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Over 20 million Americans suffer from chronic kidney disease (CKD)1,2, resulting in a 10-15-fold increase in morbidity and mortality and over $58 billion in Medicare spending.3 As early-stage CKD is often clinically silent, individuals can go undiagnosed until they reach end-stage renal disease (ESRD)1, and in more 1 in 10 ESRD cases, the cause is said to be “unknown”3. Available data suggest that, for many patients, CKD has a genetic component, with 10-29% of patients reporting a positive family history across ethnicities and clinical etiologies.4-6 Yet, hereditary and non-hereditary forms are frequently indistinguishable using the prevailing diagnostics of clinical history and renal biopsy. Thus, in many cases the precise etiology remains unidentified, hindering physicians from providing patients with a specific diagnosis and targeted treatment. Genomic technologies such as microarray and whole-exome sequencing (WES) have been used to unravel the molecular basis of many disorders, and have begun to be applied successfully at the bedside as well as at the bench. In studies of pediatric CKD cohorts, we and others have incorporated these technologies to detect diagnostic copy number variants (CNVs) and single-nucleotide variants (SNVs) and find novel causal genes. However, the broader utility of genomic diagnostics for CKD, across demographic and clinical subgroups, has yet to be assessed. Furthermore, the capacity of this integrated genomic approach to enable genetic discovery as well as diagnosis requires additional study. The proposed project aims to evaluate the diagnostic yield of microarray and WES in a large, diverse CKD cohort, and identify novel candidate genes for CKD through integrated analysis of CNVs and SNVs. My preliminary data demonstrate that these genetic diagnostics can identify causal variants in a substantial proportion of patients, supporting their value in nephrology. I hypothesize that rare genic CNVs and SNVs contribute to a substantial proportion of CKD, such that integrated analysis, using both microarray and WES data, will enable detection of both diagnostic variants and novel candidate genes. To test this hypothesis, I propose the following Aims. In Aim 1, I will assess the diagnostic yield of microarray and WES in a large, diverse CKD cohort. Assessing diagnostic yield overall and comparing yield between demographic and clinical subtypes will give insight into which groups of CKD patients may benefit most from these genomic diagnostics. In Aim 2, I will evaluate gene-level burden of rare functional SNVs and gene-disrupting CNVs in order to identify novel candidate genes for CKD. I will also conduct gene set-based burden tests to explore more complex genetic models of disease and to pinpoint additional candidate genes. These studies will help ascertain the diagnostic utility of microarray and WES for CKD and identify candidate causal loci for all-cause CKD and specific subtypes, informing use of genomic diagnostics in clinical nephrology and providing candidate genes for further study.