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Clinical genetic testing for APOL1: Are we there yet?

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Abstract

Endstage renal disease (ESRD) disproportionately affects African Americans, who are 2–4 times more likely than European Americans to develop ESRD. Two independent variants of the Apolipoprotein L1 (*APOL1*) gene, G1 and G2, have been associated with a 7 to 10-fold greater risk of developing non-diabetic ESRD in African Americans. Those who inherit two risk variants (G1/G1, G2/G2 or G1/G2) are also more likely to develop ESRD at a younger age and to have progression of chronic kidney disease (CKD). Currently it is not known what proportion of persons with high-risk genotypes will develop ESRD in the general population; the exact mechanism of injury for *APOL1*-related risk; its relation to environmental exposures; or whether those with co-morbid conditions are more likely to develop ESRD. To address these uncertainties, research that includes assessment of *APOL1* status is needed before guidelines for general testing can be endorsed. Currently, *APOL1* testing has been proposed as part of kidney transplant protocols both for living donors and recipients. Yet because of uncertainties regarding the clinical implications of *APOL1* variants, testing could generate confusion, anxiety or stigma. Multiple forms of evidence, including the views of community members, are needed to support responsible approaches to providing information about *APOL1* status as part of clinical care or in population

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screening. Informed consent with subsequent counseling regarding the risks and benefits of APOL1 testing should be considered for those at high risk.

Keywords

genetic testing; African Americans; APOL1; apolipoprotein L1; kidney disease

Apolipoprotein L1 (*APOL1*) and Current Clinical Knowledge

Gene variants in the *APOL1* gene are associated with an increased risk of end stage renal disease (ESRD). Among United States (US) populations, these variants are found primarily in African Americans. There are many uncertainties about the gene-disease association, however, and the utility of clinical *APOL1* testing is controversial. Genetic testing in kidney disease was last reviewed in the 2010 issue of Seminars in Nephrology. The current manuscript will review the literature regarding genetic testing and *APOL1*.

The persistently increased incidence of end stage renal disease (ESRD) among African Americans compared to European Americans has long raised the possibility that the difference might be partially genetic in origin. Numerous investigations of this question culminated in localization to chromosome 22 of an inherited risk for non-diabetic kidney disease, originally attributed to a variant of the *MYH9* gene.^{1,2} Further evaluations led to the discovery that two *APOL1* variants (named G1 and G2) located on chromosome 22 in tight linkage with *MYH9* were, in fact, associated with the increased risk.^{3,4} The G1 variant encompasses two nonsynonymous coding region SNPs that replace amino acids at positions 342 (ser->gly) and 384 (ile->met), while the G2 variant is defined by a 6-bp deletion that results in the in-frame removal of amino acids 388 and 389 (asp and tyr, respectively); each occurs on a distinct haplotype background, i.e. the variants are independent of one another.⁵ The initial studies found that African Americans with two risk variants (G1/G1, G2/G2, or G1/G2) were at 10.5-fold (95% CI 6.0–18.4) greater risk of focal segmental glomerulosclerosis (FSGS)-associated ESRD, 7.3-fold greater risk of hypertensive ESRD (95% CI 5.6–9.5), and 7.5-fold greater risk of HIV associated nephropathy (HIVAN) ESRD compared to African Americans with one or no copies of the *APOL1* variants.³ Initial studies showed that greater than 30% of African Americans carry at least one risk allele,⁶ and the prevalence of the two-risk allele diplotype among African Americans is approximately 12%.⁷ Greater ESRD risk is attributed to the G1 variant compared to the G2 variant.³ Subsequent work has shown that the *APOL1* variants are associated with an increased risk of chronic kidney disease (CKD),⁸ lower age of dialysis initiation,^{9,10} sickle cell kidney disease,¹¹ and increased risk of kidney transplant failure.¹² Additional analyses in large population-based cohort studies have shown that African Americans with two risk variants of *APOL1* had a 5.71-fold (95% CI 3.6–8.9) greater odds of incident albuminuria that decreased to 3.5-fold (95% CI 2.1–5.7) after adjustment for clinical and socioeconomic risk factors, while in those with one or no risk variant, the odds decreased from 2.32 (95% CI 1.7–3.1) to 1.21 (95% CI 0.9–1.7) when compared to similarly aged European Americans.¹³ However, known risk factors for CKD progression and socioeconomic factors, such as income, did not attenuate the risk of progression attributed to *APOL1* in subjects

with CKD,^{14,15} raising the possibility that the genetic risk may play a greater role in disease progression than in initiation of disease. Thus, additional research with replication is needed to determine the public health risk of development of kidney disease associated with *APOL1* in the general population, appropriate measures to alleviate risk, and whether widespread screening for *APOL1* should be recommended for African Americans.

***APOL1* Testing in Research and Clinical Care**

Many questions thus remain regarding the association between the *APOL1* risk variants and kidney disease, including the extent to which the G1 or G2 variants increase CKD risk in healthy people and the apparent absence of an effect on diabetic nephropathy.¹⁶ More fundamentally, the biological mechanism by which the *APOL1* variants influence kidney function remains unknown. Further research could lead to a better understanding of CKD risk in African Americans and provide important new therapeutic insights. However, to pursue this research agenda, many more African Americans will need to become involved in relevant research, and as they participate, their *APOL1* status will need to be ascertained. Given changing norms with regard to the communication of individual research findings,^{17–19} decisions will have to be made about whether, and if so how, to return such information to research participants. African American patients may also be offered *APOL1* testing in clinical settings, based on the assumption that individuals with increased risk might benefit from careful monitoring of blood pressure and kidney function, together with lifestyle coaching to reduce other risk factors for CKD. However, the effectiveness of this approach to prevention of ESRD remains to be proven.²⁰ It has also been suggested that *APOL1* testing might be used to screen renal transplant donors.²¹

Attitudes Toward Genetic Testing among African-Americans

There is a mixed-history of attitudes towards genetic testing among African Americans, such that exploration of views regarding testing is warranted. One example of particular relevance to nephrology is testing for sickle cell disease (SCD) and trait (SCT). Sickle cell screening programs were originally initiated in the 1970s and generated considerable mistrust within the African-American community. Many programs were mandated by state law, and were implemented with inadequate privacy protections, counseling, and clinical follow-up^{22–25} Confusion between SCD and SCT was common, and made worse by poor physician knowledge.^{26,27} Social stigma and diverse forms of discrimination occurred,^{27–30} and sickle screening came to be viewed by many in the African-American community as an effort on the part of a white power structure to impose a stigmatizing genetic screening program on a minority population.²⁷ This negative history has been to some extent supplanted by more positive programs. Newborn screening for SCD, for example, was instituted in the 1980s, based on evidence that early initiation of penicillin treatment could be lifesaving.³¹ With those national programs in place, those with SCT are identified at birth; however, few parents are notified of SCT status and even fewer adults of childbearing age know their SCT status.³² In a community-based study evaluating SCT status, only 37% of parents were notified that their newborn had SCT.³³ It is additionally unclear whether parents understand the implications of a positive test and if information is shared with the affected child during adolescence, when decisions regarding sexual activity and participation in sports may be

occurring. There is evidence of lingering mistrust of genetics and genetic testing among African Americans in other clinical settings, such as testing for breast cancer risk alleles.^{34,35} In the context of this history, genetic testing to assess kidney disease risk poses trade-offs for African Americans and their health care providers. SCT has been shown to be a risk factor for CKD,¹⁶ making the issue of SCT testing more complex, with uncertainties about the clinical value of identifying the kidney disease risk because of uncertainty about the benefits of interventions to reduce risk.

Testing for *APOL1* gene variants raises even more questions because of the uncertainties about their clinical impact. It is unclear whether genetic testing to identify kidney disease risk should be considered until more information is known, particularly concerning the views the general population of African-Americans about such testing. In considering this question, three clinical situations merit attention. Each of these poses potential benefits and risks for which community input would be helpful.

Assessing APOL1 Status in Research

The prospect of testing people for *APOL1* status raises ethical questions across a number of contexts. One question concerns the return of *APOL1* results to research participants and whether the participants should be told their individual research results. The benefits of returning information must be weighed against both the potential for participant harm (such as stigma or anxiety deriving from risk information and misunderstanding of results, in particular for those found to have one *APOL1* risk variant) and the potential for unwarranted diversion of research resources to the disclosure process.

APOL1 testing in Clinical Care

A second question concerns *APOL1* testing of individual patients with *CKD* risk factors, weighing the potential benefits of more aggressive preventive management for those with positive results (e.g., more intensive blood pressure management, more frequent assessment of kidney function) against potential harms (including stigma, anxiety, and misunderstanding of positive results, as well as inappropriate treatment and treatment costs based on over-estimation of risk, or in the case of negative findings, false reassurance). This use of *APOL1* testing in the GUARDD study (Genetic testing to Understand and Address Renal Disease Disparities) is a randomized trial designed to determine the effects, challenges, and clinical outcomes associated with incorporating clinical *APOL1* genetic information in a primary care setting in the treatment of hypertension in blacks.²⁰ The study will be one of the first that shows how implementation of a precision medicine tool may be used in a clinical service, and may provide important insights into how clinicians and patients respond to genetic information of unclear clinical utility.

Genetic Testing in Transplantation

A third question concerns *APOL1* testing of prospective kidney donors, weighing the donor's potential interest in retaining a kidney (as a hedge against future kidney disease) against the recipient's need for a kidney and also, at a societal level, weighing efforts to

assure recipients the “best possible” kidney against the severe organ shortage faced by African Americans seeking kidney transplants. Genetic testing for *APOL1* status of potential living transplant donors or potential recipients of a kidney transplant is controversial, even as some transplant centers have begun *APOL1* genetic testing of potential donors and recipients and clinical decisions are being made depending on *APOL1* status.³⁶ Screening of all African Americans for high-risk alleles may lead to exclusion of up to 13% of African Americans, and negatively affect the availability of living donor transplants for African Americans and potentially other kidney transplant recipients. Recent data suggest that receipt of a kidney from a donor positive for *APOL1* high-risk genotypes was associated with decreased survival of the kidney.¹² In response, Lee and colleagues evaluated 119 African Americans and found 58 (48.7%) carried high-risk genotypes. No differences in kidney survival were found at 5 years after adjusting for kidney type; however, no information on recipient genotypes was available.³⁷ Reilla and Sheridan suggest that not enough information is available to advocate for genetic testing of high-risk variants in all living donors of African-descent.³⁸ There is also insufficient data to justify an absolute contraindication to kidney donation based on the presence of two high-risk *APOL1* alleles. If testing is done, clinicians need to stress the relative increase in risk of kidney disease with potential at-risk donors-particularly the young. The absolute versus relative risk and the limitations of available data must also be carefully explained to both potential kidney donors and recipients. Data should be collected prospectively on donors to understand the true risk of *APOL1* high-risk variants and risk of ESRD in living donors. Developing appropriate counseling approaches, and training nephrologist to provide them, is important, as is consideration of the risk of lower kidney survival from a high-risk donor for transplants involving young patients (children, adolescents, young adults).³⁸

General Screening for *APOL1*

A fourth question involves a public health scenario where screening of *APOL1* in African Americans is considered, weighing potential benefits (if any) of knowing a population's or individual's potential risk for kidney disease (aggressive treatment of potential risk factors (obesity, diabetes, and hypertension) versus potential harms (lack of data showing reduced risk of CKD or ESRD with treatment of risk factors in population based studies; anxiety, stigma, and guilt). Additional research is needed to identify whether nephrology clinicians are comfortable with providing genetic testing results and counseling; what information patients wish to receive regarding *APOL1* in various clinical scenarios; whether African-American communities want public screening for *APOL1*, given the prior history of screening with sickle cell screening; and whether *APOL1* should be a component of precision medicine in primary care settings.

Community Views

In each of these clinical scenarios, *APOL1* testing poses potential benefits and risks. In essence, the question is whether risk information can be helpful when there is uncertainty about the best course of action to take to reduce risk. Little is known about African American community views on this issue. Freedman and colleagues evaluated attitudes regarding return of genetic testing information in African Americans and European

Americans with first degree relatives on dialysis and found that both African and European Americans wished to know test results if risk of disease could be reduced by diet and exercise, medical treatment, and many would want to know even if no treatment were available; respondents also noted that they would share this information with family. Given this was a limited survey study in a small population, results point toward the need for larger studies that address issues regarding receipt of genetic testing information in large ethnic populations.³⁹

Principles of Genetic Testing for Nephrologist and Renal Clinicians

Many nephrologists who provide care to adult patients have little experience with genetic testing, yet are still providing and making diagnosis of genetic kidney diseases to patients. Some manage patients with autosomal-dominant polycystic kidney disease, which is one of the most common genetic disorders in nephrology, affecting 1:500 to 1000 people worldwide,⁴⁰ but have little exposure to genetic counseling training.⁴¹ Compared to pediatric nephrologists, who may routinely be required to assess rare genetic associations with kidney disease and who have access to genetic counselors who can communicate differences to patients and provide counseling, adult patient nephrologists should be adequately trained in principles of genetic counseling, including: 1) what genetic test is appropriate; 2) when is research testing useful, but what are the pitfalls with using this type of testing; 3) how to obtain relevant clinical genetic family histories; 4) how to obtain informed consent, and 5) how to assist with decision making regarding genetic testing. Additional counseling techniques, which include exploring concerns, fears, feelings regarding specific testing, reflection, and re-phrasing are important tools that must be included in nephrology training.

Patient Safety in Genetic Testing

As in other areas of medical care, patient safety is a concern with genetic testing. Potential sources of medical error include: incorrect or inappropriate test ordering; failure to proceed with indicated testing; errors associated with analysis for genetic variants; and receipt of distressing genetic information associated with adverse patient outcomes.⁴² Errors can lead to increased cost for patients if incorrect testing is done or if insurance companies refuse to pay for testing, or can have unanticipated adverse outcomes if the information relayed to patients is frightening for them.⁴² Little is known regarding patient safety in genetic testing for kidney disorders. The frequency of errors in test ordering or follow-up has not been evaluated, and there is limited information about receipt of genetic testing information for *APOL1* among African Americans.

Current ongoing Research

Ongoing research for *APOL1* and risk of developing ESRD and CKD in the general population will help to elucidate the risk for African Americans. Concerns regarding different genetic alleles associated with ESRD risk remain, given the history associated with the initial identification of MYH9 and risk of ESRD in African Americans. Additional research is needed to assess the views of researchers, clinicians, and community members

regarding clinical testing and return of genetic testing results. The NIH-sponsored grant “Community-based evaluation of *APOL1* Genetic Testing in African Americans” will determine African-American community views concerning the risks and benefits of returning information about *APOL1* risk variants to research participants and testing for *APOL1* risk variants in clinical care and renal transplant programs, and will promote inclusion of those views in policy discussions. This project will incorporate a combination of community and scientific advisory boards; qualitative interviews of kidney patients, family members, community members, nephrologists and primary care providers; and deliberative groups to identify community members’ priorities and underlying rationales for preferred approaches to return of *APOL1* research results and testing in clinical contexts. The project will culminate in a national stakeholder meeting, which will review current research regarding *APOL1* and findings from the community members and community-based deliberative groups to develop guidance for national guideline development. Results from this study, will be used to identify critical next steps in determining best practices related to the return of *APOL1* research results and use of clinical *APOL1* testing.

Recommendations

Findings from the above study will provide a deeper understanding of the concerns and issues that are most salient for individuals considering whether or not to pursue or receive information about their *APOL1* status. Information about preferences related to on-going community involvement in the development of policies and practice standards related to return of *APOL1* research results and clinical *APOL1* testing are crucial moving forward with clinical guidelines for return of *APOL1* genetic testing results to the African American community. Results could inform the study design of randomized trials intended to evaluate different approaches to return of results and clinic testing, educational strategies, and/or mechanisms for community input and oversight. In that regard, some transplant nephrologists feel that use of *APOL1* genetic testing is “premature” and that use of this information would adversely affect African Americans and “is likely to disadvantage African American patients waiting for a transplant, result in more discards, and contribute to lower wait list survival for those who should have been transplanted”,⁴³ while others feel that every African American should be tested for *APOL1*. To address these concerns, additional prospective data is needed to determine absolute and population attributed risks for decreased survival of kidneys from donors with one or two risk variants, as well as for potential recipients who have one or two *APOL1* risk alleles.

Conclusions

While clinical testing for *APOL1* is in its infancy, controversy exists as to whether clinical testing should be considered prior to the availability of specific data that address all the above concerns. Precision medicine approaches to *APOL1* testing and treatment are currently being considered, but nephrologists need to have relevant genetic counseling tools in order to provide prospective study participants and patients with accurate information for genetic testing, educational information for patients and family members interested in genetic testing, and public policy guidelines regarding who should be tested, how testing should be done, who will pay for testing, and how testing results should be given back to

those tested. In addition, nephrology trainees need training in genetic education in order to address these issues in clinical practice. Future research will address many of these issues, but prior to those results, the question remains as to whether or not genetic testing should be done. Currently, there is not enough evidence for guidance in one direction or another, and may be prudent to conduct testing only in high-risk individuals who wish to pursue genetic testing after being informed of all known risks and benefits that are associated with it.

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Table.

Pros and Cons of APOL1 Genetic Testing

Pros	Cons
Evidence for decreased cadaveric transplant survival	No evidence of decreased transplant survival based on recipient genotype
Increased risk of non-diabetic kidney ESRD	No general population information regarding risk of developing ESRD with one or more genotypes
Societal benefit for transplant distribution	Individual right to know or not know the results
Right of transplant recipient to know if living donor kidney has APOL1 genotypes	No evidence that kidneys from living donors with APOL1 high risk genotypes have decreased kidney survival
Testing for APOL1 to institute preventive measures for development of kidney disease, such as hypertension, obesity, diabetes control	No evidence to suggest that preventive measures decrease the risk of development of kidney disease among those with low or high risk APOL1 genotypes
Living donors have a right to know whether they might be at increased risk of kidney disease, based on their APOL1 genotype	No evidence that unilateral nephrectomy increases the risk of development of CKD or ESRD in living kidney donors.
Piece of mind in known test results	Increased anxiety, fear, and mistrust of the medical establishment, since evidence of risk is currently unknown