



**LEARNING OBJECTIVE:** Readers will recognize recent advances in the understanding of chronic kidney disease in African Americans

**JOSEPH V. NALLY, JR, MD**

Former Director, Center for Chronic Kidney Disease;  
Clinical Professor of Medicine, Cleveland Clinic Lerner College  
of Medicine of Case Western Reserve University

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# Chronic kidney disease in African Americans: Puzzle pieces are falling into place

## ABSTRACT

Recent decades have seen great advances in the understanding of chronic kidney disease, spurred by standardizing disease definitions and large-scale patient surveillance. African Americans are disproportionately affected by the disease, and recently discovered genetic variants in *APOL1* that protect against sleeping sickness in Africa provide an important explanation for the increased burden. Studies are now under way to determine if genetic testing of African American transplant donors and recipients is advisable.

## KEY POINTS

Patients with chronic kidney disease are more likely to die than to progress to end-stage disease, and cardiovascular disease and cancer are the leading causes of death.

As kidney function declines, the chance of dying from cardiovascular disease increases.

African Americans tend to develop kidney disease at a younger age than whites and are much more likely to progress to dialysis.

About 15% of African Americans are homozygous for a variant of the *APOL1* gene. They are more likely to develop kidney disease and to have worse outcomes.

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*Editor's note: This Medical Grand Rounds was presented as the 14th Annual Lawrence "Chris" Crain Memorial Lecture, a series that has been dedicated to discussing kidney disease, hypertension, and health care disparities in the African American community. In 1997, Dr. Crain became the first African American chief medical resident at Cleveland Clinic, and was a nephrology fellow in 1998–1999. Dr. Nally was his teacher and mentor.*

**A**FRICAN AMERICANS have a greater burden of chronic kidney disease than whites. They are more than 3 times as likely as whites to develop end-stage renal disease, even after adjusting for age, disease stage, smoking, medications, and comorbidities. Why this is so has been the focus of much speculation and research.

This article reviews recent advances in the understanding of the progression of chronic kidney disease, with particular scrutiny of the disease in African Americans. Breakthroughs in genetics that help explain the greater disease burden in African Americans are also discussed, as well as implications for organ transplant screening.

## ■ ADVANCING UNDERSTANDING OF CHRONIC KIDNEY DISEASE

In the 1990s, dialysis rolls grew by 8% to 10% annually. Unfortunately, many patients first met with a nephrologist on the eve of their first dialysis treatment; there was not yet an adequate way to recognize the disease earlier and slow its progression. And disease definitions were not yet standardized, which led to inadequate metrics and hampered the ability to move disease management forward.

## CHRONIC KIDNEY DISEASE IN AFRICAN AMERICANS

				Albuminuria stages, description, and range (mg/g)				
				A1		A2	A3	
				Optimum and high-normal		High	Very high and nephrotic	
				< 10	0–29	30–299	300–1,999	≥ 2,000
GFR stages, descriptions, and range (mL/min/1.73 m <sup>2</sup> )	G1	High and optimum	> 105					
			90–104					
	G2	Mild	75–89					
			60–74					
	G3a	Mild-moderate	45–59					
	G3b	Moderate-severe	30–44					
	G4	Severe	15–29					
	G5	Kidney failure	< 15					

**FIGURE 1.** Prognosis of chronic kidney disease (CKD) by glomerular filtration rate (GFR) and albuminuria.

Reprinted from Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int* 2011; 80:17–28; copyright 2011, with permission from Elsevier; www.sciencedirect.com/science/journal/00852538?sd=1.

### Standardizing definitions

The situation improved in 2002, when the National Kidney Foundation published clinical practice guidelines for chronic kidney disease that included disease definitions and staging.<sup>1</sup> Chronic kidney disease was defined as a structural or functional abnormality of the kidney lasting at least 3 months, as manifested by either of the following:

- Kidney damage, with or without decreased glomerular filtration rate (GFR), as defined by pathologic abnormalities or markers of kidney damage in the blood, urine, or on imaging tests
- GFR less than 60 mL/min/1.73 m<sup>2</sup>, with or without kidney damage.

A subsequent major advance was the recognition that not only GFR but also albuminuria was important for staging of chronic kidney disease (Figure 1).<sup>2</sup>

### Developing large databases

Surveillance and monitoring of chronic kidney

disease have generated large databases that enable researchers to detect trends in disease progression.

**US Renal Data System.** The US Renal Data System has collected and reported on data for more than 20 years from the National Health and Nutrition Examination Survey and the Centers for Medicare and Medicaid Services about chronic and end-stage kidney disease in the United States.

**Cleveland Clinic database.** Cleveland Clinic has developed a validated chronic kidney disease registry based on its electronic health record.<sup>3</sup> The data include demographics (age, sex, ethnic group), comorbidities, medications, and complete laboratory data.<sup>4</sup>

**Alberta Kidney Disease Network.** This Canadian research consortium links large laboratory and demographic databases to facilitate defining patient populations, such as those with kidney disease and other comorbidities.

TABLE 1

### Causes of death in patients with non-dialysis-dependent chronic kidney disease

Cause of death, n (%)	Overall (n = 6,661)	eGFR 45–59 (n = 3,308)	eGFR 30–44 (n = 2,261)	eGFR < 30 (n = 1,092)
<b>Cardiovascular disease</b>	2,311 (34.7)	1,017 (30.7)	862 (38.1)	432 (39.6)
Ischemic heart disease	1,227 (18.4)	532 (16.1)	457 (20.2)	238 (21.8)
Heart failure	163 (2.4)	61 (1.8)	75 (3.3)	27 (2.5)
Cerebrovascular disease	255 (3.8)	123 (3.7)	94 (4.2)	38 (3.5)
Other cardiovascular disease	666 (10.0)	301 (9.1)	236 (10.4)	129 (11.8)
<b>Malignant neoplasm</b>	2,117 (31.8)	1,282 (38.8)	616 (27.2)	219 (20.1)
<b>Other cause</b>	2,233 (33.5)	1,009 (30.5)	783 (34.7)	441 (40.3)

eGFR = estimated glomerular filtration rate

Adapted from reference 9.

**Kaiser Permanente Renal Registry.** Kaiser Permanente of Northern California insures more than one-third of adults in the San Francisco Bay Area. The renal registry includes all adults whose kidney function is known. Data on age, sex, and racial or ethnic group are available from the health-plan databases.

### DEATHS FROM KIDNEY DISEASE

The mortality rate in patients with end-stage renal disease who are on dialysis has steadily fallen over the past 20 years, from an annual rate of about 25% in 1996 to 17% in 2014, suggesting that care improved during that time. Patients with transplants have a much lower mortality rate: less than 5% annually.<sup>5</sup> But these data also highlight the persistent risk faced by patients with chronic kidney disease; even those with transplants have death rates comparable to those of patients with cancer, diabetes, or heart failure.

### Death rates correlate with GFR

After the publication of definitions and staging by the National Kidney Foundation in 2002, Go et al<sup>6</sup> studied more than 1 million patients with chronic kidney disease from the Kaiser Permanente Renal Registry and found that the rates of cardiovascular events and death from any cause increased with decreasing estimated GFR. These findings were

confirmed in a later meta-analysis, which also found that an elevated urinary albumin-to-creatinine ratio (> 1.1 mg/mmol) is an independent predictor of all-cause mortality and cardiovascular mortality.<sup>7</sup>

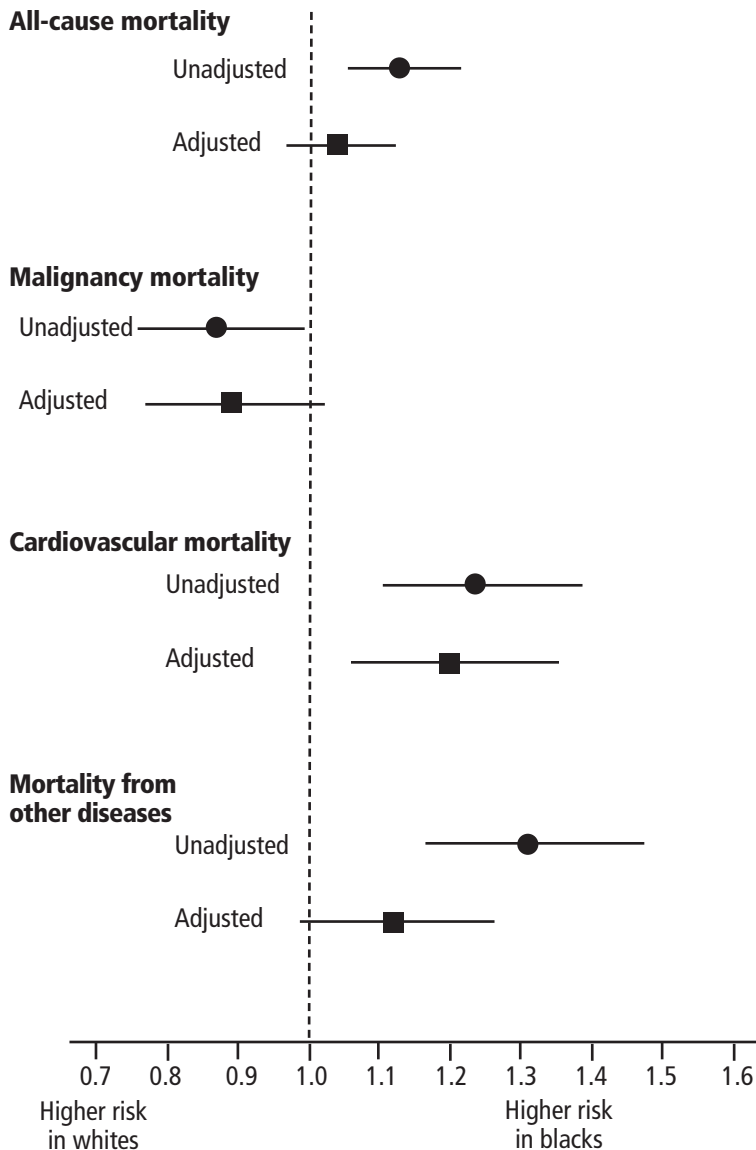
Keith et al<sup>8</sup> followed nearly 28,000 patients with chronic kidney disease (with an estimated GFR of less than 90 mL/min/1.73 m<sup>2</sup>) over 5 years. Patients with stage 3 disease (moderate disease, GFR = 30–59 mL/min/1.73 m<sup>2</sup>) were 20 times more likely to die than to progress to end-stage renal disease (24.3% vs 1.2%). Even those with stage 4 disease (severe disease, GFR = 15–29 mL/min/1.73 m<sup>2</sup>) were more than twice as likely to die as to progress to dialysis (45.7% vs 19.9%).

### Heart disease risk increases with declining kidney function

Navaneethan et al<sup>9</sup> examined the leading causes of death between 2005 and 2009 in patients with chronic kidney disease in the Cleveland Clinic database, which included more than 33,000 whites and 5,000 African Americans. During a median follow-up of 2.3 years, 17% of patients died, with the 2 major causes being cardiovascular disease (35%) and cancer (32%) (Table 1). Interestingly, patients with fairly well-preserved kidney function (stage 3A) were more likely to die of cancer than heart disease. As kidney function de-

**African Americans are more than 3 times likelier than whites to develop end-stage renal disease**

## Hazard ratios for blacks compared with whites



**FIGURE 2.** Risk for all-cause and major cause-specific death in black vs white patients.

Adapted from Navaneethan SD, Schold JD, Arragain S, Jolly SE, Nally JV Jr. Cause-specific deaths in non-dialysis-dependent CKD. *J Am Soc Nephrol* 2015; 26:2512–2520.

clined, whether measured by estimated GFR or urine albumin-to-creatinine ratio, the chance of dying of cardiovascular disease increased.

Similar observations were made by Thompson et al<sup>10</sup> based on the Alberta Kidney Disease Network database. They tracked cardiovascular causes of death and found that regardless of estimated GFR, cardiovascular deaths were most often attributed to ischemic

heart disease (about 55%). Other trends were also apparent: as the GFR fell, the incidence of stroke decreased, and heart failure and valvular heart disease increased.

## AFRICAN AMERICANS WITH KIDNEY DISEASE: A DISTINCT GROUP

African Americans constitute about 12% of the US population but account for:

- 31% of end-stage renal disease
- 34% of the kidney transplant waiting list
- 28% of kidney transplants in 2015 (12% of living donor transplants, 35% of deceased donor transplants).

In addition, African Americans with chronic kidney disease tend to be:

- Younger and have more advanced kidney disease than whites<sup>11</sup>
- Much more likely than whites to have diabetes, and somewhat more likely to have hypertension
- More likely than whites to die of cardiovascular disease (37.4% vs 34.2%) (**Figure 2**).<sup>9</sup>

Overall, the prevalence of chronic kidney disease is slightly higher in African Americans than in whites. Interestingly, African Americans are slightly less likely than whites to have low estimated GFR values (6.2% vs 7.6% incidence of  $< 60$  mL/min/1.73 m<sup>2</sup>) but are about 50% more likely to have proteinuria (12.3% vs 8.4% incidence of urine albumin-to-creatinine ratio  $\geq 30$  mg/g).

## More likely to be on dialysis, but less likely to die

Although African Americans have only a slightly higher prevalence of chronic kidney disease (about 15% increased prevalence) than whites,<sup>12</sup> they are 3 times more likely to be on dialysis.

Nevertheless, for unknown reasons, African American adults on dialysis have about a 26% lower all-cause mortality rate than whites.<sup>5</sup> One proposed explanation for this survival advantage has been that the mortality rate in African Americans with chronic kidney disease before entering dialysis is higher than in whites, leading to a “healthier population” on dialysis.<sup>13</sup> However, this theory is based on a small study from more than a decade ago and has not been borne out by subsequent investigation.

### African Americans with chronic kidney disease: Death rates not increased

African Americans over age 65 with chronic kidney disease have all-cause mortality rates similar to those of whites: about 11% annually. Breaking it down by disease severity, death rates in stage 3 disease are about 10% and jump to more than 15% in higher stages in both African Americans and whites.<sup>5</sup>

However, African Americans with chronic kidney disease have more heart disease and much more end-stage renal disease than whites.

### Disease advances faster despite care

The incidence of end-stage renal disease is consistently more than 3 times higher in African Americans than in whites in the United States.<sup>5,14</sup>

Multiple investigations have tried to determine why African Americans are disproportionately affected by progression of chronic kidney disease to end-stage renal disease. We recently examined this question in our Cleveland Clinic registry data. Even after adjusting for 17 variables (including demographics, comorbidities, insurance, medications, smoking, and chronic kidney disease stage), African Americans with chronic kidney disease were found to have an increased risk of progressing to end-stage renal disease compared with whites (subhazard ratio 1.38, 95% confidence interval 1.19–1.60).

We examined care measures from the Cleveland Clinic database. In terms of the number of laboratory tests ordered, clinic visits, and nephrology referrals, African Americans had at least as much care as whites, if not more. Similarly, African Americans' access to renoprotective medicines (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, statins, beta-blockers) was the same as or more than for whites.

Although the frequently attributed reasons surrounding compliance and socioeconomic issues are worthy of examination, they do not appear to completely explain the differences in incidence and outcomes. This dichotomy of a marginally increased prevalence of chronic kidney disease in African Americans with mortality rates similar to those of whites, yet with a 3 times higher incidence of end-stage

renal disease in African Americans, suggests a faster progression of the disease in African Americans, which may be genetically based.

### GENETIC VARIANTS FOUND

In 2010, two variant alleles of the *APOL1* gene on chromosome 22 were found to be associated with nondiabetic kidney disease.<sup>15</sup> Three nephropathies are associated with being homozygous for these alleles:

- **Focal segmental glomerulosclerosis**, the leading cause of nephrotic syndrome in African Americans
- **Hypertension-associated kidney disease** with scarring of glomeruli in vessels, the primary cause of end-stage renal disease in African Americans
- **Human immunodeficiency virus (HIV)-associated nephropathy**, usually a focal segmental glomerulosclerosis type of lesion.

The first two conditions are about 3 to 5 times more prevalent in African Americans than in whites, and HIV-associated nephropathy is about 20 to 30 times more common.

### African sleeping sickness and chronic kidney disease

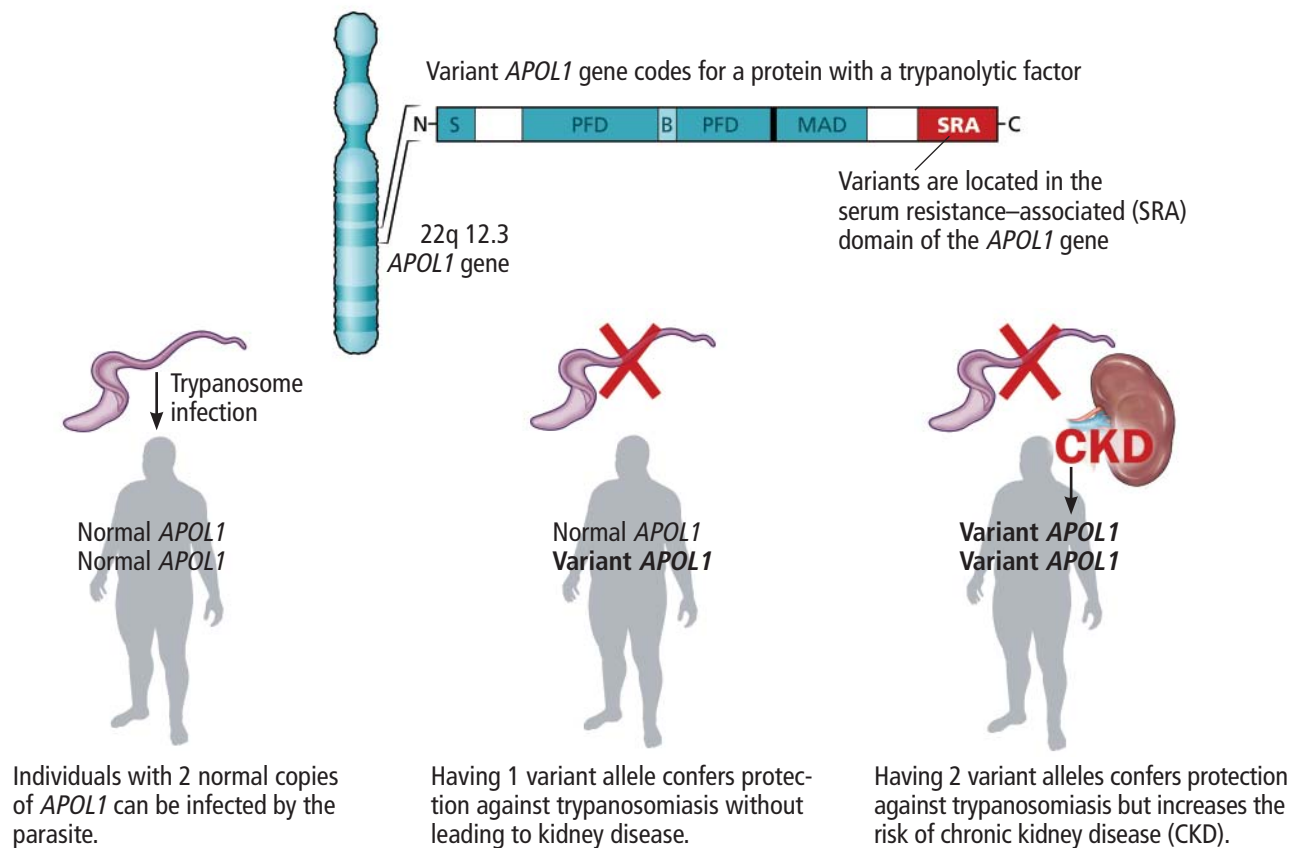
The *APOL1* variants have been linked to protection from African sleeping sickness caused by *Trypanosoma brucei*, transmitted by the tsetse fly (**Figure 3**).<sup>16</sup> The pathogen can infect people with normal *APOL1* using a serum resistance-associated protein, while the mutant variants prevent or reduce protein binding. Having one variant allele confers protection against trypanosomiasis without leading to kidney disease; having both alleles with the variants protects against sleeping sickness but increases the risk of chronic kidney disease. About 15% of African Americans are homozygous for a variant.<sup>17</sup>

Retrospective analysis of biologic samples from trials of kidney disease in African Americans has revealed interesting results.

The African American Study of Kidney Disease and Hypertension (AASK) trial<sup>18</sup> evaluated whether tighter blood pressure control would improve outcomes. Biologic samples were available for DNA testing for 693 of the 1,094 trial participants. Of these, 23% of African Americans were found to be homozy-

**Cardiovascular events and deaths from any cause increase with decreasing GFR**





**FIGURE 3.** Variants in the *APOL1* gene that are common in sub-Saharan Africa protect against African sleeping sickness, but homozygosity for these variants increases the risk of chronic kidney disease.

gous for a high-risk allele, and they had dramatically worse outcomes with greater loss of GFR than those with one or no variant allele (**Figure 4**). However, the impact of therapy (meeting blood pressure targets, treatment with different medications) did not differ between the groups.

The Chronic Renal Insufficiency Cohort (CRIC) observation study<sup>18</sup> enrolled patients with an estimated GFR of 20 to 70 mL/min/1.73 m<sup>2</sup>, with a preference for African Americans and patients with diabetes. Nearly 3,000 participants had adequate samples for DNA testing. They found that African Americans with the double variant allele had worse outcomes, whether or not they had diabetes, compared with whites and African Americans without the homozygous gene variant.

## Mechanism not well understood

The mechanism of renal injury is not well understood. Apolipoprotein L1, the protein

coded for by *APOL1*, is a component of high-density lipoprotein. It is found in a different distribution pattern in people with normal kidneys vs those with nondiabetic kidney disease, especially in the arteries, arterioles, and podocytes.<sup>19,20</sup> It can be detected in blood plasma, but levels do not correlate with kidney disease.<sup>21</sup> Not all patients with the high-risk variant develop chronic kidney disease; a “second hit” such as infection with HIV may be required.

Investigators have recently developed knockout mouse models of *APOL1*-associated kidney diseases that are helping to elucidate mechanisms.<sup>22,23</sup>

## EFFECT OF GENOTYPE ON KIDNEY TRANSPLANTS IN AFRICAN AMERICANS

African Americans receive about 30% of kidney transplants in the United States and represent about 15% to 20% of all donors.

Lee et al<sup>24</sup> reviewed 119 African American recipients of kidney transplants, about half of whom were homozygous for an *APOL1* variant. After 5 years, no differences were found in allograft survival between recipients with 0, 1, or 2 risk alleles.

However, looking at the issue from the other side, Reeves-Daniel et al<sup>25</sup> studied the fate of more than 100 kidneys that were transplanted from African American donors, 16% of whom had the high-risk, homozygous genotype. In this case, graft failure was much likelier to occur with the high-risk donor kidneys (hazard ratio 3.84,  $P = .008$ ). Similar outcomes were shown in a study of 2 centers<sup>26</sup> involving 675 transplants from deceased donors, 15% of which involved the high-risk genotype. The hazard ratio for graft failure was found to be 2.26 ( $P = .001$ ) with high-risk donor kidneys.

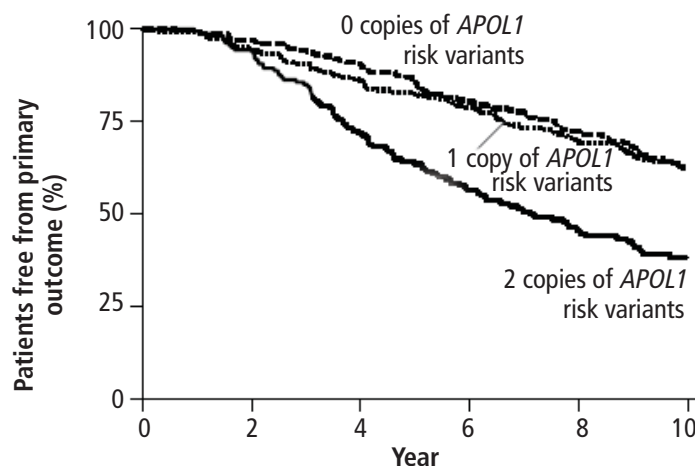
These studies, which examined data from about 5 years after transplant, found that kidney failure does not tend to occur immediately in all cases, but gradually over time. Most high-risk kidneys were not lost within the 5 years of the studies.

The fact that the high-risk kidneys do not all fail immediately also suggests that a second hit is required for failure. Culprits postulated include a bacterial or viral infection (eg, BK virus, cytomegalovirus), ischemia or reperfusion injury, drug toxicity, and immune-mediated allograft injury (ie, rejection).

### Genetic testing advisable?

Genetic testing for *APOL1* risk variants is on the horizon for kidney transplant. But at this point, providing guidance for patients can be tricky. Two case studies<sup>27,28</sup> and epidemiologic data suggest that donors homozygous for an *APOL1* variant and those with a family history of end-stage kidney disease are at increased risk of chronic kidney disease. Even so, most recipients even of these high-risk organs have good outcomes. If an African American patient needs a kidney and his or her sibling offers one, it is difficult to advise against it when the evidence is weak for immediate risk and when other options may not be readily available. Further investigation is clearly needed into whether *APOL1* variants and other biomarkers can predict an organ's success as a transplant.

### *APOL1* variants increase the risk of chronic kidney disease



**FIGURE 4.** Proportion of patients free from progression of chronic kidney disease, according to *APOL1* genotype, in the African American Study of Kidney Disease and Hypertension. The primary outcome was reduction in the glomerular filtration rate (as measured by iothalamate clearance) or incident end-stage renal disease.

From Parsa A, Kao WH, Xie D, et al; AASK Study Investigators; CRIC Study Investigators. *APOL1* risk variants, race, and progression of chronic kidney disease. *N Engl J Med* 2013; 369:2183–2196. Reprinted with permission from Massachusetts Medical Society.

The National Institutes of Health are currently funding prospective longitudinal studies with the *APOL1* Long-term Kidney Transplantation Outcomes Network (APOLLO) to determine the impact of *APOL1* genetic factors on transplant recipients as well as on living donors. Possible second hits will also be studied, as will other markers of renal dysfunction or disease in donors. Researchers are actively investigating these important questions.

### KEEPING SCIENCE RELEVANT

In a recent commentary related to the murine knockout model of *APOL1*-associated kidney disease, O'Toole et al offered insightful observations regarding the potential clinical impact of these new genetic discoveries.<sup>23</sup>

As we study the genetics of kidney disease in African American patients, we should keep in mind 3 critical questions of clinical importance:

**Will findings identify better treatments for chronic kidney disease?** The AASK trial found that knowing the genetics did not affect

**African Americans: 12% of the US population, but 31% of patients with end-stage renal disease**

outcomes of routine therapy. However, basic science investigations are currently underway targeting *APOL1* variants which might reduce the increased kidney disease risk among people of African descent.

**Should patients be genotyped for *APOL1* risk variants?** For patients with chronic kidney disease, it does not seem useful at this time. But for renal transplant donors, the answer is

probably yes.

**How does this discovery help us to understand our patients better?** The implications are enormous for combatting the assumptions that rapid chronic kidney disease progression reflects poor patient compliance or other socioeconomic factors. We now understand that genetics, at least in part, drives renal disease outcomes in African American patients. ■

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**ADDRESS:** Joseph V. Nally, Jr., MD, Glickman Urological and Kidney Institute, Q7, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; nallyj@ccf.org