life-expectancy and patient-centered results be better incorporated into transplant programs and quality metrics to assess 'success' in older patients?

Several datasets and cohorts are available to explore general and organ-specific questions about the role of age in issues of organ allocation, donor and recipient selection, long-term outcomes and health disparities (Table 1). However, efforts to collect and test the role of novel risk predictors in older adults, particularly those not in registries, are critical, as existing registries lack the granularity required to move this field forward. Future research will require multidisciplinary collaborations, harmonization of existing databases with primary data collection, and a uniform language of variables to include in new studies. This research will also need measures that are reliable, reproducible, easy to use, and focused on end points valued by older recipients. Some of these measures could aid in predicting

Table 1: Questions and potential datasets or cohorts for future biomedical, health outcomes and public policy research

Area	Question or cohort
Organ allocation	1. How do we balance age, functional status, expected years of life to be gained and alternative therapies in a severity of illness-based allocation system?
	2. Who are the right candidates to receive organs from older or other 'marginal' donors, how can we educate those candidates, and how can we match ECD organs to the best recipients?
	3. Should organ allocation algorithms for thoracic transplant attempt to age-match donors and recipients?
	4. Can we expand donor criteria further; how old is too old? How do we reduce the rate of organ discard?
	5. What strategies can be taken to increase the opportunity for heart transplant for older adults?
	6. What safety issues should be considered for older living donors?
	7. What is the impact of regulatory policies that emphasize very low rates of graft failure and mortality on transplant centers' willingness to transplant older recipients?
Reducing health disparities	1. What are the best methods for providers to communicate with minority patients and their families about treatment options? Do these vary by age and/or life experiences?
	2. What are the best ways to engage in shared decision making and educate minority patients about treatment options?
	3. What are the best ways to ensure compliance with established Medicare standards without unintended adverse effects?
	4. What biologic, behavioral and social mechanisms contribute to the racial and ethnic differences in long-term posttransplant outcomes?
	5. Can racial and ethnic disparities be separated from socioeconomic disparities?
Recipient selection	1. What are the age-specific barriers to becoming transplant eligible?
	2. What are the age-related factors (e.g. functional status, cognitive impairment), for which age is currently used as a surrogate marker, that affect long-term outcomes?
	3. Since comorbidity and poor physiologic reserve is common even at younger ages in those with end-stage organ failure, could younger recipients also benefit from a comprehensive 'geriatric' assessment to identify those at risk for adverse outcomes?
	4. What is the rationale for colonoscopy, stress testing and mammography before transplantation in older adults?
	5. Do specific cognitive, health literacy and medication adherence tests predict transplant outcomes? Can they be used to optimize candidate selection at all ages?
Recipient counseling	1. Are there age-related differences in risk acceptance for transplant? Are older adults less or more interested in the risk trade-offs of the transplant?
	2. Are age-specific interventions, for example counseling about higher posttransplant mortality or improved quality of life, effective in motivating older individuals to decide to move toward transplantation?
Immunobiology and immunosuppression	1. How does aging impact innate and cellular (T and B cell) responses to organ transplantation?
	2. Are immune senescence and exhaustion the same or different phenomena? How are they affected by end-stage organ failure?
	3. Do age-related immune defects arise from a loss of immune-activating responses, a gain of inhibitory responses, or both? Should this influence selection of immune suppression strategy?
	4. Are age-related immune changes primarily intrinsic (e.g. donor dominant), extrinsic (e.g. recipient dominant), or both?
	5. What are the roles of specific viruses, such as cytomegalovirus or Epstein Barr virus, or their combinations in immune senescence or exhaustion?
	6. How does aging alter the development of processes potentially accelerated by chronic viral infection (e.g. chronic vasculopathy)?
	7. Should immunosuppressive strategies and infection prophylaxis vary by age and/or be based on measures of immune exhaustion or senescence? How do comorbidities alter this interplay?
	8. What clinical or laboratory parameters could guide immunosuppressive strategies in older adults?
	9. To what extent do immunosuppressive drug absorption, distribution, metabolism and excretion change in the older adult?
	10. Are older recipients at higher risk for immunosuppressant-related side effects?
	11. How do drug pharmacodynamics change in older recipients?
	12. What should the therapeutic level targets be in older patients?
	13. What factors place older recipients at high risk for drug-related side effects, and what strategies can be used to reduce toxicities?
	14. What is the impact of treating acute rejection and using immune modulatory therapy in older recipients?
	15. Can novel measures of immune status that are more valuable in older patients be developed?

Table 1: Continued

Area	Question or cohort
Pre-, peri- and postoperative management	16. How does immunosuppression influence the development or progression of coronary artery disease or other inflammation-related illness?
	1. How does aging impact ischemia/reperfusion injury?
	2. What are the best practices for perioperative care (for example, tight glucose control) in older transplant recipients?
	3. What is the optimal approach to pain management in older transplant recipients?
	4. Are exercise interventions beneficial and safe in older transplant recipients?
	5. Does pretransplant exercise improve adherence to an exercise program after transplant?
	6. What are the most effect methods to counsel transplant recipients with respect to exercise?
	7. Should delirium prevention approaches differ between transplant recipients and other postoperative patients?
	8. Can transitional care and skilled nursing care needs be anticipated before a transplant?
Outcomes of transplantation	1. What are acceptable short- and long-term outcomes for older adults?
	2. Can comprehensive geriatric assessments predict outcomes, resource use and cost drivers in older adults? Are these assessments superior to current expert opinion (the 'eyeball test')?
	3. Are there biomarkers of acute kidney injury in the setting of kidney transplantation?
	4. Are postrejection therapy recovery times for T cell numbers and function longer for older patients?
	5. Is the increased risk for infection in older transplant recipients related to changes in immunity, organ physiology, or other factors?
	6. Are there correlations between immune function and other posttransplant outcomes?
	7. How can risk for poorer long-term outcomes be assessed in patients with abnormal ejection fractions or patients who have been revascularized because of coronary artery disease? Can coronary angiograms be graded to assess this risk?
	8. How can poor heart function in renal transplant patients be dissected from the effects of kidney failure?
	9. Does the increased incidence of cancer among older transplant recipients arise from elevated risk or earlier onset?
	10. What mechanisms contribute to the malignancies more common in transplant recipients?
	11. At what ages is cancer screening in transplant recipients reasonable?
	12. Are older transplant recipients more susceptible to declines in health-related quality of life (HRQOL) with age? Are current instruments accurate for assessing pre- and posttransplant HRQOL in older recipients?
	13. What strategies are needed to optimize posttransplant HRQOL in older patients?
	14. Will HRQOL benefits be sustained in less 'ideal' older transplant recipients?
Organ-specific research needs	
Heart	1. Defined characteristics of an acceptable marginal heart, including studies of stored tissues to identify characteristics of hearts that might have been used for transplantation
	2. Improved risk models based on physiological age
	3. Improved benchmarks for utility, attitudes and expectations
	4. Improved use of mechanical device support as a bridge to transplant, as well as a definition of conditions under which mechanical device support should be the final goal
Kidney	1. Better understanding of the relationships among physiologic decline, early allograft function and long-term posttransplant outcomes
	2. Comparative effectiveness studies of dialysis versus transplantation, specific to older adults and informed by novel risk prediction metrics, such as functional status and frailty
	3. Studies of early risk and long-term outcomes in older living donors
	4. Continued study and discussion of the best allocation policies for older transplant candidates
	5. Dissemination studies of evidence-based practices regarding expanded criteria donors
Lung	1. Studies to understand the referral bias for lung transplantation
	2. Studies on the use of biomarkers to stratify older lung recipients according to risk
	3. Studies on how medication management, bronchoscopic surveillance and monitoring for acute rejection, and rehabilitation differ by age
	4. Studies of palliative care in the management of organ transplant candidates and recipients
	5. Better tools to predict, prevent and manage delirium and atrial fibrillation
Liver	1. Understanding of how hepatic carcinoma, an indication for liver transplant, affects risk for posttransplantation malignancy and postcirrhotic outcomes
	2. Understanding of how age affects the risk for morbidity and mortality of living donors
	3. Studies on the value of adding geriatric assessments and related tools to risk models such as MELD

Table 1: Continued

Area	Question or cohort
	4. A panel of objective clinical, biochemical, imaging, genomic, proteomic and other biomarkers to define a risk index
	5. Objective measures, including function, muscle mass, bone density and fat in liver and muscle to understand the feasibility and efficacy of intervention studies to mitigate age-associated effects and improve long-term outcomes
	6. Improved donor–recipient matching to minimize waste
	7. Assessments of tolerance, immune activation and immune surveillance in predicting outcomes before and after transplantation
Datasets and Cohorts	
Organ transplantation	• SRTR (all organs)
	• Transplant center-specific biorepositories (all organs)
	• Intermacs, an LVAD registry (heart)
	• International Society of Heart and Lung Transplantation (ISHLT) Registry (heart, lung)
	• Clinical Trials in Organ Transplantation (CTOT, heart, kidney, liver)
	• Lung Transplant Outcomes Group (lung)
	• Genomics of Chronic Allograft Rejection (GoCAR, kidney)
	• The Long-Term Deterioration of Kidney Allograft Function (DeKAF, kidney)
	• The Long-Term Deterioration of Kidney Allograft Function Genomics (DeKAF Genomics, kidney)
	• Adult to Adult Living Donor Liver Transplantation study (A2ALL, liver)
	• NIDDK Liver Transplant Database (liver)
Geriatric	• Medicare Advantage
	• Nurses Health Study
	• Physicians Health Study
	• National Institute on Aging longitudinal cohorts (for example, Health and Retirement Study, Baltimore Longitudinal Study on Aging, Multi-Ethnic Study of Atherosclerosis)
Genomics/biomarkers	Genomics of Transplantation Cooperative Research Program
Quality of Life	Database on Health-Related Quality of Life (Singer)

postoperative outcomes and in stratifying candidates based on anticipated risk.

Workshop speakers were as follows:

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