alternative, but until now, no promising drug candidates are broadly available, to the best of our knowledge.

DISCLOSURES

None.

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See related article, "Macrophage Uptake of Necrotic Cell DNA Activates the AIM2 Inflammasome to Regulate a Proinflammatory Phenotype in CKD," on pages 1165–1181.

Evaluation of Potential Living Kidney Donors in the *APOL1* Era

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Inheriting two apolipoprotein L1 gene (*APOL1*) renal risk variants accounts for the majority of the excess risk for nondiabetic ESRD in individuals with recent African ancestry.[1] *APOL1* renal risk variants are common in blacks in the United States, with about 13% carrying two variants (defining the high-risk genotype), whereas 39% have one variant and 48% have no variant. In contrast, *APOL1* renal risk variants are virtually absent in nonadmixed European, Asian, and Hispanic populations. Approximately 20% of those with the *APOL1* high-risk genotype ultimately develop CKD, supporting the postulate that modifying factors are necessary to trigger development of nephropathy.[2]

The effect of having two *APOL1* renal risk variants extends beyond native kidney disease. Kidney transplants from deceased black donors with the *APOL1* high-risk genotype fail more quickly than allografts from donors with zero or one *APOL1* renal risk variant.[3] The outcomes of kidneys from deceased black donors with zero or one *APOL1* renal risk variant approximate those of kidneys from white donors.[3,4] Furthermore, serum creatinine concentrations are higher in recipients with functioning kidneys from donors with the *APOL1* high-risk genotype, raising concerns that additional allografts will also fail over longer intervals.[3,5] The poorer outcome of these allografts is independent of the ethnicity of the recipient, indicating that the effect of the genotype travels with the kidney.[6] Nonetheless, such as is the case for native kidney disease, the association of the *APOL1* high-risk genotype with a poor outcome is far from universal. Indeed, most allografts from deceased black donors with the *APOL1* high-risk genotype function well for prolonged intervals, again suggesting that modifying factors initiate or accentuate renal damage.

More recently, the kidney transplant community has begun to examine a possible effect of *APOL1* renal risk variants on outcomes in living donor transplantation. Living black kidney donors more often develop ESRD than donors from other racial groups, with frequencies about 3.5- to 5.3-fold higher than in age- and sex-matched whites[7] (Figure 1). Patient reports have described the loss of kidneys from living black donors with the *APOL1* high-risk genotype several years after transplantation due to proteinuric disease, with subsequent development of ESRD in the donor.[8] These reports raise the question: does the presence of the *APOL1* high-risk genotype adversely affect postdonation renal function in black living kidney donors?

In this issue of the *Journal of the American Society of Nephrology*, Doshi *et al.*[9] addressed that question by studying a cohort of 136 black living kidney donors with mean age of 37 years and mean follow-up of 12 years. Nineteen (14%) patients had the *APOL1* high-risk genotype, a frequency similar to that in the general black population. They found that the mean eGFR before nephrectomy was significantly lower in *APOL1* high-risk donors than in donors with zero or one *APOL1* renal risk variant. This difference suggests that deterioration of renal clearance function started before donation, although without clinical manifestations that would preclude acceptance as a kidney donor. Nephrectomy decreased eGFR by 25–30 ml/min per 1.73 m^2 in both donor subgroups, but the decline in

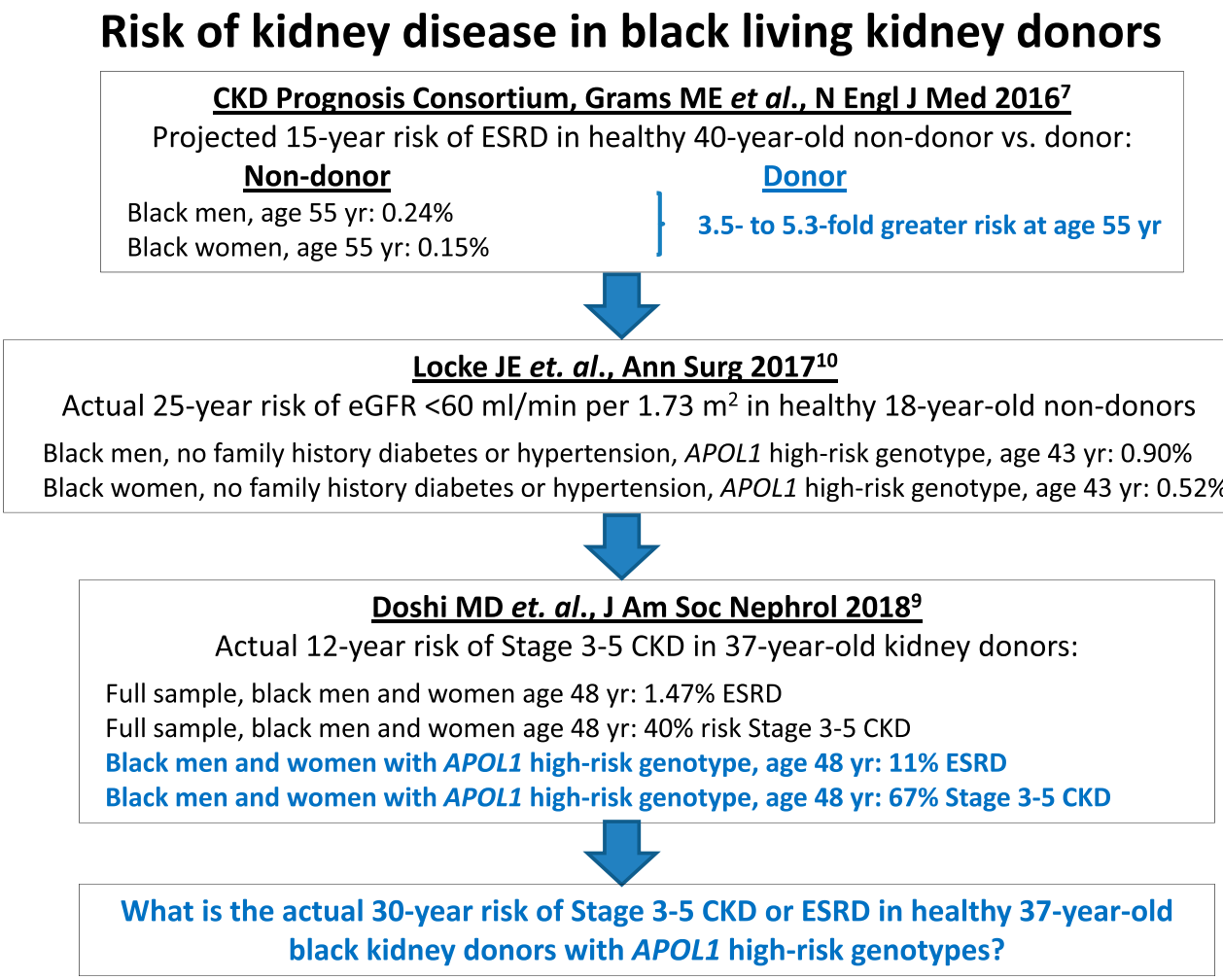

Figure 1. Higher risk of advanced CKD or ESRD in living kidney donors with the high-risk *APOL1* genotype, compared to low risk genotypes.

eGFR after recovery from nephrectomy was more rapid in *APOL1* high-risk donors. Of concern, both donors who developed ESRD due to proteinuric kidney disease had an *APOL1* high-risk genotype, comprising 11% of this donor subgroup. Furthermore, stage 3 or worse CKD developed in 67% of *APOL1* high-risk donors compared with 36% of donors with zero or one *APOL1* renal risk variant (Figure 1). A subset of 115 donors was matched with nondonor controls from the Coronary Artery Risk Development in Young Adults (CARDIA) Study for baseline age, sex, systolic BP, family history of ESRD in first degree relatives, *APOL1* genotype, and duration of follow-up. The annual decrements in eGFR in nondonors and donors after nephrectomy, grouped by *APOL1* genotype, were similar. At the end of the study, severity of microalbuminuria was similar in donors and nondonors but worse in *APOL1* high-risk donors versus *APOL1* low-risk donors. Prevalence of hypertension at the end of the study did not associate with the *APOL1* high-risk genotype. Hypertension developed in nearly one half of donors in both subgroups, was often untreated, and was more common than in nondonors.

These data, although preliminary and from a small sample, raise concerns for the long-term kidney health of black living kidney donors. Although *APOL1* high-risk living donors had a follow-up eGFR of 57 ml/min per 1.73 m^2, their mean age after 12 years of follow-up was only 48 years. A continued 1.1 ml/min per 1.73 m^2 per year (95% confidence interval, 0 to 2.3 ml/min per 1.73 m^2 per year) postnephrectomy decline in eGFR will likely culminate in stage 4 or 5 CKD for a sizable number of donors. ESRD is probably more likely in younger donors with their extra postnephrectomy years and greater potential exposure to additional kidney disease risk factors, such as diabetes, obesity, and nephrotoxic agents. An analysis in a larger sample of the CARDIA Study participants examined the risk for CKD in young adults[10] (Figure 1). A cohort of 3438 participants (48% black; mean age of 24.8 years) who satisfied criteria for potential kidney donation was used to assess the effect of the *APOL1* genotype on kidney function over a 25-year span. The presence of two *APOL1* renal risk variants increased the risk of the eGFR decreasing below 60 ml/min

per 1.73 m^2 by fivefold in blacks compared with their white counterparts and by 2.5- to threefold compared with blacks with no *APOL1* renal risk variants. The *APOL1* two-renal-risk-variant genotype was the strongest of all 11 risk factors for development of CKD stage 3 or higher. Furthermore, presence of one *APOL1* renal risk variant also increased risk of CKD, although to a lesser degree.

Considering *APOL1* genotypes may be less critical in older candidates for living donor nephrectomy. Some older individuals with two *APOL1* renal risk variants will already manifest kidney disease and will not satisfy screening criteria. Moreover, they will presumably encounter fewer opportunities to develop renal injury or initiate *APOL1*-associated kidney damage given their shorter life expectancies.

The findings of Doshi *et al.*[9] should heighten our concern about an adverse effect of the *APOL1* two-renal-risk-variant genotype on the long-term kidney health of black living kidney donors. Without a uniformly consistent poor outcome, the effect of *APOL1* and the biochemical implications remain unclear. Additional studies are needed to clarify this apparent effect. Ideally, these studies will also uncover other factors that modify the risk for CKD/ESRD in some individuals with two *APOL1* renal risk variants. The newly launched National Institutes of Health prospective *APOL1* Long-Term Kidney Transplantation Outcomes Network (APOLLO) Study is addressing these issues. The APOLLO Study is evaluating allograft survival of kidneys from deceased and living black donors and the long-term renal outcomes of black living donors. In the meantime, black donor candidates should be informed of the association of *APOL1* renal risk variants with CKD/ESRD. Although it is not yet possible to quantify the risk in an individual, young two *APOL1* renal risk variant donors with a family history of ESRD, hypertension, or other risk factors likely face the highest risk. All donors should be counseled to adopt a healthy lifestyle after nephrectomy, with avoidance of tobacco, control of weight, regular assessments of kidney health, and periodic monitoring of blood glucose and BP (with treatment of hypertension). We must learn from the candidates their perception of benefits and risks of donation for themselves and the recipients. The amount of risk that is acceptable to a donor will vary between individuals and by relationship of the donor to the recipient. We anticipate that future investigations will clarify how an *APOL1*-associated process that can culminate in a proteinuric kidney disease reduces eGFR in its early stages, often with minimal albuminuria. This new knowledge will hopefully lead to novel approaches to preserve kidney function.

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DISCLOSURES

Wake Forest University Health Sciences and B.I.F. have rights to an issued United States patent related to *APOL1* genetic testing. B.I.F. is a consultant for Ionis Pharmaceuticals. B.A.J. reports no disclosure relevant to this work.

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See related article, "*APOL1* Genotype and Renal Function of Black Living Donors," on pages 1309–1316.

Gender Disparities and Financial Barriers to Living Kidney Donation

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