Findings

In Selected Patients, Genetic Testing Shows Value in Transplant Selection

A multidisciplinary approach to genetic testing in the kidney transplant evaluation clinic provides useful input for selection of kidney donors and management of transplant recipients, suggests an evaluation in *Transplantation*.

The authors describe their experience in implementing a multidisciplinary genetic testing approach for potential kidney donors and recipients at the transplant clinic of a major medical center. Between 2018 and 2020, recipients were considered for genomic evaluation, based on previously published criteria. Genetic testing was also considered for potential donors to biologically related recipients with genetic causes of kidney diseases.

Genomic DNA testing was performed using a custom-curated exome slice gene panel, comprising 344 genes linked to various kidney diseases and candidate genes highly expressed in the kidney. Each patient considered for genetic testing was reviewed by a nephrology genomic board consisting of nephrologists with expertise in genetic causes of kidney diseases, renal pathologists, researchers, medical geneticists, and genetic counselors with expertise in kidney diseases.

Of 1100 transplant evaluations performed between 2018 and 2020, 34 recipients were selected for genetic testing. Approximately three-fourths of patients were non-Hispanic White individuals. Testing was canceled in four patients, mainly due to reimbursement issues.

Testing led to genetic diagnosis of a pathogenic or likely pathogenic variant in 13 of 30 patients—a rate of 43.4%. Of 24 tested patients with focal segmental glomerulosclerosis (FSGS), 10 (41.6%) had a genetic diagnosis. Collagen type 4 gene variants were detected in 7 of the 24 patients with FSGS.

Other genetic diagnoses included tubulointerstitial nephritis, nephrolithiasis, and unknown causes of kidney diseases. The only clinical characteristic associated with positive versus negative results was family history of kidney diseases: 76.9% versus 29.4%, respectively. Testing of five potential donors led to exclusion of one individual with a pathogenic or likely pathogenic variant.

With a careful selection approach, diagnosis of a pathogenic or likely pathogenic variant is made in approximately 40% of patients selected for genetic testing at a transplantation clinic. This approach "facilitated the screening of potential living related donors and counseling of recipients about risk of recurrence of their native disease, which are of particular importance in FSGS," the researchers write. They emphasize the importance of a multidisciplinary approach, focused on achieving transplant-specific goals while providing patients with genetic counseling both before and after testing [El Ters M, et al. Incorporation of genetic studies in the kidney transplant evaluation clinic: The value of a multidisciplinary approach. *Transplantation* 2023; 107:952–960; doi: 10.1097/TP.0000000000004363].

Cystatin C-Based eGFR May Affect Staging

Cystatin C- and creatinine-based estimated glomerular filtration rate (eGFR) values are strongly correlated with each other, whereas cystatin C-based estimates can have a substantial impact on chronic kidney disease (CKD) staging, reports a study in *Kidney Medicine*.

The retrospective analysis included 1783 patients who had cystatin C and creatinine levels measured within 24 hours of each other in a large health system for over 4 years. Analysis focused on correlations between eGFR values based on cystatin C versus creatinine and their impact on CKD staging and delivery of kidney care.

The results showed that cystatin C-based eGFR was "very strongly correlated" with creatinine-based eGFR. In multivariable analyses, older age was progressively associated with lower cystatin C-based eGFR at a given creatinine-based eGFR level, at all stages of CKD.

Compared with creatinine eGFR, cystatin C eGFR was associated with a change to a later CKD stage in 27% of patients, an earlier stage in 7%, and no change in 66%. Change to a later stage was less likely for Black compared with White patients (odds ratio [OR], 0.53). Older patients were more likely to have change to a later stage (OR, 1.03/year), as were those with higher comorbidity (OR, 1.22/point on an Elixhauser score). The most common reason for ordering a cystatin C measurement was diagnostic workup (48%), followed by transplant evaluation (21%).

A recent report by the Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases called for increased use of cystatin C to confirm eGFR in clinical decision-making. The new analysis shows a very strong correlation between cystatin C- and creatinine-based eGFR in a large and diverse patient sample.

Cystatin C led to a CKD change in approximately one-third of patients, mainly to a later stage. These changes are affected by factors such as age, race, and comorbidity. The authors discuss the implications for care delivery as cystatin C measurement comes into routine clinical use [Gottlieb ER, et al. Estimated GFR with cystatin C and creatinine in clinical practice: A retrospective cohort study. *Kidney Med* 2023; 5:100600; doi: 10.1016/j.xkme.2023.100600].

Mycophenolate Mofetil Reduces Progression of IgAN

In patients with high risk of immunoglobulin A nephropathy (IgAN), adding mycophenolate mofetil (MMF) to standard care reduces the risk of disease progression, concludes a randomized trial in *JAMA Network Open*.

The open-label Effect of Mycophenolate Mofetil on Renal Outcomes in Advanced Immunoglobulin A Nephropathy (MAIN) study enrolled 238 adult patients with IgAN at high risk of kidney function loss. Patients underwent a 3-month run-in period of optimized supportive care (SC), including losartan. Those who did not achieve a urinary protein excretion rate of 0.75 g/day or greater were randomly assigned to 3 years of treatment with MMF added to SC or to SC only. The initial MMF dose was 1.5 g/day for 12 months, maintained at 0.75–1.0 g.

Of 170 randomized patients, 55.3% were men; the mean age was 36.6 years. The mean estimated glomerular filtration rate (eGFR) was 50.1 mL/min/1.73 m^2, and the proteinuria level was 1.9 g/day. The analysis focused on two co-primary outcomes: a composite of doubling of serum creatinine, end stage kidney disease, or death due to kidney or cardiovascular disease and progression of chronic kidney disease (CKD).

Of 168 patients who completed the trial, 157 were alive and free of dialysis or transplantation. A primary composite outcome event occurred in 7.1% in the MMF group versus 21.2% with SC only. Rates of CKD progression were 8.2% and 27.1%, respectively; for both outcomes, the adjusted hazard ratio was 0.23.

The benefits of MMF were apparent across subgroups. After the end of the study and withdrawal of MMF in 66 patients, annual loss of eGFR increased from 2.9 to 6.1 mL/min/1.73 m^2. Adverse events were similar between treatment groups.

There are conflicting data on the effectiveness of immunosuppressive therapy for IgAN. MMF is relatively lymphocyte selective compared with other immunosuppressive agents and is a stronger inhibitor of B cell antibody production.

Adding MMF to SC can reduce disease progression in high-risk patients with IgAN, the MAIN results suggest. The researchers conclude that MMF "may be an alternative therapy for patients with IgAN, particularly those with CKD and subnephrotic proteinuria despite receiving SC, as well as those not appropriate for steroid therapy" [Hou FF, et al. Effectiveness of mycophenolate mofetil among patients with progressive IgA nephropathy: A randomized clinical trial. *JAMA Network Open* 2023; 6:e22254054; doi: 10.1001/jamanetworkopen.2022.54054].

Metformin Shows Benefits after Kidney Transplant

Treatment with metformin may reduce the risk of graft failure and death in diabetic kidney transplant recipients (KTRs), reports a study in the *American Journal of Kidney Diseases*.

The retrospective analysis included 1995 patients with type 2 diabetes who underwent kidney transplantation at six centers in the Republic of Korea from 2000 through 2019. Of these, 1193 patients used metformin for longer than 90 days after kidney transplant; 802 patients did not receive metformin. The two groups were compared for all-cause mortality and death-censored graft failure (DCGF), with biopsy-proven acute rejection (BPAR) and lactic acidosis events as secondary outcomes. Analyses accounted for the impact of changes in metformin dose and hemoglobin A1c over time.

There were some differences in patient characteristics: 3 months after transplantation, metformin-treated KTRs had better kidney function but poorer glycemic control. During a mean follow-up of 65 months, 5.1% had graft failure. Patients using metformin had lower DCGF (adjusted hazard ratio, 0.47 on a fully adjusted analysis). Metformin was associated with lower DCGF and all-cause mortality for patients with pre-transplant and post-transplant diabetes.

Among KTRs with post-transplant diabetes, metformin was associated with a lower risk of BPAR, although this difference was not significant in the fully adjusted analysis. There were no confirmed cases of metformin-associated lactic acidosis. Among metformin users, those receiving higher doses had lower rates of DCGF and BPAR.

Metformin is increasingly recommended for patients with advanced chronic kidney disease, based on evidence of a survival benefit and renal protective effect with a low risk of lactic acidosis. Few studies have evaluated the use of metformin in KTRs with pre-transplant or post-transplant diabetes.

This retrospective study shows a reduced risk of DCGF in diabetic KTRs treated with metformin, with no evidence of lactic acidosis. The benefits may be greater in patients receiving higher metformin doses. The researchers call for randomized trials to validate their findings [Kwon S, et al. Metformin use and long-term clinical outcomes in kidney transplant recipients. *Am J Kidney Dis*, published online ahead of print March 23, 2023. doi: 10.1053/j.ajkd.2023.01.446; https://www.ajkd.org/article/S0272-6386(23)00578-4/fulltext].