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Genomics in Chronic Kidney Disease: Is this the Path Forward?

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Abstract

Recent advances in genomics and sequencing technology have led to a better understanding of genetic risk in chronic kidney disease. Genetics could account in part for racial differences in treatment response for medications including antihypertensives and immunosuppressive medications due to its correlation with ancestry. However, there is still a substantial lag between generation of this knowledge and its adoption in routine clinical care. This review summarizes the recent advances in genomics and chronic kidney disease, discusses potential reasons for its underutilization and highlights potential avenues for application of genomic information to improve clinical care and outcomes in this particularly vulnerable population.

Keywords

Genomics; Disparities; Genetics; Chronic Kidney Disease; Kidney Failure; Pharmacogenomics

INTRODUCTION

Chronic kidney disease (CKD) affects an estimated 10% to 15% of individuals in the United States.¹ CKD is a largely asymptomatic yet serious condition associated with premature mortality, decreased quality of life, and increased health care expenditure. Untreated, it can result in end-stage renal disease (ESRD) and necessitate dialysis or kidney transplantation. It is also a major independent risk factor for cardiovascular disease (CVD), mortality and all-cause mortality.^{2,3} Approximately two thirds of CKD are attributable to diabetes (40% of CKD cases) and hypertension (28% of cases).⁴ There exist significant racial and socioeconomic disparities in the incidence and progression of CKD.^{5,6} African Americans/Blacks disproportionately suffer from progressive CKD, and more than three-fold incidence of ESRD when compared to Whites.^{7,8}

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There are currently no specific therapies for diabetes and hypertension associated CKD. The cornerstones of management include early diagnosis, accurate risk stratification, control of underlying illnesses such as diabetes and hypertension, and management of complications. The aims of this review are to summarize the recent advances in genomic understanding of CKD and highlight the potential future applications that genomic approaches might hold for the diagnosis, stratification and management of this condition.

What do we know about genomics and CKD?

CKD/ESRD clusters within families and the heritability of estimated glomerular filtration rate (eGFR) has been estimated to be at 40–75% in population based studies.^{9,10} Using genome wide association studies, multiple loci have been identified for CKD, however the overall contribution to both eGFR and CKD disease understanding was minimal.^{11–14}

However, one of the first major discoveries of genetic variants that significantly and substantially increases the risk of a chronic disease is a variant that increases the risk of CKD and ESRD by five to ten-fold. And, these high-risk variants are nearly exclusively found in people of African descent, thus contributing to the understanding of CKD disparities. This finding emerged from a search for genetic loci underlying disparities in focal segmental glomerulosclerosis (FSGS) that identified a genetic locus on the long arm of chromosome 22 and initially focused on the myosin, heavy chain 9, non-muscle gene (*MYH9*).^{15,16} Further fine mapping and subsequent studies demonstrated that two distinct alleles of the *MYH9*-neighboring Apolipoprotein L1 (*APOL1*) gene confer substantially increased risk for a number of kidney diseases in AAs, including FSGS, human immunodeficiency virus-associated nephropathy, and hypertension-attributable kidney disease.^{17,18,19}

APOL1 risk alleles are defined by variants in the last exon of *APOL1*, that were found to confer resistance to lethal *Trypanosoma brucei* infections in sub-Saharan Africa, resulting in their selection and considerably higher frequency in individuals of African Ancestry compared with other populations.²⁰ This difference partly accounts for health disparities in kidney disease and end stage renal disease (ESRD) in individuals of African descent.^{17,21,22} This risk is particularly evident in adults with hypertension and without diabetes. After kidney transplant, shorter graft survival rates have been observed from donors with *APOL1* risk genotype.²³ This has influenced clinical practice; with some transplant centers testing and considering *APOL1* risk variants during the transplant evaluation for living donors.²⁴

Does Genomics Risk Explain Racial Disparities in CKD?

Although the *APOL1* risk genotype increases the risk of CKD development and progression in people of African descent, particularly with hypertension, this does not explain all racial differences in CKD. First, having African ancestry and self-identifying in the social categories of African-American or Black are not completely linked. Second, a recent study in the Atherosclerosis Risk in Communities (ARIC) study demonstrated that high-risk *APOL1* variants did not associate with acute kidney injury among African Americans; accounting for differences in income and/or insurance status attenuated the differences in AKI incidence between African Americans and Caucasians.²⁵ Considering that AKI and

CKD are inextricably linked,²⁶ this highlights that other determinants of kidney disease disparities must be acknowledged. These include socioeconomic status, access to care and social determinants of health.^{27–31} Research will need to assess and address multiple (clinical, social, environmental, *and* genomic) reasons for CKD disparities.

Pharmacogenomics in CKD: An avenue of opportunity?

There are currently no specific, targeted therapies for the vast majority of patients with CKD. Current practice guidelines recommend tight control of blood pressure and/or hyperglycemia in particular in the presence of albuminuria to reduce ESRD and CVD risks in CKD patients.³² One of the mainstays of therapy is blockade of the renin–angiotensin–aldosterone system (RAAS). This is a major pathway involved in the pathogenesis of diabetic nephropathy, and RAAS blockade with Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), has been proven to reduce CKD progression.^{33–35} The widespread use of RAAS blockers provides a potential avenue for pharmacogenomics study and intervention.

It is well known that there are significant racial/ethnic differences in response to antihypertensive. For example African Americans/Blacks respond more significantly to diuretics and calcium channel blockers than European Americans/Whites, while their response to ACE inhibitors less robust.³⁶ The ACE gene encodes ACE, a key enzyme involved in the RAAS. There is a high inter-individual variability in circulating ACE levels, with a polymorphism located in intron 16 being the most extensively studied ACE genetic variant. The genetic diversity of ACE is particularly high in people of African descent. Although, these differences could have socio-demographic components including access to care, the genomic part of this puzzle cannot be ignored. In the future, testing for this polymorphism may be useful for prediction of patient response to RAAS therapy. Studies also show that diabetic patients with differing genotypes of ACE gene have differing renal outcomes including mortality, decline in albuminuria, decreased blood pressure and ESRD.^{38–41} Thus, ACE genotype guided therapy could provide a prototype for further investigation and implementation of pharmacogenomics-guided management in CKD.

Another important and actionable area related to pharmacogenomics and disparities is among renal transplant recipients. With higher rates of end stage renal disease than Whites/European Americans, Blacks/African Americans have poorer outcomes post-transplant, including a 42% higher risk of graft loss at five years.⁴² This disparity is, in part, due to inadequate immunosuppression, which can lead to allograft rejection. Among the mainstays of immunosuppression are calcineurin inhibitors and one of the most commonly used is tacrolimus. Blacks require higher doses of tacrolimus than Whites to have the same mean blood levels and thus the same immunosuppression.⁴³ This is in part because Blacks are more commonly supermetabolizers of the drug. One reason is for this difference is that common genetic variants in the cytochrome P450 system that control metabolism are more common in Blacks (are virtually non-existent in Whites), and these variants lead to lower blood concentrations, even after adjusting for clinical factors.^{43,44} Specifically, the wild-type gene, CYP3A5*1, which allows for significant production of CYP3A5, is reportedly absent in 60–90% Whites and present in more than half Blacks.⁴⁵ In fact, a recent clinical

trials showed a lower dosing and favorable pharmacokinetic profile for Blacks who were switched from twice-daily tacrolimus to an extended release formulation.⁴⁶ Again, there are other reasons for disparities in outcomes, including non-adherence to immunosuppressive agents, lack of adequate follow-up, social support and difficulty receiving medications.^{47,48} However, genetic data can uncover patients who will need higher doses of tacrolimus as they are super-metabolizers, as opposed to being labelled as non-adherent due to their consistent low drug levels on monitoring.

Is Nephrology Keeping Pace with Genetic and Genomic Discoveries?

The few discoveries in genomics and nephrology to date are quite important and actionable. *APOL1* is one of the first genetic variants that have been shown to increase risk for a common chronic disease. Addressing disparities in metabolism of tacrolimus could greatly reduce racial disparities in survival post transplant.

Unfortunately, to date, there are insufficient numbers of clinical trials in nephrology in general. In fact, nephrology has the lowest number of clinical trials of any subspecialty and these trials are likely to be smaller and poorer quality.⁴⁹ CKD patients continue to be excluded from major cardiovascular disease trials,⁵⁰ in part because “hard end-points” mandated by the FDA occur in a minority of patients, which leads to underpowered trials. In addition, kidney disease is indolent and thus significant time is needed to accrue end points. Nephrology researchers should consider expanding their portfolios and collaborators to focus on genomic medicine, and including baseline genomics into trial enrollment, the trial population could be enriched for those most likely to progress within a shorter time window, leading to shorter, more efficient trial design.

Making the most of what we already know: How do we bring providers and patients up to speed?

Current and future information about genetics and CKD will not substantively improve clinical care and patient outcomes for diverse populations without adequate education and engagement of healthcare providers and patients. For example, while *APOL1* genomic information may be used for risk stratification for routine clinical care, a number of challenges still hinder its routine adoption and dissemination. These include: 1) complexity of genomic information to be processed by physicians; 2) limited physician proficiency and familiarity with genetics, interpreting and using genomic information; 3) hindering of clinical workflow by genomic information; 4) lack of adequate patient centered information and education to disseminate information to patients; and 5) reimbursement for tests.^{51,52}

There are many ongoing initiatives to overcome these challenges. For example, the National Institute of Health’s (NIH) Inter-Society Coordinating Committee for Practitioner Education in Genomics aims to improve genomic literacy of physicians and other practitioners and to enhance the practice of genomic medicine through sharing of educational approaches and joint identification of educational needs. This inter-professional committee warehouses high quality resources to enhance education.⁵³ Other groups work to identify which genetic variants are actionable. A major component of this work involves utilizing clinical

information collected from medical records for genomic research and clinical applicability by the Electronic Medical Records and Genomics (eMERGE) Network. Work conducted by this network involves genomic research, genomic medicine implementation, ethical issues associated with genomic research and return of genetic results to study participants.⁵⁴ The IGNITE (Implementing GeNomics In pracTice) group of the NHGRI supports development of methods for incorporating genomic information into clinical care and effective implementation, diffusion and sustainability in diverse clinical settings, reimbursement for testing, and has a toolbox of materials for clinical use. IGNITE's toolbox has provider, patient, investigator and educator materials.⁵⁵

Similarly, patient and community education about genomics is underway. For example, The Education and Community Involvement Branch and hosted by the National Human Genome Research Institute (NHGRI) at the NIH hosts discussions and shares guidelines, there are educational presentations and videos for diverse audiences,⁵⁶ a website for patients to understand genetic testing and their results (<http://myresults.org>) and a magazine for the public on genomics (<http://genomemag.com>).

Still other groups are working to improve the ability for providers to utilize genetic testing efficiently and effectively by means of clinical decision support (CDS). CDS entails providing healthcare providers and patients with pertinent knowledge and/or person-specific information, presented at appropriate times, using point-of-care tools at time of health delivery to enhance health care processes and patient outcomes.⁵⁷ An important criteria for any desired CDS is that relevant information should be provided within the clinical workflow and at the point and time of clinical decision-making within the electronic health record (EHR) environment.⁵⁸

An example of CDS in genomics is The Genetic Testing to Understand and Address Renal Disease Disparities (GUARDD) study. Part of the IGNITE Network, GUARDD was designed to generate essential insights in dissemination of genomic medicine in diverse clinical settings providing care for underserved African Ancestry populations with an excess burden of hypertension associated CKD.^{59,60} A multidisciplinary team of investigators is using community-engaged approaches to test patients with African descent for *APOL1* variants. Patients are informed about their genetic risk status and its implications for their healthcare by trained study coordinators. Their providers receive CDS stratified by *APOL1*-positive or -negative results in form of best practice alerts and one-click links to study-specific provider and patient information. There is privacy-protected, accurate dataflow between the EHR, genetic testing lab and study collection team. CLinical Implementation of Personalized Medicine through Electronic health Records and Genomics (CLIPMERGE) is the CDS engine, and has bi-directional real-time communication with the EHR.⁶¹ This study will help gain valuable insights in the utility and role of returning genetic testing results in an ethnic population at high genetic risk for kidney disease.

What is the path forward?

Incorporating genomics into routine clinical care of CKD patients holds promise. With decreasing costs of high-throughput sequencing, new discoveries are likely, and testing

could become a commonly available and affordable resource for routine clinical care.⁶² Just as we send a serum creatinine test, and providers and patients can rapidly grasp and discuss the implications of the result, we will be able to use *APOLI* and other tests to predict risk, and perhaps to develop treatments, or even cures for CKD. Pharmacogenomics is already guiding therapy.

However, the future of practical application of genomics in prevention and treatment of renal diseases will depend on the degree of penetration into and adoption by healthcare practitioners, and the degree of genetic research and discovery in nephrology. It will also require genetics and genomics education beginning early in clinical training, and clinical decision support processes to facilitate transfer and adoption of this rapidly advancing knowledge base. Clinicians, researchers, patients and advocates should work together to develop new research questions and strategies, and the best ways to translate findings into tangible actions. Team efforts involving geneticists, pharmacists, counselors, health care providers, investigators and advocates will help engage patients and stakeholders and utilize genomic information to improve care and outcomes of all patients, particularly people African Americans/Blacks, who are disproportionately impacted by CKD and ESRD. Finally, while genetic differences are an important piece of the disparities-CKD puzzle, this information should not supplant other well-known reasons for disparities such as social determinants of health that must remain active areas for research and action.

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CLINICAL SUMMARY

- Recent advances in genomics and discovery of the Apolipoprotein L1 risk genotype have explained a part of the racial disparities between Blacks and Whites and genetic polymorphisms could explain the differences in treatment response with antihypertensives and immunosuppressive medications seen in Blacks
- Genetic differences are an important piece of the disparities-chronic kidney disease puzzle; this information should not supplant already well-known socio-demographic reasons for disparities.
- Genomics could improve clinical outcomes and trial enrollment but adoption by providers during routine clinical care is limited.
- Efforts are underway to educate patients and providers using a variety of resources as well as implement point of care and clinical decision support systems.