

# Clinical Integration of Genomic Testing in Kidney Transplantation Clinics

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In 2019, Groopman et al set out to assess the diagnostic utility of exome sequencing in a diverse, all-cause, chronic kidney disease cohort of over 3000 individuals and demonstrated the existence of a monogenic form of kidney disease in approximately 10% of cases.<sup>1</sup> Furthermore, the diagnostic yield was even higher (17.1%) among individuals with kidney disease of unknown etiology. This groundbreaking study brought to light how the high genetic and phenotypic heterogeneity of monogenic diseases, coupled with our limited appreciation for the full spectrum of their clinical manifestations, contributes to diagnosis delays and disease misclassifications. Today, with greater clinical access to molecular tests, we are increasingly able to establish the molecular diagnosis for a growing number of monogenic kidney diseases. Recent studies have demonstrated the clinical utility of genomic testing as part of the diagnostic evaluation of patients with kidney disease, which supports personalized management by guiding choice of therapy, informing targeted disease surveillance, and identifying at-risk family members for cascade screening.<sup>2-5</sup>

However, genomic tests are still relatively new diagnostic tools for most subspecialties of medicine and surgery and not widely used in routine care. Although various factors likely contribute to their limited clinical use, it is important to understand that broader implementation of genomic testing in the clinical domain relies largely on providers' appreciation for a breadth of core knowledge specific to genomic medicine.<sup>6</sup> This includes understanding specialized terminology (eg, penetrance, phenotype, carrier frequency, etc), various sequencing approaches (eg, single-gene tests, gene panels, exome and genome sequencing, etc), categories of genomic results (eg, polygenic risk scores, risk alleles, primary results and otherwise medically actionable secondary findings, variants of uncertain significance, etc), and an awareness of the complex ethical,

legal, and technical considerations that come with genomic sequencing. Given the complexity of using genomic data in medical decision-making, as well as kidney experts, limited experience diagnosing monogenic diseases and using genomic technologies, a multidisciplinary approach is often needed to guide interpretation of raw genomic data, clinical correlation, and the integration of diagnostic findings in patient care.<sup>2-5,7-9</sup>

In this issue of *Transplantation*, El Ters et al share their experience using molecular testing in the evaluation of individuals presenting to Mayo's adult kidney transplant clinic. In total, 30 prospective transplant recipients (the majority [n = 24, 80%] who had histopathologic evidence of focal segmental glomerulosclerosis pattern lesions on biopsy) plus an additional 5 prospective living donors underwent clinical-grade exome sequencing to try to identify an underlying monogenic form of kidney disease. In their study, they used a semi-masked approach to analyze the exome data by focusing their search to deleterious variants in a subset of 344 genes associated with hereditary forms of kidney disease. They considered potentially diagnostic variants to be those that met the American College of Medical Genetics and Genomics' standards for classification as either pathogenic or likely pathogenic.<sup>10</sup> The authors then reviewed these identified variants with a multidisciplinary team of molecular and clinical genetic specialists to ensure agreement in the adjudication of each variant's classification and ensure the findings were consistent with the patients' clinical presentations before deeming the findings diagnostic. They then reported that among the 30 prospective transplant recipients who underwent sequencing, 13 (43%) individuals were found to have a diagnostic variant in one of these known kidney disease genes. The most common findings they reported were deleterious variants in the *COL4A3/4/5* genes, which were identified in 7 of these 13 individuals, and are diagnostic for type IV collagen-associated nephropathies, which encompasses Alport syndrome, thin basement membrane disease, hereditary nephritis, and some hereditary forms of focal segmental glomerulosclerosis. In addition, the authors report that 1 of the 5 prospective living donors that underwent sequencing was found to have a pathogenic/likely pathogenic variant in a gene associated with a hereditary form of kidney disease and was excluded from donation.

Overall, this study reinforces the clinical utility of using molecular testing in the diagnostic evaluation of patients with kidney disease, specifically within the workflow of a kidney transplant clinic. Although the authors do not describe a novel approach in their implementation of genomic testing in the context of kidney disease patients,

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they demonstrate how diagnostic findings can inform the selection of prospective living kidney donors among at-risk family members, underscoring the important role genomic testing can play in transplant clinics. Moreover, their study reminds us of the precaution providers must take when adopting clinical genomics in patient care and the value added by employing a multidisciplinary approach that includes genomic experts. Studies like this one offer institution-specific experiences and lessons learned that can inform future genomic implementation initiatives. Further study is needed to identify innovative approaches that effectively advance the operationalization of precision nephrology care that can be scaled for use across distinct workflows and institutions.

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