Published in final edited form as:

Curr Opin Nephrol Hypertens. 2020 November ; 29(6): 645–655. doi:10.1097/MNH.0000000000000653.

Apolipoprotein L1: Role in the Evaluation of Kidney Transplant Donors

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Structured Abstract:

Purpose of review: To summarize the current state of evidence regarding the role of apolipoprotein L1 (*APOL1*) genotyping in evaluating donors for kidney transplantation.

Recent findings: African ancestry (AA) is associated with an increased risk of kidney failure following living donation. Moreover, kidney transplants from AA deceased donors have an increased risk of graft failure. Preliminary evidence suggests that *APOL1* genotype may mediate at least a portion of this racial variation, with high-risk *APOL1* genotypes defined by presence of 2 renal risk variants (RRVs). A pilot study 136 AA living donors found that those with *APOL1* high-risk genotypes had lower baseline kidney function and faster rates of kidney function decline after donation. To date, three retrospective studies identified a 2-to-3-times greater risk of allograft failure associated with kidneys from donors with high risk *APOL1* genotype. Active research initiatives seek to address unanswered questions, including reproducibility in large national samples, the role of “second hits” injuries, and impact of recipient genotype, with a goal to build consensus on applications for policy and practice

Summary: As evidence evolves, *APOL1* genotyping may have applications for organ quality scoring in deceased donor kidney allocation, and for the evaluation and selection of living donor candidates.

Keywords

Apolipoprotein L1; Genetics; Kidney failure; Kidney Transplantation; Organ donors

Introduction

Living kidney donation: The variation in donor outcomes based on ancestry

Persons of African Ancestry (AA) have an increased risk of chronic kidney disease (CKD) and end-stage kidney disease (ESKD)¹⁻⁵ and over the last decade, AA has been associated

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Conflicts of interest: K.L.L. is a consultant for CareDx, Inc. and serves on a Sanofi speakers' bureau. RBM has no relevant conflicts of interest to declare.

with increased risk of CKD and ESKD after living kidney donation (Table 1). While review of laboratory values reported to the U.S. Organ Procurement and Transplantation Network (OPTN) registry showed no appreciable differences in estimated glomerular filtration rate (eGFR) among AA compared to white donors within 6 months of donation (2000-2005),⁶ linkage of registry data with administrative billing claims to provide an average of 7.7 years follow-up revealed twice the likelihood of CKD diagnoses (adjusted hazard ratio 95%LCL(aHR)95%UCL, 1.482.32_{3.62}) and more than 3-times the likelihood of CKD stage 3 or higher diagnoses (aHR, 1.373.60_{9.39}) in AA versus white donors. Subsequent work extended these patterns of higher postdonation renal risk in AA versus white donors to older donors in the Medicare population,⁷ and to a broader range of kidney condition diagnoses including proteinuria (5.7% versus 2.6%; aHR, 1.322.27_{3.89}) and nephrotic syndrome (1.3% vs 0.1%; aHR, 2.9715.78_{3.0}).³ By integrating national U.S. donor registry data with kidney transplant candidate registrations, Gibney et al. observed that although AAs composed 12% of U.S. living kidney donors in 1996-2007, they represented 43% of 148 donors listed for kidney transplantation after donation;^{8,9} ESKD also developed earlier after donation. Linkage of OPTN donor registration data with Center for Medicare and Medicaid Services (CMS) ESKD reporting forms found nearly 5-times the rates of postdonation ESKD among AA as white donors (0.423 vs. 0.086 per 1000 years at risk; relative risk (RR), 2.794.92_{8.66}).¹⁰

The importance of “race” in donor candidate risk assessment was quantified in a tool developed as part of the 2017 Kidney Disease: Improving Global Outcomes (KDIGO) “Guideline for the Evaluation and Care for Living donors” evaluation framework to project ESKD incidence based on a candidate’s profile on demographic and health characteristics.¹¹ The risk model, developed by Grams et al. from meta-analysis of data from nearly 5 million healthy persons identified from 7 general population cohorts who are similar to kidney donor candidates, estimates higher ESKD risk (in the absence of donation) among AA individuals (termed “predonation risk”), particularly among young men of AA.¹² For example, for a 40-year-old person with health characteristics similar to those of age-matched kidney donors, the 15-year projected ESKD risk in the absence of donation is 0.24% among men of AA, 0.15% among AA women, 0.06% among white men, and 0.04% among white women.

Perspectives of risk in living donation

Comparisons of living donor subgroups, and of donors to the general population, can provide important perspectives of risk, but the last decade has also brought recognition of the importance of comparing donors to healthy nondonor controls for estimation of donation-attributable risks.¹³ Based on linking data for 96,217 living donors from the U.S. donor registry and healthy participants drawn from National Health and Nutrition Examination Survey (NHANES) III to national ESKD reporting forms, Muzaale *et al.* quantified the cumulative incidence of ESKD at 15 years as 30.8 per 10,000 in donors compared with 3.9 per 10,000 in matched donors (risk attributable to donation of 26.9 per 10,000).¹⁴ AA living donors had the highest absolute risk of ESKD postdonation as well as the highest risk attributable to donation. A tool for individualized prediction of *donation-attributable* risk (i.e., the incremental impact of donation based on demographic and health profile) is not yet available. However, a recent tool that estimates risk if the individual

donates (based on a more limited profile of health factors than the predonation tool¹²) also predicts higher risk in donors of AA.¹⁵

Sources of racial variation in renal risk: The role of *APOL1* renal risk variants

Racial variation in the risk of ESKD in living donors may relate to the incidence of hypertension and diabetes,^{1,7,16} access to health care, and other unmeasured environmental factors. Importantly, it is now recognized that at least a portion of kidney failure previously attributed to hypertensive nephrosclerosis in persons of AA may be genetically-mediated by coding variants in the gene for a secreted lipoprotein, apolipoprotein L1 (*APOL1*). The discovery of the G1 and G2 renal risk variants (RRVs) in the *APOL1* gene in 2010 marked one of the most striking recent developments in nephrology and in precision medicine.^{17,18} Approximately 13% of persons of AA possess 2 *APOL1* RRVs (high-risk genotypes), and another 30-45% have 1 RRV.^{19,20} In 2010, a case-control study from the 1000 Genomes Project first identified correlation of homozygosity or compound heterozygosity for RRVs with than 7-times of odds of ESKD in AA compared with 0 risk alleles (odds ratio (OR), 7.3), while 1 RRV bore modest association with ESKD (OR, 1.26).¹⁷ When recalculated as a relative risk, ESKD risk was more than doubled with the presence of 2 RRVs.²¹ Subsequently, a rapidly evolving literature linked *APOL1* high-risk genotypes with focal segmental glomerulosclerosis (FSGS), HIV-associated nephropathy, proteinuria, reduced eGFR and younger age at dialysis initiation.²²⁻²⁵ Data from case series suggests that insults such as viral infections may provide a “second hit” by inducing inflammation, potentially upregulating *APOL1* gene expression, and leading to podocyte foot process effacement and FSGS.²⁶ Larger studies including data on putative “second hit”, biospecimens and histopathology are needed to define the type and nature of exposures that may modify the impact of *APOL1* genotype on allograft survival.

Variation in transplant recipient outcomes: Donors of AA

Receipt of a kidney transplant from a deceased donor of AA (versus white) is associated with shortened renal allograft survival.²⁷⁻²⁹ Among living donor transplant recipients, transplantation from an AA donor correlates with approximately 25% higher risk of 10-year allograft failure (aHR, 1.15-1.25_{1,37}).²⁹ However, the overall robust benefits of living donor transplant over deceased donor transplant, and especially over dialysis, generally warrant acceptance of a living donor allograft from any motivated, healthy person for whom donation is deemed safe from the perspective of the donor’s risk. In the context of deceased donor transplantation, allografts from AA donors have approximately 20% higher risk of five-year graft loss as organs from white donors (aHR, 1.196), as parameterized in the Kidney Donor Risk Index (KDRI) score used to grade organ quality in the U.S. Kidney Allocation System (KAS).³⁰

APOL1 and deceased donor kidney allograft outcomes: Impact of donor genotype

Data available to date have dominantly supported that *APOL1*-related posttransplant risk is conferred by the donor *APOL1* genotype (i.e., that risk is conferred by the allograft rather than a circulating factor, at least for kidneys). Three retrospective studies identified strong associations between AA deceased donor high-risk *APOL1* genotypes and risk of allograft failure, compared with AA donors having 0 or 1 RRVs (Table 2). In 2011, Reeves-Daniel

examined *APOL1* deceased donor genotypes for 136 transplants at one center, and found that 2 *APOL1* RRVs was associated with nearly 4-times the risk of allograft loss over mean 26.4 months follow-up, compared to 0 or 1 RRVs (aHR, 3.84; P=0.008).³¹ Subsequently, analysis of 675 deceased donor transplants (organ recovery at 2 Organ Procurement Organizations; transplantation at 55 centers) found that 2 *APOL1* RRVs in the deceased donor was associated more than twice the risk of allograft failure over median 2 years follow-up, compared to 0 or 1 RRV (HR, 1.372.26_{3.74}; p=0.001).³² However, there was a center effect with a significantly lower risk of allograft failure (HR 0.35; 0.21-0.58; p<0.01) from one of the two centers. After expansion of the cohort to encompass 1153 deceased donor transplants, a high-risk *APOL1* genotype was associated with twice the graft failure risk, compared to 0 or 1 RRVs, over an average 3 years follow-up (HR, 1.392.05_{3.02}; p=0.0003).³³

By comparison, the role of *recipient APOL1* genotype in transplant outcomes is uncertain. In a study of 119 kidney transplant recipients of AA performed at 2 centers, 48.7% had 2 RRVs. While FSGS or glomerulonephritis as the cause of native kidney disease appeared to be more common in recipients with 2 RRVs, death-censored allograft survival over up to 5 years did not differ in recipients with 2 versus 0 or 1 RRV (aHR 0.610.96_{1.48}; P=0.84).³⁴ This study lacked information on donor genotype, and larger studies seek to examine associations of both donor and recipient genotype on allograft outcomes.³⁵

***APOL1* and living donor outcomes: Impact of donor genotype for donor risk assessment**

Currently, there are no large studies of association of living donor *APOL1* RRVs with recipient graft outcomes after living donor kidney transplantation. Case reports suggest that transplantation of a kidney from a living donor with 2 *APOL1* RRVs can lead to FSGS with early allograft failure in the recipient, and importantly, subsequent ESKD in a previously healthy donor.^{36,37} The greater issue is the decision regarding living donor selection, where donor health outcomes are of course paramount. To simulate application among donor candidates, Locke et al. examined data for healthy persons in the CARDIA cohort, and found that *APOL1* RRVs discriminated racial variation in the risk of low eGFR at 25 years. While persons of AA without RRVs had statistically similar risk of compared to white persons (aHR, 0.801.75_{3.82}; P=0.16), AA persons with 2 RRVs had 5-fold risk (aHR, 2.254.94_{10.86}; P<0.0001).³⁸ A recent pilot study by Doshi et al. provides the first data among a living donor cohort (Table 2).³⁹ In this sample of 136 AA living kidney donors at 2 centers, those with 2 *APOL1* RRVs had lower baseline kidney function and faster rates of decline in eGFR after donation; 11% (2/19) developed ESKD after median 12 year follow-up.³⁹ High-risk *APOL1* genotype did not modify the association between donation and rate of decline in eGFR compared to healthy controls; however, because individuals with 2 RRVs appear to have lower eGFR post-donation and faster decline in eGFR after donation, they may reach ESKD sooner than if they had not donated.

Considerations for applications of *APOL1* genotyping in current practice

To evaluate the state of evidence and applications for transplantation practice, the American Society of Transplantation (AST) convened an Expert Consent Conference in December 2015, and the consensus statement was published in the *American Journal of Transplantation*

in December 2016.⁴⁰ With regard to deceased donor transplantation, the AST consensus group deemed that it was premature, in the absence of nationwide data, to integrate *APOL1* RRVs into algorithms for deceased donor kidney allocation, acceptance criteria for deceased donor organs, or recipient informed consent. The supporting rationale includes: 1) observations that despite the relative risk increase in the non-transplant setting, absolute risk remains low; 2) uncertainty regarding whether a ‘second hit’ is necessary for kidney injury associated with *APOL1* RRVs, and the nature and modifiability of such events; and 3) concern for promoting non-utilization (“discard”) of kidneys that may be appropriately used like other non-ideal kidneys. The work group encouraged more research such as generation of data from large national consortia to help clarify these questions. Subsequently, a pilot study using data from 622 deceased AA donors suggested that replacing “donor race” with *APOL1* genotype in KDRI better defines risk associated with kidneys transplanted from these donor and substantially improves KDRI score for 85–90% of the kidneys offered from AA donors.⁴¹ Finally, as donor populations continue to be studied, additional genes that impact allograft failure have been identified and may operate independently or by interacting with *APOL1* but need further study to independently validate their role.²⁰

In contrast to deceased donation policy, application of *APOL1* genotyping to living donor evaluation can be elected at the program level. With the availability of CLIA-certified testing in 2011, some transplant programs began to perform *APOL1* genotyping to evaluate AA living donor candidates and to use this information in the donor selection and counseling processes, based on extrapolation from other populations.²¹ While the outcome of the living donor allograft is of concern to the donor, recipient and transplant program, there remains considerable uncertainty and controversy regarding use of *APOL1* genotyping in the evaluation and selection of AA living kidney donors.^{42,43} Most living donors do not develop advanced CKD,^{39,40,44,45} and excluding individuals from donation based solely on *APOL1* genotyping may have the unintended consequence of worsening disparities in access to living donor kidney transplantation among persons of AA.⁴⁶ The 2017 KDIGO living donor guideline recommends informing AA donor candidates that having 2 *APOL1* RRVs increases the lifetime risk of kidney failure but that the precise kidney failure risk for an affected individual after donation cannot currently be quantified.¹¹ The guideline also emphasizes the need for ongoing research to define the role of *APOL1* genotyping in the living donor candidate evaluation.

An approach to living donor candidate evaluation at this time, grounded on the KDIGO quantitative risk framework,¹¹ is summarized in Table 3. Under this framework, decision-making is guided by comparing the donor candidate’s predicted risk of ESKD to the transplant program’s acceptable risk threshold, where the latter is defined as the upper limit of acceptable risk established by a program for donor candidate selection. When a living donor candidate’s estimated risk is above the acceptable threshold, the transplant program is justified in declining the candidate and can ground its decision in a quantitative framework. When a donor candidate’s estimated risk is below the acceptable risk threshold, the transplant program should accept a donor candidate, and it should be the candidate’s decision whether to proceed with living kidney donation after being informed and understanding the risks. However, the guideline notes areas of uncertainty, including in the context of younger age, and that familial and genetic risk are not captured in the current tool.

While the impact of high-risk *APOL1* genotype on outcomes after donation is not yet defined, extrapolating from general populations,^{17,18} estimated risk could be considered higher or lower based on genotype. It is important to note that rather than assuming that knowing *APOL1* genotype will only serve to exclude donor candidates, the information can have a positive effect on the donation decision. Identification low-risk genotype could suggest lower than average risk for the individual of AA, and perhaps support proceeding with caution in a candidate with borderline risk based on their demographic and clinical profile (Figure 1). Notably, approximately 8 or 9 in 10 candidates are expected to have low-risk *APOL1* genotypes.³⁹ If donor *APOL1* genotyping is adopted, center protocols should include education for candidates on the available evidence and its limitations, and involve candidates in shared-decision making regarding the decision to test and the potential implications of results.

To define the role of *APOL1* genotyping in deceased and living donor kidney transplantation, large national initiatives such as the National Institutes of Health (NIH) sponsored *APOL1*-Long Term Outcomes (APOLLO) study and the Living Donor Extended Time Outcomes (LETO) study have been launched.³⁵ APOLLO seeks to characterize donor and recipient *APOL1* genotypes in 2,614 deceased donor-recipient pairs recruited prospectively across the country, wherein eligibility is defined by donor AA, presence of next of kin authorization for research, and recipient consent (regardless of recipient ancestry). APOLLO will also examine outcomes in living-kidney donor-recipient pairs and unpaired deceased-donor kidneys. LETO will retrospectively assess kidney function and proteinuria in AA living kidney donors who donated ~15-20 years ago, and also assess graft outcomes in their recipients, based on *APOL1* genotype. Combination of well-powered, nationally representative data from APOLLO and rapid genotyping should inform whether *APOL1* genotype can refine allograft quality scoring in the U.S. KAS. While recruitment for these studies began in 2019 and 2020 respectively, outcomes will not be available for approximately five years. Thus, particularly in the case of living donor evaluation, transplant programs need to establish positions on use of genotyping in current practice, which can be modified based on emerging evidence.

Stakeholder opinions and consensus-building

Recently, Gordon et al. performed semi-structured interviews of 23 donors and found that 87% reported they would have wanted to undergo *APOL1* genotyping before donation, although 61% indicated they would have wanted to donate even if they had 2 RRVs.⁴⁷ Participants expressed an array of concerns related to the testing and implications, including related to their own health, risks of discrimination related to testing, and recipient outcomes. The investigators also surveyed physicians using contact information from U.S. transplant and professional societies.⁴⁸ Among 383 respondents, most believed that *APOL1* genotyping can help AA living donor candidates make more informed donation decisions (87%), and that the addition of *APOL1* testing provides better clinical information about eligibility for donation than existing evaluation approaches (74%). Among respondents who evaluate living donors (n=345), while a minority reported using *APOL1* testing routinely (4%) or on a case-by-case basis (14%), 63% indicated they would definitely or probably begin or continue using *APOL1* testing in the next year. As scientific evidence evolves,

consensus-building efforts across stakeholders regarding what potential donors should be told about *APOL1* testing, how test results should be used to determine suitability for donation, if and when recipients should have access to results, and how clinical policy regarding *APOL1* testing should be established, are ongoing.^{49,50}

Conclusions

AA is associated with increased risk of ESKD in living donors, and kidney transplants from AA deceased donors have increased risk of graft failure compared to organs from non-AA donors. Preliminary evidence suggests that *APOL1* genotype may mediate at least a portion of this racial variation. Active research initiatives seek to address unanswered questions, including reproducibility in large national samples, the role of “second hits” and impact of recipient genotype, and to build consensus on applications for policy and practice. Pending more evidence, the incorporation of *APOL1* genotyping as part of the comprehensive risk of assessment of living donor candidates within a shared decision-making framework may not be uniform but should be discussed in the context of current data.

Acknowledgments

Financial support and sponsorship: K.L.L. and R.B.M receive research funding related to *APOL1* in transplantation from the National Institutes of Health (U01DK116042 and R01DK120551). K.L.L. is supported by the Mid-America Transplant/Jane A. Beckman Endowed Chair in Transplantation, and receives *APOL1*-related research funding from the Mid-America Transplant Foundation. R.B.M. is supported by research funds from Nebraska Medicine.

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Key Points

- African ancestry (AA) is associated with increased risk of kidney failure after living donation, and apolipoprotein L1 (*APOL1*) genotyping holds promise for refining risk assessment of AA living donor candidates.
- The presence of 2 *APOL1* renal risk variants (RRVs) in an AA deceased donor has been associated with higher rates of recipient allograft failure in several cohort studies; national generalizability is being examined in a prospective study funded by the National Institutes of Health.
- The presence of 2 *APOL1* RRVs is not deterministic for living donor kidney failure or recipient allograft failure, and the role of additional injuries or “hits” is also under being examined in the NIH study.
- Emerging research on *APOL1* in donation and transplantation has potential to impact living donor evaluation guidelines and organ quality scoring in deceased donor allocation policy.

Figure 1.

Example of application of *APOL1* genotyping with integrated risk projection tools in the evaluation of a young AA living donor candidate. “Predonation” risk refers to risk in the absence of donation. A tool for estimating projected 15-year and lifetime ESKD risk, based on 10 demographic (“race”, age, sex) and health factors, was developed by Grams et al.¹² Projected postdonation risk can be estimated by multiplying by the best available estimate for donation attributable risk (e.g. Grams et al report a multiple of 3.5 to 5.3), or by using a postdonation tool developed with a more limited set of five factors.¹⁵ Identification low-risk *APOL1* genotype could suggest lower than average risk for the AA candidate.

Table 1. Summary of studies of associations of African ancestry with renal outcomes in living kidney donors

Reference	Data source/design	Racial composition of sample/representation of AA LKD	Outcome, measures and follow-up	Risk perspective	Findings
Gibney et al, <i>Transplantation</i> 2007 ⁸	• Linkage of OPTN LKD registry (1993–2005) and transplant waitlist registration data (1993–2005)	• 8,889 LKD: 14% AA and 68% white	• Transplant waitlist registrations among prior LKD as a measure of ESKD	• Between donors	<ul style="list-style-type: none"> • 102 LKD waitlisted for transplant, at median 17.6 yr postdonation • Among listed LKD, 44% were AA (compared with 14% total AA donors, $P<0.0001$) and 40% were white (compared with 14% total AA donors, $P<0.0001$) • ESKD identified in 11 LKD, at an average of 22.5±10.4 yr (180 cases PMPY) • While only 45 (1.2%) of full LKD cohort were non-white, 3 of 11 (27.3%) LKDs who developed ESRD were non-white
Ibrahim et al, <i>N Engl J Med</i> 2009 ⁵¹	• Cohort study of LKD at one center in Minnesota, USA (1963–2007)	• 3,698 LKD: 98.8% white	• ESKD requiring dialysis or transplantation based on report of the LKD or recipient	• Between donors	<ul style="list-style-type: none"> • Overall, CKD reported in 5.2% at 5 yr • Adjusted CKD risk twice as likely among AA (aHR 2.32, $P<0.001$) or Hispanic (aHR 1.90, $P<0.001$) compared to white LKD • CKD stage 3 higher in AA (aHR 3.60, $P=0.009$) or Hispanic (aHR 4.2, $P=0.006$) vs white LKD
Lentine et al, <i>N Engl J Med</i> 2010 ¹	• Linkage of OPTN LKD registry (1987–2007) with administrative billing claims from a private health insurer (2000–2007 claims)	• 4,650 LKD: 13.1% AA, 8.2% Hispanic, and 76.3% white	• CKD diagnosis over median 7.7 yr follow-up	• Between donors	<ul style="list-style-type: none"> • ESKD significantly higher in AA compared with white LKD: 0.423 vs. 0.086 per 1000 years at risk (RR 4.92, $P<0.05$). • ESKD in LKD did not exceed national reports for general US population (0.998 and 0.273 per 1000 for AA and white Americans, respectively)
Cherikh et al, <i>Am J Transplant</i> 2011 ¹⁰	• Linkage of OPTN LKD registry (1987–2003) and national renal replacement treatment records (1987–2009)	• 56,458 LKD: 13% AA and 71% white	• ESKD defined by CMS Medical Evidence Form 2728	• Between donors	<ul style="list-style-type: none"> • ESKD in LKD did not exceed national reports for general US population (0.998 and 0.273 per 1000 for AA and white Americans, respectively)
Lentine et al, <i>Transplantation</i> 2013 ⁷	• Linkage of OPTN registry data (starting 1987) with administrative billing claims for privately-insured (2000–2007 claims) and Medicare-insured (2000–2008 claims) LKD	<ul style="list-style-type: none"> • 4,650 privately-insured LKD: 13.1% AA and 76.3% • 4,007 Medicare-insured LKD: 8.1% AA, 83.4% white 	<ul style="list-style-type: none"> • CKD and proteinuria diagnoses • Median follow-up 7.7 yr for the privately insured and 6 yr for the Medicare-insured samples 	• Between donors	<ul style="list-style-type: none"> • At 5 yr, CKD reported in 5.2% of the privately-insured and 21.8% of the Medicare-insured LKD, and proteinuria in 2% and 5%, respectively • Adjusted CKD risk higher for AA LKD in the privately-insured (aHR 2.32, $P<0.001$) Medicare (aHR 1.84, $P<0.001$) samples • Adjusted proteinuria risks higher for AA LKD in privately-insured (aHR 2.27, $P<0.05$) and Medicare (aHR 2.44, $P<0.001$) samples
Muzaale et al, <i>JAMA</i> 2014 ¹⁴	• Linkage of OPTN LKD registration (1994–2011) and national renal replacement treatment records	• 96,217 LKD: 12.9% AA and 74.6% white	• ESKD reported in national registries (initiation of maintenance dialysis, waitlist placement or transplant)	• LKD vs healthy nondonors	<ul style="list-style-type: none"> • ESKD higher among LKD compared to healthy nondonors (3.9 vs 30.8 per 10,000 over 15 yr, $P<0.001$) • AA LKD had highest cumulative incidence of ESKD and highest absolute risk increase (donation-attributable increase per 10,000 over 15 yr by "race": 50.8 in AA, 25.9 in Hispanic and 22.9 in white LKD)

Reference	Data source/design	Racial composition of sample/representation of AA LKD	Outcome, measures and follow-up	Risk perspective	Findings
Lentine et al, <i>Transplantation</i> 2015 ³	• Linkage of OPTN registry data with private insurance medical claims, as above ⁵²	• 4,650 LKD: 13.1% AA and 76.3% white	• CKD diagnosis over median 7.7 yr follow-up	• Between donors	<ul style="list-style-type: none"> • At 7 yr, significantly more ($P<0.05$) AA compared to white LKD had renal condition diagnoses: CKD (12.6% vs 5.6%; aHR 2.32), proteinuria (5.7% vs 2.6%; aHR 2.27), nephrotic syndrome, (1.3% vs 0.1%; aHR 15.7), and any renal condition (14.9% vs 9.0%; aHR 1.72)
Massie et al, <i>JASN</i> 2017 ¹⁵	• Linkage of OPTN LKD registry (1987–2014) and national renal replacement treatment records	<ul style="list-style-type: none"> • 133,493 LKD without ESKD: 12.5% AA • 331 LKD with ESKD: 34.4% AA 	• ESKD defined by the CMS Medical Evidence Form 2728	• Between donors	<ul style="list-style-type: none"> • ESKD risk significantly ($P<0.01$) higher with AA (aHR 2.96), male sex (aHR 1.88), higher BMI (aHR 1.61 per 5 kg/m²), and first-degree relationship to recipient (aHR 1.70) • Among non-AA LKD, ESKD risk increased with older age (aHR 1.40 per decade) • Among AA LKD, older age not significantly associated with ESKD risk (HR 0.88, $P=0.3$)
Wainright et al, <i>Am J Transplant</i> 2018 ⁵³	• Linkage of OPTN LKD registry (1994–2016) and national renal replacement treatment records	<ul style="list-style-type: none"> • 123,308 LKD without ESKD: 12.3% AA • 218 LKD with ESKD: 32.1% AA 	<ul style="list-style-type: none"> • ESKD reported in national registries, as per⁴ • Median follow-up: 10.3 yr 	• Between donors	<ul style="list-style-type: none"> • 218 developed ESKD, at a median of 11 yr • Among white LKD, ESKD risk increased with older age (aHR 1.26 per decade) • Among AA LKD, ESKD risk decreased with older age (aHR 0.75 per decade)
Muzaale et al, <i>AJKD</i> 2020 ⁵⁴	• Linkage of OPTN KKD registry (1987–2017) and national renal replacement treatment records	<ul style="list-style-type: none"> • 143,750 LKD: • AA 12.4% • White 71.6% 	<ul style="list-style-type: none"> • ESKD defined by the CMS Medical Evidence Form 2728 • Median follow-up 12yr (maximum 30 yr) 	• Between donors	<p>Compared to unrelated LKD among AA donors, ESKD risk was:</p> <ul style="list-style-type: none"> • 22.5-fold for identical twins • 4.1-fold for full siblings • 2.7-fold for offspring • 3.1-fold for parents • 1.3-fold for half-sibling or other biological relatives <p>Compared to unrelated LKD among white donors, ESKD risk was:</p> <ul style="list-style-type: none"> • 3.5-fold greater for identical twins • 2.0-fold for full siblings • 1.4-fold for offspring • 2.9-fold for parents • 0.8-fold for half-sibling or other biological relatives

Adapted with permission from^{2,55} and updated with subsequent data. AA, African ancestry; aHR, adjusted hazard ratio; BMI, body mass index; CKD, chronic kidney disease; CMS, Centers for Medicare & Medicaid Services (CMS); ESKD, end-stage kidney disease; LKD, living kidney donor; NHANES, National Health and Nutrition Examination Survey; OPTN, Organ Procurement and Transplantation Network; PMPY, per million per year

Table 2. Summary of studies of kidney donor *APOL1* genotyping and outcomes of deceased donor transplant recipients and living donors

Reference	Data source/design	Donor <i>APOL1</i> genotype distributions	Outcome, measures and follow-up	Risk perspective	Findings
Reeves-Daniel et al, <i>AJT</i> 2011 ³¹	<ul style="list-style-type: none"> 106 AA deceased donors genotyped Retrospective outcomes assessment of 136 resultant DDKT (1998-2009) at one center in North Carolina 	Donor genotype, among the DDKT: <ul style="list-style-type: none"> 0 or 1 RRV: 114 (83.8%) 2 RRV: 22 (16.2%) 	<ul style="list-style-type: none"> Allograft failure Mean follow-up: 26.4 ± 21.8 mos 	<ul style="list-style-type: none"> DDKT recipient outcomes 	<ul style="list-style-type: none"> Presence of 2 donor RRVs associated with nearly 4-times the risk of graft failure, <i>vs</i> 0 or 1 RRVs (aHR 3.84; p=0.008) 8 cases lost graft lost after DDKT from donors with 2 RRVs, among whom potential <i>APOL1</i>-associated lesions were present in 6 (75%): 1 FSGS, 2 FSGS collapsing variant and 3 donor-acquired nephron scarring with arteriosclerosis
Lee et al, <i>AJT</i> 2012 ³⁴	<ul style="list-style-type: none"> 119 recipients of DDKT at two centers (1988 to 2002) 	<i>Recipient</i> genotype <ul style="list-style-type: none"> 0 or 1 RRV: 61 (51.3%) 2 RRV: 59 (48.7%) 	<ul style="list-style-type: none"> Allograft failure Follow-up time and censoring not described (survival graphs shown to 5 yr) 	<ul style="list-style-type: none"> DDKT recipient outcomes 	<ul style="list-style-type: none"> FSGS or glomerulonephritis as the cause of <i>native</i> kidney disease appeared more common in those with 2 <i>vs</i> 0 or 1 RRV (23/58 (39.7%) <i>vs</i> 9/61 (14.8%)) Death-censored allograft survival over up to 5 years did not differ in recipients with 2 <i>vs</i> 0 or 1 RRVs (aHR 0.96; P=0.84)
Freedman et al, <i>AJT</i> 2015 ³²	<ul style="list-style-type: none"> 368 deceased donors with organ recovery at two OPOs genotyped Retrospective outcomes assessment of 675 resultant DDKT at 55 centers (years “before 2001” to “after 2010”) 	Donor genotype, among the DDKT: <ul style="list-style-type: none"> 0 RRV: 286 (42.4%) 1 RRV: 290 (42.3%) 2 RRV: 99 (14.7%) 	<ul style="list-style-type: none"> Allograft failure linked from the national registry Median follow-up to graft failure or study end: 2 donor RRV: 24 mos 0 or 1 donor RRV: 36 mos 	<ul style="list-style-type: none"> DDKT recipient outcomes 	<ul style="list-style-type: none"> Presence of 2 donor RRVs associated with more than twice the risk of allograft failure, <i>vs</i> 0 or 1 RRV (HR 2.26; P=0.001)
Freedman et al, <i>Transplantation</i> 2016 ³³	<ul style="list-style-type: none"> 624 deceased donors Retrospective outcomes assessment of 1153 resultant DDKT including 675 from the prior report³² 	Donor genotype, among the DDKT: <ul style="list-style-type: none"> 0 RRV: 462 (40.0%) 1 RRV: 519 (45.0%) 2 RRV: 172 (15.0%) 	<ul style="list-style-type: none"> Allograft failure linked from the national registry Median follow-up to graft failure or study end: 36 mos (0 or 1, and 2 RRV) 	<ul style="list-style-type: none"> DDKT recipient outcomes 	<ul style="list-style-type: none"> Presence of 2 donor RRVs associated with twice the risk of allograft failure, <i>vs</i> 0 or 1 RRV (HR 2.05; P=0.0003)
Divers et al, <i>Clin Transpl</i> 2020 ²⁰	<ul style="list-style-type: none"> 532 “discovery” deceased donors and 250 “replication” donors Retrospective outcomes assessment of 978 and 465 resultant DDKT 	Donor genotypes Discovery sample <ul style="list-style-type: none"> 0 RRV: 216 (40.6%) 1 RRV: 223 (41.9%) 2 RRV: 83 (15.6%) Replication sample <ul style="list-style-type: none"> 0 RRV: 102(40.1%) 1 RRV: 117 (46.8%) 2 RRV: 31 (12.4%) 	<ul style="list-style-type: none"> Allograft failure linked from the national registry 	<ul style="list-style-type: none"> DDKT recipient outcomes 	<ul style="list-style-type: none"> 5 SNPs were independently associated with allograft failure 6 additional SNPs were interactive with <i>APOL1</i> genotype on allograft failure risk (not significant in replication sample) Independent validation and functional genomic studies pending.
Doshi et al, <i>JASN</i> 2018 ³⁹	<ul style="list-style-type: none"> 136 LKD at two centers in Michigan (1993-2010) “Healthy” controls drawn from CARDIA cohort (n=115 matched) 	LKD genotypes: <ul style="list-style-type: none"> 0 RRV: 67 (49%) 1 RRV: 50 (37%) 2 RRV: 19 (14%) 	<ul style="list-style-type: none"> eGFR at follow-up and average annual change in eGFR from 1 yr after donation (or cohort entry for controls) Mean follow-up: 12 yr 	<ul style="list-style-type: none"> Between donors LKD <i>vs</i> healthy nondonors 	<ul style="list-style-type: none"> LKD with 2 <i>vs</i> 0 or 1 RRV had: lower eGFR (98 ± 17, <i>vs</i> 108 ± 20 ml/min per 1.73 m²; P=0.03) and uACR (8.4 <i>vs</i> 5.0 mg/g; P=0.01) before donation, and lower eGFR after donation (57 ± 20, <i>vs</i> 67 ± 15 ml/min per 1.73 m²; P=0.02) 2 LKD who developed ESKD both had 2 RRVs Compared to matched healthy non-donor controls, LKD had a lower baseline because of nephrectomy, but slopes

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Reference	Data source/design	Donor <i>APOL1</i> genotype distributions	Outcome, measures and follow-up	Risk perspective	Findings
					according to genotype were similar (annual decline: 0.5 vs 0.6 ml/min per 1.73 m ² ; P=0.39)

AA, African ancestry; aHR, adjusted hazard ratio; *APOL1*, apolipoprotein L1; CARDIA, Coronary Artery Risk Development in Young Adults study; DDKT, deceased donor kidney transplantation; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; LKD, living kidney donor; OPO, Organ Procurement Organization; RRV, renal risk variant; uACR, urine albumin-to-creatinine ratio

Table 3.

Example of a prediction tool to estimate kidney failure risk in donor candidates ⁵⁶ and a method for communicating such risks ^{13,57}

<p>1. An online tool (http://www.transplantmodels.com/esrdrisk/) estimates the projected lifetime risk of permanent kidney failure treated by dialysis or transplantation in the absence of donation according to baseline demographic (age, sex, "race") and clinical characteristics included in the online tool.</p> <p>2. This projected pre-donation risk can be multiplied by the best available estimate for donation attributable risk to obtain the projected post-donation risk. For example, Grams et al report a relative risk of 3.5 to 5.3 for 15-year kidney failure risk, according to sex and "race".</p> <p>3. The projected risk estimate can be compared to the program's post-donation threshold of acceptable risk.</p> <p>4. Use the tool cautiously when there is concern that the individual has risk factors not captured in the tool (e.g., familial or genetic risk) and for younger candidates.</p>
<p>5. When communicating kidney failure risk to donor candidates:</p> <ul style="list-style-type: none"> • Use plain language to make written and verbal materials more understandable. • Present data using absolute risks. • Present information in pictographs if graphs are included. • Present data using frequencies. • Use an incremental risk format to highlight how post donation risks change from preexisting baseline levels. • Be aware that the order in which risks and benefits are presented can affect risk perceptions. • Consider using summary tables that include all risks and benefits associated with donation. • Consider presenting only the information that is most critical to the patients' decision making, even at the expense of completeness. • Repeatedly draw patients' attention to the time interval over which a risk occurs.

A model was developed to project the estimated 15-year and lifetime risk of kidney failure in the absence of donation ("baseline risk") based on simultaneous consideration of each candidate's profile of demographic and health characteristics. In brief, cohort studies on kidney failure risk are only available for ~130,000 living donors, but are available for millions of healthy persons in the general population. To leverage the information available in general population cohorts, the Work Group collaborated with the Chronic Kidney Disease Prognosis Consortium (CKD-PC) to model the long-term risk of kidney failure in the absence of donation, based on 10 candidate predonation demographic and health characteristics. The multi-step modelling process was complex and was independently published ¹² and the risk projection tool is available online <http://www.transplantmodels.com/esrdrisk/>. For clinical application, estimates provided for the predicted incidence of kidney failure in the absence of donation are then multiplied by the donation attributable relative risk of kidney failure (which in the analysis was 3.5 to 5.3 according to sex "race" Reproduced with permission from ⁵⁸