Genetic Testing for *APOL1* Genetic Variants in Clinical Practice

Finally Starting to Arrive

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The identification of genetic variants in *APOL1* as a major driver of kidney disease in blacks has ushered in an exciting new era in glomerular disease, offering the potential for precision medicine in a range of kidney diseases in individuals with sub-Saharan African ancestry (1). The presence of *APOL1* high-risk genotypes, comprising any combination of two *APOL1* kidney risk alleles, increases the risk for several kidney diseases compared with *APOL1* low-risk individuals (defined as those carrying zero or one *APOL1* kidney risk allele). These include FSGS, HIV-associated nephropathy, focal global glomerulosclerosis with interstitial and vascular changes (overlapping with the pathologic pattern formerly termed arterionephrosclerosis), sickle cell nephropathy, lupus nephritis associated with collapsing glomerulopathy, and unexplained ESKD. Nevertheless, it seems that most *APOL1* high-risk individuals will not develop kidney disease, and our inability to predict a particular individual's lifetime risk is a major missing piece.

APOL1 high-risk status is also associated with more rapid decline in eGFR in the general population and patients with established CKD, including some patients with diabetic kidney disease. Paradoxically, *APOL1* high-risk status is associated with longer patient survival while on long-term hemodialysis. *APOL1* high-risk status in kidney allografts predicts shorter allograft survival (2). Of concern, living donors with high-risk *APOL1* genotypes are at higher risk for developing CKD compared with low-risk *APOL1* kidney donors (3).

APOL1 high-risk subjects with FSGS and nephrotic-range proteiniuria have comparable reduction in proteinuria to *APOL1* low-risk individuals, and yet, *APOL1* high-risk subjects have worse long-term outcomes, with faster progression to ESKD (4). The reasons for this discrepancy are unclear. It may be that, in *APOL1* high-risk individuals, therapy suppresses a podocyte cellular pathway that is related to proteinuria but does not affect other podocyte cellular pathways that drive progressive cell injury. Alternatively, the favorable effect of these agents on particular pathways may be transitory, such as by reducing IFN expression and thus, reducing *APOL1* gene expression, but only while therapy is administered. Finally, it is possible that socioeconomic and psychologic factors interact in some way with *APOL1* high-risk status. For example, because race is strongly related to *APOL1* risk allele carriage rates and because in the United States and certain other countries, race remains correlated with adverse socioeconomic and psychologic factors, these sociopsychologic factors could contribute to the worse outcomes associated with *APOL1* high-risk status.

Next to be considered is by far the most common manifestation of *APOL1* kidney disease, the clinical syndrome of hypertension and CKD with subnephrotic proteinuria in which causes, such as diabetes and GN, have been excluded. Pathologic manifestations characteristic of individuals with *APOL1* high-risk genotype and a pathologic diagnosis of arterionephrosclerosis include solidified and disappearing glomerulosclerosis, thyroidization-type tubular atrophy, and microcystic tubular dilations while having less arteriosclerosis than others. Analysis of the *APOL1* high-risk genotypes in the African-American Study of Kidney Disease in Hypertension demonstrated that *APOL1* high-risk individuals with hypertension and reduced eGFR tended to have heavier proteinuria and faster GFR loss compared with blacks with *APOL1* low-risk genotypes (5).

The relationship between albuminuria or proteinuria and the *APOL1*-associated CKD is not fully understood. Several patterns may be recognized. Many individuals may have stable low-level proteinuria and nonetheless, manifest progressive CKD. Others may proceed through sequential phases of increasing albuminuria and falling GFR. Still others may present with nephrotic syndrome and rapid progression to ESKD. Because it seems that the first two patterns are most common, genetic testing to identify *APOL1* high-risk individuals followed by regular screening for proteinuria beginning during teenage years or early adulthood and the initiation of antiproteinuric therapy on appearance of microalbumimnuria might yield clinical benefit, although this would have to tested in a randomized, controlled trial. Certainly, screening for albuminuria and institution of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker are standard of care in individuals with diabetes

Table 1. Preliminary recommendations for clinical testing of *APOL1* kidney risk genotype

Condition	Recommendation for *APOL1* Genetic Testing
FSGS	Consider testing in selected patients for prognosis and possibly improved adherence
HIV-associated nephropathy	Consider testing in selected patients for prognosis and possibly improved adherence
Other CKD with subnephrotic proteinuria	Consider testing in selected patients for prognosis and possibly improved adherence
Lupus nephritis	Consider testing in selected patients for prognosis and possibly improved adherence
Preeclampsia	Consider testing pregnant women to identify those at increased risk for preeclampsia and who should receive close monitoring
Living kidney transplant	Testing indicated for prognosis of donors and recipients
Deceased kidney donors	Testing indicated for prognosis of recipients
Kidney transplant recipients	No testing of recipients, because recipient *APOL1* genotype has no effect on kidney outcomes

For many of the kidney diseases shown, other factors may also contribute, such premature birth, obesity, uncontrolled hypertension, and failure to control an underlying disorder, such as HIV or lupus. Preliminary recommendations are suggested; professional society guidelines have not been published. The clinician and the patient must decide together whether the prognostic information for the particular condition would be useful to the patient, possibly increasing adherence to a particular screening or therapeutic regimen.

mellitus, both type 1 and type 2. However, *APOL1* high-risk individuals might experience an event, perhaps a prolonged viral infection, that acutely increases systemic IFN expression and results in sudden increases in kidney *APOL1* gene expression. Defining kinetics of incipient *APOL1* nephropathy as accumulative or crescendo or more likely, complex and distinct patterns among individuals will require long-term follow-up of *APOL1* high-risk individuals, starting when they have normal kidney function. The findings might inform approaches to screening.

Reidy *et al.* (6) reported that fetal, and not maternal, genotype is associated with higher risk for preeclampsia with mothers carrying fetuses with two *APOL1* risk alleles. Prospective studies are needed to determine whether early identification of increased preeclampsia risk associated with *APOL1* risk status, by prompting more intensive prenatal care, improves maternal and fetal outcomes.

Now, 9 years after the identification of the *APOL1* kidney risk variants, it remains unclear in what conditions *APOL1* genetic testing is clinically indicated. There are several steps along the path to precision medicine. One step will be understanding the molecular and cellular pathways of cell injury induced by these variants, with the goal of identifying therapeutic targets that might be suitable for the design of specific therapies. Another step will be rigorous studies of both short-term (such as proteinuria) and long-term outcomes (progressive loss of kidney function, eventuating in ESKD) in *APOL1* high-risk individuals. In the case of FSGS, *APOL1* high-risk individuals respond just as well as others with regard to reduction of proteinuria, but they progress to ESKD faster than *APOL1* low-risk blacks or whites (4). Approaches being tested now for *APOL1* kidney disease include adrenal corticotropic hormone in humans (National Clinical Trial 02633046) and antisense oligonucleotides in *APOL1* transgenic mice.

At present, there is no evidence that any particular therapeutic approach to the treatment of *APOL1* high-risk individuals with glomerular disease or hypertension or those having had kidney transplant is superior to the standard treatments. This weakens the case for clinical *APOL1* genetic testing at this time. Parsa *et al.* (7) concluded that the lack of an interaction between *APOL1* status and treatment with an angiotensin-converting enzyme inhibitor medication with regard to progression to ESKD suggested that *APOL1* high-risk individuals still benefit from this medication class. Future studies are likely to provide relevant information on these points. One argument is that genetic test results, when delivered to patient, might alter behavior in ways that would be conducive to healthy outcomes. These might include improved medication adherence, healthier diet, weight loss, smoking cessation, and other factors. Importantly, one must acknowledge that none of these interventions or lifestyle changes have been prospectively tested among individuals with this genetic risk. Recent studies of community attitudes have revealed a strong preference among at least some blacks to have more knowledge about *APOL1* genetic risk and be offered the option of genetic testing (8). Knowledge of genetic test results might also alter the practice of the physician who, with knowledge of the increased risk of adverse outcome, might stress the same points. Clearly, these effects on physician and patient behavior should be tested in prospective studies. One can argue that return of genetic results requires a full understanding of the effect of return of these results. Yet, as is often the case, physicians and patients must often make decisions in absence of convincing data from well designed, well executed studies. In Table 1, we have presented our opinions regarding the evidence level that supports clinical *APOL1* genetic testing at this time.

Perhaps the most compelling case for clinical *APOL1* testing at present relates to kidney transplantation. Data from multiple groups have established that *APOL1*-associated risk operates at the level of the kidney. First, transplanted kidneys from living and deceased *APOL1* high-risk donors fare slightly worse than non-*APOL1* high-risk kidneys. Nevertheless, the allograft survival differences are modest, and the benefits of transplant outweigh the hazards of remaining on dialysis. Second and importantly, preliminary data suggested that living donors with an *APOL1* high-risk genotype compared with those with a low-risk genotype have lower eGFR at follow-up and a faster decline in eGFR during the period after kidney donation (3). These observations are being evaluated on a broader scale in the National Institute of Diabetes and Digestive and Kidney Diseases–funded APOL1 Long Term Kidney Transplant Outcome Network (National Clinical

Trial 03615235), which aims to determine the current kidney status of all United States kidney transplant recipients who received kidneys from blacks, a number estimated to be as high as 5000 potential study participants. At present, some physicians are testing potential living donors for *APOL1* risk alleles before kidney donation and providing those with high-risk *APOL1* genotypes information about increased risk for CKD, but at present, there is not a consensus recommendation to take this approach (9).

There are many clinical situations where the role of *APOL1* genetic testing remains to be defined by focused clinical studies to establish whether genotype knowledge prompts behavioral change on the part of the individual or prompts interventions by clinicians that are known to lead to better health outcomes in many forms of CKD. These situations involve individuals with risk factors for kidney disease, including those with history of premature birth, hypertension, and obesity. This topic brings together issues of minority health and genetic testing (8) as well as the involvement of the affected communities (10). A key long-term goal is to develop effective therapy for *APOL1* kidney disease by elucidating the pathways of kidney injury and targeting these pathways to enable preventive therapy in those at greatest risk and treat these conditions more effectively than we do at present.

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