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Seminars in Nephrology: Invited article Apolipoprotein L1 gene effects on kidney transplantation

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Abstract

The pathogenesis of many common etiologies of nephropathy has been informed by recent molecular genetics breakthroughs. It is now apparent that the ethnic disparity in risk for non-diabetic chronic kidney disease between African Americans and European Americans is largely explained by variation in the apolipoprotein L1 gene (*APOL1*). Presence of two *APOL1* renal-risk variants markedly increases an individual's risk for kidney disease. In transplantation, kidneys from deceased African Americans with two *APOL1* renal-risk variants have shorter survival intervals after engraftment, regardless of the ethnicity of the recipient. Precision medicine will transform the clinical practice of nephrology and kidney transplantation, and play an important role in the allocation of kidneys from deceased and living kidney donors with recent African ancestry. This article reviews existing data on *APOL1* in deceased- and living-donor kidney transplantation. It considers the impact of including *APOL1* genotyping in decisions on the allocation and discard of deceased-donor kidneys, as well as the selection of living donors.

Keywords

African American; allocation; *APOL1*; chronic kidney disease; kidney transplantation; organ donation

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Introduction

Outcomes in patients with end-stage kidney disease (ESKD) are optimized by receipt of a kidney transplant.¹ Longer patient survival and improved quality of life follow kidney transplantation compared to all currently available dialytic therapies, and at far lower cost. The demand for deceased-donor kidneys continues to outpace their availability and many individuals lack suitable live donors. These realities limit the pool of individuals with ESKD who ultimately undergo kidney transplantation. In the past, some older candidates received deceased-donor kidney transplants from healthy young donors. This approach had the potential to lead to recipient death with a functioning allograft. That practice failed to optimally match likelihoods of anticipated transplant recipient survival with allograft quality as a surrogate for duration of allograft function. However, recent changes in policy in the organ allocation system in the United States have addressed this issue.

To maximize years of allograft function, the Kidney Donor Risk Index (KDRI) was implemented in late 2014.² Deceased organ donors now receive a KDRI score based on ten clinical parameters to estimate quality of their kidneys as allografts. The KDRI score is then compared to the median KDRI score for all deceased kidney donors in the prior available calendar year to derive the Kidney Donor Profile Index (KDPI) that ranks an individual donor's quality relative to that of other kidney donors.³ The KDPI score for a donor is used in an attempt to allocate kidneys from high-quality donors to the healthiest recipients, thereby striving to optimize long-term outcomes after deceased-donor kidney transplantation. Highly sensitized potential recipients and those with the longest intervals on dialysis also receive priority in this new allocation system.

Additional improvements in outcomes after kidney transplantation will likely result from applying recent breakthroughs in molecular genetics to clinical practice. These advances are clarifying the causes of many common forms of complex kidney disease. It is becoming increasingly possible to determine risks of subsequent kidney failure in patients based upon genotypic information. These data can improve kidney transplantation outcomes, whereby genetic information from donors may inform likelihoods for prolonged allograft survival. Risk variants in the genes influencing the metabolism of calcineurin inhibitors (pharmacogenomic effects) and genes contributing to renal fibrosis (*SHROOM3*) have already been linked to outcomes after kidney transplantation.⁴⁻⁷ In this review, we address the impact of renal-risk variants in the apolipoprotein L1 gene (*APOL1*) on outcomes after transplantation; effects on deceased- and living-donor transplantation are considered.

***APOL1* and non-diabetic chronic kidney disease**

As discussed elsewhere in this issue, up to 70% of African Americans with non-diabetic ESKD, 40% of all cases of ESKD in this population, are attributable to variants in *APOL1*.⁸⁻¹⁰ There are two renal-risk variants, G1 and G2; about 39% of the general population of African Americans have one renal-risk variant and about 13% carry two renal-risk variants. The increased risk for ESKD is associated with any of the three genotypes with two-renal-risk variants: G1/G1, G1/G2, or G2/G2. The spectrum of *APOL1*-associated chronic kidney disease (CKD) includes related forms of glomerulosclerosis, such as focal

segmental glomerulosclerosis (FSGS), HIV-associated nephropathy (HIVAN; and other forms of FSGS-collapsing variant), severe lupus nephritis, sickle cell nephropathy, and focal global glomerulosclerosis (FGGS) with renal interstitial and vascular changes, a disorder that had long been incorrectly attributed to the effects of systemic hypertension.^{11–13}

APOL1 renal-risk variants are virtually limited to individuals with recent African ancestry and explain most of the excess risk for non-diabetic ESKD in African Americans relative to European Americans.

***APOL1* effects on outcomes in deceased donor kidney transplantation**

There has been a critical need to assess the effects of *APOL1* renal-risk variants in transplantation because it had long been recognized that renal allografts from deceased African American donors frequently functioned for shorter intervals than those from donors of other racial/ethnic groups.¹⁴ The initial studies evaluating effects of donor or recipient *APOL1* renal-risk variants on outcomes of renal allografts from African American donors were retrospective reports from one or two transplant centers.^{15, 16} Subsequent multi-center studies of recipients found similar results, but no study has yet simultaneously evaluated donor and recipient *APOL1* genotypes for potential interactive effects.^{17, 18} Table 1 lists *APOL1* association studies with outcomes after deceased-donor kidney transplantation.

Reeves-Daniel *et al.* performed the first study to assess the effects of deceased-donor *APOL1* genotypes on renal-transplantation outcomes.¹⁵ This single-center study included 106 African American kidney donors (136 transplantations). Twenty-two of the 136 transplantations were from donors with two *APOL1* renal-risk variants, approximating the 13% frequency of persons with high-risk *APOL1* genotypes in the general African American population. Significantly shorter renal allograft survivals were observed for kidneys from donors with high-risk *APOL1* genotypes *versus* low-risk genotypes (zero or one renal-risk variant). In the fully-adjusted multivariate analysis, *APOL1* renal-risk genotypes displayed a hazard ratio (HR) for shorter renal allograft survival of 3.84 ($p=0.008$), compared to 1.52 ($p=0.03$) and 1.06 ($p=0.057$) for degree of HLA matching and duration of cold ischemia time, respectively. In this small study, panel reactive antibodies and recipient age were not significant predictors of renal allograft survival. Curves reflecting allograft survival began to separate widely within the initial year after engraftment; allograft failures were observed significantly earlier for kidneys from donors with two *APOL1* renal-risk variants. This report was unique with its inclusion of renal histology of the failed allografts from donors with known *APOL1* genotypes; 75% of renal lesions in failed kidney transplants from two-*APOL1*-renal-risk-variant donors revealed typical *APOL1*-associated lesions, in contrast to only 12% of the kidneys from donors with zero/one renal-risk variant.

Recipients of the 136 kidneys from deceased African American donors in the Reeves-Daniel *et al.* report were nearly evenly divided between African Americans and European Americans. Allograft survivals were similar in recipients, regardless of their ethnicity. This finding suggested that recipient *APOL1* genotypes were unlikely to have influenced outcomes after transplantation because European Americans generally lack *APOL1* renal-risk alleles. Furthermore, recipient-derived factors generated by *APOL1* renal-risk genotypes (especially circulating *APOL1* protein) were unlikely to be associated with risk for allograft

failure and, by extrapolation, native-kidney disease. Instead, expression of *APOL1* in renal cells was more likely associated with the development of native-kidney disease and post-transplant allograft failure.

Two larger multi-center retrospective studies subsequently replicated the findings. A total of 675 kidney transplants from 368 African American deceased donors were evaluated using DNA provided by the University of Alabama at Birmingham (UAB) and Wake Forest Schools of Medicine; 55 transplant centers were involved.¹⁷ The study sample was later expanded to 1,153 deceased-donor kidney transplants from 624 African American donors by including DNA samples from the Emory University School of Medicine and the Genomics of Deterioration of Kidney Allograft Function Study (DeKAF Genomics); the engraftments were performed at 113 U.S. centers.¹⁸ Results of these two studies were consistent: high-risk *APOL1* genotypes in deceased donors were strongly associated with shorter allograft survival. In addition, results were consistent in analyses of the kidney transplantations performed at only the more recently participating centers. For example, the HR for time to allograft failure based on *APOL1* genotypes limited to the 221 kidneys from UAB was 2.71 ($p=0.06$) and for the 478 kidneys from Emory and DeKAF Genomics the HR was 2.00 ($p=0.03$). In the full sample of 1,153 kidneys, the HR for *APOL1* genotype was 2.05 ($p=0.003$) in a multivariate analysis. Additional significant predictors of time to allograft failure for kidneys from deceased African American donors included increasing donor age and increasing recipient age. Thus, the effect of donor *APOL1* genotypes on allograft survival was reproducible and robust. Interaction between donor age and *APOL1* genotype was further assessed for effects on renal allograft survival. This analysis indicated that allograft survival was longest for recipients of African American kidneys from younger donors, independent of the donor *APOL1* genotypes.

Lee *et al.* directly assessed the effects of *APOL1* genotypes in African American recipients of kidneys from deceased donors.¹⁶ Of the 119 recipients at two centers, 48.7% had two *APOL1* renal-risk variants, reflecting the expected enrichment of these genotypes in African Americans with ESKD. In contrast to the effects of donor *APOL1* genotypes, recipient *APOL1* genotypes failed to impact outcomes after transplantation.

***APOL1* effects on outcomes in deceased-donor liver transplantation**

APOL1 genotypes have been determined in deceased African American liver donors for effects on outcomes after hepatic transplantation.¹⁹ This analysis was important because hepatocytes transfected with *APOL1* renal-risk variants *in vitro* demonstrated increased cellular toxicity and fibrosis, relative to cells transfected with the G0 (non-risk) allele.²⁰ In contrast to kidney transplantation, *APOL1* renal-risk variants did not adversely impact outcomes after liver transplantation. Although 639 liver transplantations were included and no trend toward statistical significance was observed, there remains the possibility that the analysis was underpowered. As such, a larger study is necessary to confirm these findings.

The future: rapid *APOL1* genotyping in deceased-donor kidney transplantation, effects on kidney allocation and organ discard

Kidneys from donors with higher KDPI scores are more likely to be discarded, based upon their projected poor quality. Computation of KDRI involves 10 parameters for the deceased donor, one of which is race (African American *versus* all others). Inclusion of this characteristic was based upon the historically worse outcomes of kidneys transplanted from deceased African American donors, relative to that of kidneys from European Americans and donors of other ethnic groups. KDRI was developed prior to identification of *APOL1* as the major cause of non-diabetic kidney disease in populations with recent African ancestry. Relative to a causative gene variant (or biologic cause), self-reported ethnicity is a far less precise predictor of risk for diseases that display ethnic variation.

Thirteen percent of African Americans in the general population possess two *APOL1* renal-risk variants and are at heightened risk for nephropathy, the remaining 87% are at lower risk.⁸ Potential deceased kidney donors are evaluated for evidence of kidney disease; those with signs of kidney disease are excluded. Therefore, fewer than 13% of potential African American deceased kidney donors would be expected to harbor high-risk *APOL1* genotypes because those with clinically apparent renal disease will have been excluded. The current KDRI equation deems all African American donors to be at equivalent higher risk than donors of other races because *APOL1* genotypes are not considered.

Julian *et al.* proposed that replacing the African American race variable with a weighting for *APOL1* genotypes would more accurately predict the quality of kidneys from deceased African American donors.²¹ To compare the potential effect of this modification of the equation on the KDRI score, and the derived KDPI, a 10-fold cross-validation approach was applied to estimate the contribution of *APOL1* risk genotypes to a revised KDRI in 1,149 recipients of kidneys from 622 deceased African Americans. Of these donors, 93 had high-risk *APOL1* genotypes (two renal-risk variants; 170 allografts) and 529 donors had low-risk genotypes (zero or one renal-risk variant; 979 allografts). Cross-validation was repeated 10,000 times to generate the distribution of effect size. The average effect size was then used to derive a revised KDRI weighting. The weighting for *APOL1* high-risk genotypes corresponded to hazard ratio of 1.51 *versus* 1.20 for African American race in the current KDRI. The mean KDRI for all donors calculated using the current equation was 1.4930, whereas the mean revised KDRI was 1.2518 for donors with low-risk *APOL1* genotypes *versus* 1.8527 for donors with high-risk genotypes. The original and revised KDRI had comparable survival prediction errors and c-indices at one, three, and five years post-engraftment, with substantially different effects on the KDPI-based kidney allocation system. The investigators concluded that replacing race with *APOL1* genotype in the KDRI would more accurately quantitate risk associated with kidneys from African American donors, without diminishing the accuracy of predicted outcomes, and improve the match between donor quality and recipient need on which KDPI-based allocation was built. Defining donor risk by *APOL1* genotypes instead of race would likely reduce organ discard rates for low-risk donors and could support allocation of kidneys from high-risk donors to recipients for whom an organ from an expanded-criteria donor in the prior allocation system

would be appropriate. It is critical that a prospective national study be performed with an adequate number of kidneys from African American donors to define the role of *APOL1* genotyping in donors and recipients of those kidneys, to improve outcomes and reduce discard rates.

Motivation for living kidney donation

More than 100,000 patients are currently waiting for a kidney transplant, yet only about 11,000 receive an allograft each year.²² Annual death rates among waitlist registrants range from 5 to 15%, and many die before receiving a kidney.²² As such, patients often turn to family and friends to be living donors on their behalf. In addition to eliminating the need to wait, live-donor kidney transplants last twice as long and more than double the remaining interval for patient survival compared to deceased-donor renal allografts (https://optn.transplant.hrsa.gov/PublicComment/pubcommentPropSurveyExhibit_37.pdf).²³ In fact, even with high-risk transplantation, such as for HLA-incompatible recipients, live-donor transplantation improved long-term survival benefit compared with dialysis or remaining on the list waiting for deceased-donor kidney transplantation.²⁴

Not surprisingly, increases in live donation have been stimulated by the organ shortage, superior outcomes with live-donor kidneys, and the advent of laparoscopic donor nephrectomy. Every year in the United States about 6,000 healthy individuals undergo live-donor nephrectomy.²² Living kidney donors derive no medical benefit from donation and, as such, understanding long-term health risks post-donation is of paramount importance.

Long-term post-donation health risks among living kidney donors

Assessing long-term post-donation health risks among living kidney donors has proven to be challenging. To date, the transplant community has fallen short of maintaining longitudinal medical records for living kidney donors. In fact, the Organ Procurement and Transplantation Network (OPTN), the entity responsible for tracking transplant donors and recipients, did not start collecting social security numbers of living kidney donors until 1994. This practice precluded linkages with the Social Security Master Death file (SSMDF) or Centers for Medicare/Medicaid Services (CMS) and, therefore, ascertainment of death and/or development of ESKD after donation. Moreover, the OPTN did not require transplant centers to obtain follow-up data until 2000, and centers are currently required to follow donors for only two years post-donation.²³ This limited follow-up time is insufficient to assess life-time risk for development of comorbid diseases, such as diabetes, hypertension, and CKD/ESKD. Moreover, ascertainment of life-time health risk is further complicated by inconsistencies in contacts of living donors with healthcare organizations. For example, living donors are often not followed at the transplant center where the nephrectomy was performed, and currently there is no national system for tracking these donors over their lifetimes.

In the absence of a longitudinal cohort of living kidney donors, ascertainment of long-term health risks has been relegated to single-center studies and national retrospective studies

using data from administrative claims to assess outcomes post-donation. To date, seven such studies have been performed:

- Ibrahim *et al.* 2009²⁵ This is the largest cohort study (n=3,698) of live donors to date and is widely cited as evidence that “living kidney donation is safe.” No difference was found for donor lifespan compared to life-table estimates for the general population. ESKD developed in 11 donors (3 non-European Americans) for a rate of 180 cases/million/year, lower than the national rate of 268 cases/million/year. The study was limited due to inclusion of few African Americans (<1%) and lack of an appropriate comparison group.
- Segev *et al.* 2010²⁶ OPTN data were linked to the SSDMF to determine post-donation mortality in an ethnically diverse, national cohort of 80,347 persons who donated a kidney between 1994 and 2009. As a registry study, the only assessed outcome was death. With a median follow-up of six years, African American donors had a 30% higher adjusted hazard of death compared with European American donors. However, the study was limited by the lack of non-donor controls. As such, it was not possible to determine whether the observed ethnic differences in mortality were attributable to complications after donor nephrectomy.
- Lentine *et al.* 2010²⁷ OPTN data from 4,650 donors were linked to private health insurer administrative claims. Male gender, older age, and African American race were associated with higher risk of post-donation CKD and ESKD. However, in the general population, African Americans have higher rates of hypertension and CKD/ESKD. Therefore, in the absence of non-donor controls, attributing disease risk to living donation was not possible.
- Cherikh *et al.* 2011²⁸ The OPTN linked their data to CMS databases to identify donors who later developed ESKD. Of 56,458 donors (nephrectomy between 1987 and 2003), 126 developed ESKD, and the risk of post-donation ESKD was 4.92-fold higher in African Americans compared with European Americans (95% CI 2.79–8.66, p<0.001). This trend of higher risk among African American donors is consistent with the findings in other studies of claims/registry data. However, the observation is similarly limited, in that lack of an appropriate control group renders assignment of the increased risk to donation impossible.
- Muzaale *et al.* 2014²⁹ The investigators matched a cohort of 96,217 living kidney donors using the Scientific Registry of Transplant Recipients (SRTR) to healthy non-donors in the National Health and Nutrition Examination Study III (NHANES III). Data were further linked to the CMS database to ascertain cumulative incidence rates of ESKD. ESKD attributable to live-donation developed in 51 per 10,000 for African American donors *versus* 23 per 10,000 in European American donors (p<0.001).
- Grams *et al.* 2015³⁰ This study used risk associations from a meta-analysis of seven general-population cohorts to project the estimated long-term incidence of ESKD among living donor candidates (non-donor controls). The authors then

compared 15-year projections with the observed risk among actual living kidney donors. The observed risk of ESKD among living kidney donors was 3- to 5-fold higher than the projected risk without donation.

- Ibrahim *et al.* 2016³¹ This single-center study of 3,956 European American donors found that ESKD after donation was uncommon (28 donors affected) and highly correlated with post-donation development of diabetes and hypertension. The study was limited by the lack of African American donors and non-donor controls.

While informative, these studies have significant limitations and highlight current gaps in our understanding of the risks for live-donor nephrectomy, particularly among African Americans. Current methods for assessing living-donor long-term health risks are imprecise. Improving prediction of long-term health outcomes among living kidney donors through novel methodologies is crucial. Genetic determinants of long-term health risks may prove to be one such method.

Is the greater risk of CKD/ESKD in African Americans after donor nephrectomy related to *APOL1* genotype?

Genotyping of potential living kidney donors for *APOL1* renal-risk variants has been incorporated in the standard evaluation of potential living kidney donors at some medical centers.³²

However, to the best of our knowledge, no cohort study has assessed potential associations between this genetic variant and renal disease after living-donor nephrectomy. Furthermore, even for centers that have banked DNA from living kidney donors, the absence of long-term follow-up data renders assessment of any potential effect of *APOL1* genotype on renal function after donation difficult.

To date, the literature is limited to two case reports. One reported an Afro-Caribbean man who donated a kidney to his 21-year-old identical twin brother with ESKD of undocumented origin.³³ Immunosuppressive therapy after engraftment was limited to a short course of glucocorticoids. Six months after transplantation, the recipient developed proteinuria 1.2 g/d with severe hypertension and eGFR 100 mL/min/1.73 m²; a kidney biopsy was non-diagnostic. Two years later, his eGFR had decreased to 43 mL/min/1.73 m² with persistent proteinuria and a biopsy revealed FSGS. He was treated with high-dose prednisone for four months but progressed to ESKD five years after transplantation. The donor initially developed proteinuria five years after nephrectomy. Proteinuria progressed to 2.5 g/d two years later; however, a kidney biopsy was not performed. Genotyping revealed that both men had two *APOL1* renal-risk variants as G1/G2 heterozygotes. In a second report, a 42-year-old African American man donated a kidney to a non-relative and developed nephrotic syndrome with proteinuria 18 g/d and serum creatinine concentration 1.9 mg/dl four years after donation.³⁴ Kidney biopsy revealed FSGS (collapsing variant) and C1q deposition. He failed to respond to glucocorticoid treatment and progressive renal failure ensued. Genetic testing initially revealed two E1 risk haplotypes in the non-muscle myosin heavy chain 9 gene (*MYH9*); he was later found to have two *APOL1* renal-risk variants.

Testing potential living kidney donors for *APOL1* genotype

Performance of *APOL1* genotyping in the setting of living-donor kidney transplantation has potential benefits and shortcomings (Table 2). One rationale for *APOL1* genotyping is that discovery of the presence of two renal-risk variants with the increased risk for CKD/ESKD will be a significant factor in counseling a prospective donor about long-term medical risks of nephrectomy. The risk for kidney disease associated with two renal-risk variants will likely be highest for young adults with life expectancies longer than those for middle-age or older donors. For the latter, they have avoided kidney disease for substantial portions of their expected lifetimes and face shorter futures for development of disease. A major confounding factor in counseling prospective donors and recipients is the lack of certainty for *APOL1* genotype to predict disease risk. Many African Americans with two *APOL1* renal-risk variants do not manifest renal disease.³⁵ Similarly, most allografts from two-renal-risk-variant deceased donors function for extended intervals after engraftment.¹⁸ Identifying modifying factors that interact with genotype to increase risk for CKD would be helpful in this regard.

Individuals deemed to be at risk for future kidney disease based on their *APOL1* genotype may not be considered as candidates for donation, particularly if they present at younger ages. Although the risk for CKD post-donation remains imprecise, healthy middle-aged and older individuals with two *APOL1* renal-risk variants may choose to donate despite knowledge of their risk for subsequent nephropathy. A concern with performing genetic testing as part of the donor evaluation is that at-risk individuals may become anxious about their future health, whether or not they proceed with donor nephrectomy. Donors with two *APOL1* renal-risk variants may also become apprehensive due to potential prospects for a less than optimal outcome for the recipient. They may choose not to donate, in part, for that reason. For individuals with two renal-risk variants who are declined as donors or choose not to donate, they may develop a sense of guilt about not helping a potential recipient with treatment for life-shortening ESKD. However, they should be encouraged to become the “donor champion” and help to identify other potential live donors.

In contrast, individuals with zero or one renal-risk variant may be more inclined to proceed with nephrectomy, due to diminished anxiety about their long-term health and less worry about the risk of early allograft failure for the recipient. In counseling potential donors, the risks should be discussed in absolute as well as relative terms. The perception of substantial *versus* modest degrees of risk will vary between individuals and the circumstances of the relationship with the prospective recipient. In any event, counseling about the risks of donor nephrectomy must be addressed on a case-by-case basis, and should take factors beyond *APOL1* genotype into account. We suggest caution for younger potential donors with high-risk genotypes; here, lack of kidney disease might not equate with future risk. Despite increased risk based on genotypes, some potential donors may choose to proceed with nephrectomy. Individuals with two *APOL1* renal-risk variants should be encouraged to have life-long screenings for kidney disease whether they donate or not. This is particularly important in the presence of a family history of kidney disease.

Additionally, confidentiality of genetic test results must be assured. Any breach in confidentiality could lead to higher costs for health, disability, and life insurance. We note that there are many potential reactions to the receipt of one's own genotype data. In practice, many individuals we treat were pleased when informed of their genetic results, whether they had high- or low-risk genotypes. We previously surveyed relatives of African American and European American patients with ESKD in a non-transplant setting to determine their desire to learn of genetic risk for kidney disease.³⁶ The vast majority of relatives wanted their genetic data even if specific therapies were not yet available. This finding is similar to what we have seen in clinical practice.

From the viewpoint of prospective recipients, learning that donors with zero or one renal-risk variant are not at risk for *APOL1*-associated kidney disease may be comforting. If engraftment ensues in this setting, the recipients may also be relieved that they are not at increased risk for *APOL1*-associated early loss of the allograft. In some cases, prospective recipients may elect to pursue other options for transplantation rather than accepting an allograft from a two-*APOL1*-renal-risk-variant donor. Exclusion of allografts from living donors with two *APOL1* renal-risk variants may reduce access to transplantation for some African American patients with ESKD. African Americans with no living-donor who are listed for deceased-donor kidney transplantation may wait longer than patients of other races because of the differences in blood types compared with those of European Americans who comprise the majority of deceased kidney donors in the United States.

Conclusions

The presence of two *APOL1* renal-risk variants in deceased donors shortens survival of their renal allografts. No study has examined the potential interaction of *APOL1* genotype of the donors, deceased or living, and recipients, or fully accounted for other factors that likely reduce survival rates, including rejection, bacterial or viral infections, recurrent disease, and donor-specific anti-HLA antibodies. We agree with other investigators that adequately powered prospective studies are urgently needed to better define the potential effects of *APOL1* genotypes in kidney transplantation^{37, 38}

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APOL1 associations with outcomes after deceased-donor kidney transplantation, multivariate models

Table 1

Group	Model	Clinical Effect	# Transplants	Hazard Ratio; P-value	Reference
Donors	Recessive	Earlier allograft failure	136	3.84; 0.008	15
Donors	Recessive	Earlier allograft failure	675	2.26; 0.001	17
Donors	Recessive	Earlier allograft failure	1153	2.05; 3.0×10^{-4}	18
Recipients	Recessive	No effect	119	0.96; 0.84	16

Table 2Pros and cons of *APOL1* genotyping in living-donor kidney transplantation

<p>Donor Effects Pros:</p> <ul style="list-style-type: none"> - Potential donors have the right to make the most informed decision about risks of donation. - Individuals with two renal-risk variants who are at increased lifetime risk for CKD (versus African Americans with zero or one variant) could benefit from increased medical surveillance. - Individuals with zero or one renal-risk variant who are at lower lifetime risk for CKD (versus African Americans with two variants) may be more inclined to proceed with donor nephrectomy. - Individuals with zero or one renal-risk variant may have diminished anxiety about their health. - Individuals with zero or one renal-risk variant may worry less about the risk of early allograft failure in the recipient.
<p>Cons:</p> <ul style="list-style-type: none"> - Presence of two renal-risk variants does not universally associate with development of CKD. - Individuals with two renal-risk variants may become anxious about their future health due to a sense of vulnerability, regardless of whether donor nephrectomy is ultimately performed. - Individuals with two renal-risk variants who donate may become apprehensive that the potential benefit of transplantation for the recipient would be less than optimal. - Individuals with two renal-risk variants who do not donate may develop a sense of guilt about not helping the potential recipient with treatment for life-shortening ESKD.
<p>Recipient Effects Pros:</p> <ul style="list-style-type: none"> - Recipients of a kidney from a donor with zero or one renal-risk variant may be comforted that the donor is not at increased risk for subsequent <i>APOL1</i>-associated kidney disease. - Recipients of a kidney from a donor with zero or one renal-risk variant may be relieved that they are not at increased risk for <i>APOL1</i>-associated early loss of the allograft.
<p>Cons:</p> <ul style="list-style-type: none"> - Recipients of a kidney from a donor with two renal-risk variants may be anxious or feel guilty that the donor is at increased risk for subsequent development of <i>APOL1</i>-associated CKD. - Recipients of a kidney from a donor with two renal-risk variants may worry that they are at increased risk for <i>APOL1</i>-associated earlier allograft failure. - Prospective recipients who do not receive a kidney from a potential donor based on genotyping will likely spend more time on the waiting list due to greater difficulty for a match based on race-associated differences in prevalence of HLA and blood types in the current donor pool.