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Race, Ancestry, and Genetic Risk for Kidney Failure

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Racial and ethnic disparities in chronic kidney disease (CKD), up to and including kidney failure, have been well documented in the United States and globally.[1,2] There are myriad factors underlying these observations, including race-based inequities in the distribution of health-affirming resources and opportunities (eg, structural racism),[3] the cumulative burden of psychological and neurohormonal stress termed "weathering,"[4] and more, that contribute to the development and/or progression of major CKD risk factors (hypertension and diabetes), CKD, cardiovascular disease, and other chronic diseases.[1]

In addition to these factors, recent discoveries have shown that having 2 coding variants of the apolipoprotein L1 (*APOL1*) gene (G1/G1, G1/G2, G2/G2) is associated with an increased likelihood of developing CKD and kidney failure.[5,6] This "high-risk"-for-CKD genotype is found almost exclusively in persons of West sub-Saharan African ancestry, thereby typically impacting a subset of persons who self-identify as Black or African American. These polymorphisms are hypothesized to have developed as a protective response to trypanosomiasis-induced sleeping sickness.[5] Notable features of the high-risk *APOL1* genotype and associated "*APOL1*-associated nephropathy" include the following: (1) an ancestral heritage that primarily relates back to persons from West sub-Saharan Africa; (2) risk of kidney disease that is apparently only increased in persons with 2 *APOL1* risk alleles (ie, high-risk genotype); (3) knowledge that not all individuals with a high-risk genotype develop kidney disease (only an estimated 20% do); (4) the incidence and progression of many forms of *APOL1* nephropathies are associated with "second hit" triggers, such as HIV infection,[7] SARS-CoV-2 infection,[8,9] systemic lupus erythematosus,[10] other proinflammatory stimuli including iatrogenic interferons,[11] and reduced nephron endowment following kidney donation;[12] (5) a typical histologic profile of glomerular sclerosis accompanied by tubulointerstitial and vascular changes;[13,14] and (6) although this *APOL1*-associated genetic risk is unrelated to societal differences, disease activation is grounded in many factors that are driven by societal inequities.

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The current lack of specific treatment for *APOL1*-associated kidney disease and the incomplete penetrance of kidney disease risk in persons with a high-risk *APOL1* genotype raise the question regarding the utility of testing self-identified Black or African American persons for *APOL1* genotype. For example, establishing that a patient with early-stage CKD also carries a high-risk *APOL1* genotype may lead to the patient's becoming worried and anxious about the possibility of progressing rapidly to kidney failure with no opportunity for treatment to potentially slow progression. Similarly, informing a healthy person who is currently free of kidney disease that they have a high-risk *APOL1* genotype may also provoke anxiety about the future and may possibly lead to life or health insurance discrimination. Although the Genetic Information Nondiscrimination Act bars the use of genetic information in health insurance and employment, it does not bar its use for life insurance purposes, and such laws are not fully protective.[13] It is not surprising that recommendations from broad constituent groups have been equivocal regarding *APOL1* genetic testing in the clinical setting (Box 1).[13] However, early surveys show that many people in the African American community are indeed interested in knowing their *APOL1* genotype, and only a paucity have expressed concerns or worry about their results and the implications of those results.[15–17] Whether disclosing *APOL1*-associated nephropathy testing results to patients and their clinicians may have a positive effect on patients' health is unknown. The availability of such knowledge might better inform the decision to test persons at risk for *APOL1*-associated nephropathy.

Interestingly, not all studies have found that clinicians, researchers, and community members are equally positive about the use of *APOL1*. West et al[18] reported more than 80% of a group of 76 stakeholders (clinicians, researchers, and community members) expressed the opinion that research participants should be offered their *APOL1* results, with the majority of those reluctant being clinicians and researchers. A study by Young et al[16] reported similar findings, with clinicians and researchers generally being more negative than community members about *APOL1* testing in routine clinical care. These concerns ranged from possibly causing patient and family members psychological harm to potential provider frustration having to return a test result with important clinical implications for which there is no treatment.[16,17]

Given these patient and provider concerns of a patient having knowledge of a high-risk *APOL1* genotype, Nadkarni et al[19] examined the effects of testing *APOL1* genotype in patients with hypertension and without CKD who self-reported as having African ancestry and disclosing the results to both patients and their providers.

What Does This Important Study Show?

The study by Nadkarni et al used a pragmatic randomized clinical trial design that enrolled more than 2,000 patients from 15 academic, community, and safety-net practices across 2 health systems. Inclusion criteria were patients who were English speaking, were 18-70 years of age with an electronic health record diagnosis of hypertension and/or taking antihypertensive medications, and were receiving primary care at a participating site in the past year. Exclusion criteria included diabetes, CKD, cognitive impairment, pregnancy, and

moving away during the study period. Patients and providers were assigned to receive results immediately (intervention) or after a 12-month delay (wait-list control).

Primary study outcomes included both the change in 3-month systolic blood pressure (BP) and 12-month urine kidney disease screening between intervention group patients with high-risk *APOL1* genotypes compared to those with low-risk *APOL1* genotypes. Secondary outcomes compared the same clinical outcomes between intervention group patients with high-risk *APOL1* genotypes and wait-list controls. Exploratory analyses included psychobehavioral factors including lifestyle changes and medication adherence.

Participants had a mean age of 53 years and a mean BP of 134/86 mm Hg. Patients received *APOL1* genetic testing results from trained staff; in addition, their providers received results through electronic health records. In response to disclosure of *APOL1* results, the study team found that patients with high-risk *APOL1* genotype had a more robust response in taking positive action in almost all health domains compared to those with low- or no-risk *APOL1* genotype. Those with high-risk compared to low-risk *APOL1* genotype reported more positive lifestyle changes (eg, better dietary and exercise habits; 59% vs 37%; $P < 0.001$), increased urine testing for albuminuria (12% vs 7%), increased BP medication use (10% vs 5%; $P = 0.005$), and a trend toward a greater fall in systolic BP (6 vs 3 mm Hg; $P = 0.01$). Importantly, 97% of patients reported they would get tested again. In addition, the exploratory assessment of psychobehavioral factors found significantly more patients with high-risk *APOL1* genotypes than patients with low-risk *APOL1* genotypes reported making positive lifestyle changes and improved medication adherence.

This study is the first to report that disclosing the presence of high-risk *APOL1* genotype profile to patients with hypertension and their clinicians led to improved CKD prevention/early intervention actions without report of untoward psychologic effects from the knowledge of having a high-risk medical condition. These findings support the potential of implementing genetic testing in the primary care setting as well as the importance of using trained professionals to transmit sensitive genetic results.

The study has some limitations. The study excluded patients with CKD, and their response as well as that of their providers may differ in that setting. There may have also been confounding (eg, kidney function, severity and treatment of hypertension, lifestyle factors) that could affect study outcomes. The study was unable to capture the impact of returning patient results on their family members. This study also had several strengths. Nadkarni et al used a unique approach by testing *APOL1* status in patients with self-reported African ancestry and CKD risk (hypertension) treated in a primary care setting. With poor control of hypertension being both a traditional CKD risk factor and a potential accelerator of *APOL1*-associated nephropathy, the impact of knowledge regarding additional CKD risk on both patient and provider actions was assessed and found to be helpful. This has powerful implications for a large percentage of patients who may feel less internalized blame with this knowledge and thus be more motivated to do all they can do. Moreover, the use of trained staff supervised by a senior genetic counselor to return test results in a sensitive and consistent manner was another strength of this study.

How Does This Study Compare With Prior Studies?

The study by Nadkarni et al assessed the impact of testing of *APOL1* status in a group of patients at risk for CKD, in contrast to most studies that have examined perceptions of *APOL1* testing in patients with CKD (including kidney transplant recipients) and, to a lesser extent, kidney donors. Recent studies by Umeukeje et al,[15] Young et al,[16] and West et al[18] used a series of interview or focus group techniques that included African American community participants, scientific advisors, researchers, clinicians, bioethicists, patient advocates, and representatives from professional organizations and/or federal funding agencies. They found strong support from study participants for developing educational materials about *APOL1* for community members and clinicians, the use of *APOL1* testing in kidney transplant programs, returning *APOL1* results to research participants, and the need to building trust between the African American community and the broader medical community.[16] However, given the lack of treatment and the potential risk of activating psychological burdens, such as stigma, discrimination, and more, there was mixed support offering *APOL1* testing in a clinical care setting, though a trend to offer support was noted more so from patient stakeholders than from health professionals.[15-17] Similar conclusions were reached by a multidisciplinary group that used a Delphi consensus process and conducted a systematic literature review regarding practical measures for caring for patients who may have *APOL1*-associated nephropathy.[13] They further suggested there was a need to increase awareness of both racial health disparities in CKD and of *APOL1*-associated nephropathy among key stakeholders, as well as an urgent need for research to develop a specific treatment.

What Are the Implications for Nephrologists?

It is important for practicing physicians to recognize that a patient with unclear reasons for the development or progression of CKD may have an underlying high-risk genetic disorder such as *APOL1*-associated nephropathy.[20,21] A family history of CKD as well as a family history of West African ancestry would help to prioritize testing for the presence of a high-risk *APOL1* genotype. However, the lack of such history should not preclude *APOL1* genotype testing, especially in patients with glomerular sclerosis, because high-risk *APOL1* genotype may be found in subsets of such patients who may not self-identify as Black or African American.[21] Thus, such testing should be included alongside the continued search for other causes of CKD progression, such as nonadherence, occult inflammatory disease, and autosomal dominant polycystic kidney disease, among other possible causes. Moreover, the significant benefits associated with reporting *APOL1* genotype results to patients with hypertension without CKD in the study by Nadkarni et al argues in favor of returning *APOL1* results to not only research participants but also patients at risk. The finding that providing *APOL1* test results led to a reduction in systolic BP, increased kidney disease screening, and improved self-reported behavior changes in patients with high-risk genotypes was unexpected, given a prior Cochrane Review by Hollands et al[22] that found communicating DNA-based risk estimates did not change behavior. This novel finding can, however, help to allay the previously reported concerns by some providers of there being no tangible clinical management action from returning *APOL1* results to patients. If the *APOL1* result is entered into a privacy-protected section of the patient's electronic medical record,

it may lessen concern about discrimination by life insurance providers. As providers, we also need to be cognizant of not only the potential impact of *APOL1* testing for the patient but also the potential implications for family members. Such information from knowing a nonactionable risk result may also cause them anxiety and concern regarding potential stigma and discrimination and may cause them to possibly act upon the information inappropriately if misunderstood, especially if it is not transmitted by a trained professional. As our understanding evolves regarding CKD—including *APOL1*-associated nephropathy—and its treatment, we must remain diligent regarding the intersection of social and biological determinants of health if we are to bring the best care to all of our patients each and every day.

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Box 1.

Adapted Excerpts from Consensus Statements on *APOL1*-Associated Nephropathy

- *APOL1*-associated nephropathy should be considered in all patients with progressive kidney disease and a family history of CKD, particularly those with West African ancestry.
- Regardless of ancestry, *APOL1*-associated nephropathy should be considered in all patients with kidney disease and a family member with a confirmed high-risk *APOL1* genotype.
- Clinical factors that are relevant to considering *APOL1*-associated nephropathy include hypertension, nondiabetic nephropathy, and rapid progression of CKD despite quality care.
- For a patient with *APOL1*-associated nephropathy, important advantages of learning their *APOL1* status may include:
  - a better understanding of the likelihood of rapid disease progression
  - an awareness that they are not to blame for their disease
  - greater knowledge about their ancestry
  - increased motivation to live a healthy lifestyle and control CKD risk factors
  - the potential for family members to learn their own *APOL1* status and potential risk for CKD
  - the potential opportunity to participate in a clinical trial testing a treatment for *APOL1*-associated nephropathy
- Clinicians will require confidence in communicating the findings from *APOL1* testing to patients in a clear and effective way that minimizes patient confusion and misunderstanding of *APOL1* testing in patients at risk.
- Effective communication is necessary to minimize patients' fear, distress, anxiety, or a sense of futility, as well as any confusion about the meaning of high-risk *APOL1* status, as a potential outcome of *APOL1* testing.
- Potential concerns related to *APOL1* testing that each patient should be aware of include:
  - cost associated with testing
  - implications of a positive test
  - fear of being diagnosed with *APOL1*-associated nephropathy
  - concern about disease progression

- discrimination (eg, job, life insurance), as well as future health insurance access and cost
- concern that there is no treatment and therefore no value in knowing
- concern for family members who may have a high-risk *APOL1* genotype

- When health care professionals discuss *APOL1* testing with their patients, they should be honest and transparent about our current understanding of *APOL1*, take time to discuss *APOL1* with patients, listen to their concerns, answer questions, and provide information sources that are balanced, easy to use and understand, and reliable.

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