Developing a genetic testing panel for evaluation of morbidities in kidney transplant recipients

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Cardiovascular disease, infection, malignancy, and thromboembolism are major causes of morbidity and mortality in kidney transplant recipients (KTR). Prospectively identifying monogenic conditions associated with post-transplant complications may enable personalized management. Therefore, we developed a transplant morbidity panel (355 genes) associated with major post-transplant complications including cardiometabolic disorders, immunodeficiency, malignancy, and thrombophilia. This gene panel was then evaluated using exome sequencing data from 1590 KTR. Additionally, genes associated with monogenic kidney and genitourinary disorders along with American College of Medical Genetics (ACMG) secondary findings v3.2 were annotated. Altogether, diagnostic variants in 37 genes associated with Mendelian kidney and genitourinary disorders were detected in 9.9% (158/1590) of KTR; 25.9% (41/158) had not been clinically diagnosed. Moreover, the transplant morbidity gene panel detected diagnostic variants for 56 monogenic disorders in 9.1% KTRs (144/1590). Cardiovascular disease, malignancy, immunodeficiency, and thrombophilia variants were detected in 5.1% (81), 2.1% (34), 1.8% (29) and 0.2% (3) among 1590 KTRs, respectively. Concordant phenotypes were present in half of these cases. Reviewing implications for transplant care, these genetic findings would have allowed physicians to set specific risk factor targets in 6.3% (9/144), arrange intensive surveillance in 97.2% (140/144), utilize preventive measures in 13.2% (19/144), guide disease-specific therapy in 63.9% (92/144), initiate specialty referral in 90.3% (130/144) and alter immunosuppression in 56.9% (82/144). Thus, beyond diagnostic testing for kidney disorders, sequence annotation identified monogenic disorders associated with common post-transplant complications in 9.1% of KTR, with important clinical implications. Incorporating genetic diagnostics for transplant morbidities would enable personalized management in pre- and post-transplant care.

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Lay Summary

Cardiovascular disease, infection, malignant neoplasm, and thromboembolism are leading causes of mortality in kidney transplant recipients (KTRs). This study is the first to explore the clinical utility of panel-based exome sequencing in identifying monogenic causes of major post-transplant complications. Using the transplant morbidity panel, we show a high diagnostic rate of 9.1% in KTRs. The genetic findings would allow physicians to identify complications early, use preventive measures, initiate disease-specific therapy, refer to specialty care, and tailor make immunosuppressive regimens. Besides, although identifying causes of chronic kidney disease has important clinical implications in transplant care, ≈1 in 4 KTRs with mendelian kidney and genitourinary disorders were not diagnosed clinically. Hence, incorporating genetic diagnostics into transplant evaluation would enable personalized management and help to improve the overall prognosis.

Kidney transplantation is the ideal treatment for end-stage kidney disease (ESKD) given the marked improvements in survival and quality of life compared with dialysis.[1,2] Despite the introduction of modern immunosuppression and improvement in surgical techniques, kidney transplant recipients (KTRs) still experience substantial complications, resulting in significant morbidity and mortality.

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Besides rejection, the primary complications in KTRs are related to cardiovascular diseases, diabetes, infections, malignancies, and venous thromboembolism.[3–5] Cardiometabolic disorders are the leading cause of mortality in KTRs. A registry study from the United States showed that 25% of deaths at 1 year and 15% at 10 years after kidney transplant resulted from cardiovascular events.[4] Even a nonfatal cardiovascular event has been shown to be associated with future allograft failure and increased mortality.[6] Chronic kidney disease and maintenance immunosuppression markedly increase the risk of cardiovascular disease in KTRs through multiple mechanisms.[7,8] Corticosteroids and calcineurin inhibitors are associated with metabolic derangements, such as dyslipidemia and hyperglycemia. KTRs on mammalian target of rapamycin inhibitors consistently demonstrate worse lipid parameters compared with those on other immunosuppressive regimens.[9–14] New-onset diabetes after transplantation is a serious complication that not only increases cardiovascular risk, but also greatly compromises allograft survival and increases risk of infection.[15–17]

Infection is the second most common cause of mortality in KTRs, resulting in 15% and 8% of all-cause mortality after 1 and 10 years, respectively, post-transplant.[4] Infection is also the leading cause of post-transplant hospitalizations and associated with notable risk of allograft loss.[18–20] The life-long immunosuppression, which targets specific groups of immune cells and alters signaling pathways, renders KTRs constantly at risk of serious infections.[21,22]

Malignant neoplasm ranks number third among the leading causes of death post-transplant; and once it develops, the risk of death is high.[4,23] Studies showed KTRs had 1.8 to 1.9 times higher standard mortality ratios for all types of malignant neoplasm compared with age- and sex-matched general population.[24–26] In addition, the cumulative incidence of solid organ malignant neoplasm after kidney transplant increases from 5% after 5 years to >25% after 20 years, with the greatest increase seen with certain types of malignancies, such as skin cancers and post-transplant lymphoproliferative disorders.[26–28] For example, the cumulative incidence of skin cancers post-transplant reaches >60% after 15 years in Europe, Australia, and New Zealand.[24] Induction and maintenance immunosuppression, altered T-cell immunity, and oncogenic viruses altogether contribute to this markedly enhanced risk. Use of T-cell–depleting agents is associated with a heightened risk of colorectal cancer and thyroid cancer.[29] Studies suggested that there was a higher incidence of malignant neoplasm in KTRs with higher cyclosporine trough levels.[30] On the contrary, compared with those receiving calcineurin inhibitors, KTRs treated with mammalian target of rapamycin inhibitors had a 30% to 50% lower risk of malignant neoplasm.[31–33]

Last, KTRs are at enhanced risk of venous thromboembolism due to immobilization related to surgery and often the underlying conditions, such as systemic lupus erythematosus or antiphospholipid syndrome, that led to the loss of kidney function.[34–37] In a Canadian study of 388 KTRs, 8.9% developed an episode of venous thromboembolism during a median interval of 5.2 years, which was 7-fold higher compared with the matched general population.[37] Compared with matched KTRs who did not experience such an episode, they had 4 times higher risk of deaths and 2 times higher risk of death-censored graft loss.

These complications have multifactorial causes, but in a subset of patients, they may be caused by monogenic forms of disease. Although monogenic diseases are individually rare, it has been estimated that together they affect ≈6% of the population.[38] Many monogenic disorders are diagnosed later in life because of either mild manifestations in childhood or delayed onset due to genetic, epigenetic, or environmental factors, and many remain unrecognized.[39–41] In recent years, rapid advances in sequencing technology at an affordable cost allowed extensive genetic analysis in patients with kidney diseases, which demonstrated important diagnostic utility.[42–47] Furthermore, in a subset of patients with ESKD, a biopsy diagnosis is either not obtained due to presence of contraindications, late presentation, or patient refusal, or the biopsy findings are uninformative, resulting in underdiagnosis of underlying ESKD causes.[48,49] Identification of monogenic conditions that predispose to kidney disease requiring kidney transplantation and common post-transplant complications could enable early initiation of personalized and comprehensive management plans, starting from the perioperative period. Our study aimed to develop a morbidity gene panel to evaluate its diagnostic yield for KTRs and explore its potential impact on clinical care in kidney transplantation.

METHODS

Development of the transplant morbidity panel

We developed a transplant morbidity panel consisting of genes associated with 4 common complications of transplantation: (i) cardiometabolic disorders, (ii) adult-onset immunodeficiency, (iii) malignant neoplasm, and (iv) thrombophilia. We focused on malignancies that are either common in the general population or among KTRs, based on the definition from Kidney Disease: Improving Global Outcomes clinical practice guideline for the care of kidney transplant recipients and American Cancer Society 2022 registry data on leading sites of new cancer cases and deaths.[50,51] We initially searched for monogenic causes of these conditions from medical literature and the Online Mendelian Inheritance in Man database, then selected genes with established gene-disease association using the Gene Curation Coalition platform with preset criteria (Supplementary Table S1).

Study cohort

From October 2007 to January 2023, we recruited 1590 KTRs followed up at Columbia University Irving Medical Center in a biobanking study. All patients or their guardians consented to the study protocol. The study was approved by the Columbia University Institutional Review Board and local ethics committees (Institutional Review Board number AAS7948). Of note, 1010 of these patients were previously included in a published study investigating the diagnostic

utility of exome sequencing in patients with chronic kidney disease.[42] A total of 580 more KTRs were recruited from September 2017 to January 2023.

Exome sequencing and variant analysis

Genomic DNA was isolated from samples obtained from patients per standard protocol and captured with the use of various kits, >95% of which were Roche NimbleGen SeqCap Exome EZ v3.0 kit, and the Integrated DNA Technologies[52] xGen Exome Research Panel v1.0 kit (Supplementary Table S2). Next-generation sequencing was performed on Illumina 2500 HiSeq platform or Illumina NovaSeq 6000 platform, using 150-bp reads. The mean sequence coverage was 88×, with on average 96% of the target bases in a given sample achieving at least 10× coverage of the Consensus Coding Sequence (CCDS release 20). The sequence reads were aligned to human reference genome assembly (GRCh37/hg19) using Illumina DRAGEN, and duplicates were marked with Picard tools. Variant calling was performed using Genome Analysis Toolkit (v3.6 best practices recommendations).[53] Variants were annotated with ClinEff and custom annotations, including Genome Aggregation Database. The v2.1 frequencies and ClinVar clinical annotations were obtained via the Institute for Genomic Medicine at Columbia University in-house analysis tool for annotated variants platform.[54,55] In-house diagnostic pipeline was used to identify diagnostic variants in the 3 gene lists: (i) transplant morbidity panel developed for this study, (ii) mendelian kidney and genitourinary disorders gene panel of 625 genes previously developed by our group,[42] and (iii) American College of Medical Genetics and Genomics (ACMG) recommended 81 genes for secondary findings (SF v3.2).[56] *MUC1* (mucin 1) genotyping was performed as previously described by mass spectrometry–based probe extension assay at the Broad Institute.[57] Diagnostic analysis was performed per ACMG guidelines and the Clinical Genome Resource (ClinGen) variant curation expert panel specifications.[58–62] Diagnostic variants were defined as those classified as "pathogenic" or "likely pathogenic" and with appropriate zygosity. Variant interpretation was reviewed by a panel of nephrologists, molecular geneticists, clinical geneticists, and genetic counselors. The diagnostic variants were viewed using Integrative Genomics Viewer v2.15.4.[63]

Data analysis

Diagnostic yield of actionable variants was calculated on counts of individuals with variants classified as pathogenic or likely pathogenic. Electronic health records of KTRs were reviewed for demographics and clinical and pathologic characteristics. Reverse phenotyping was performed to search for compatible clinical features and family history. Clinical implications of diagnostic variants were studied case by case based on recommendations from major international guidelines, GeneReviews, and the medical literature.[64–75]

RESULTS

Transplant morbidity panel

The transplant morbidity panel consisted of 355 genes. The gene list, genomic locations, associated disorders, and mode of inheritance are shown in Supplementary Table S3 and Supplementary Table S4. Genes associated with cardiovascular diseases and with diseases associated with increased risk for cardiovascular events, such as hypercholesterolemia or diabetes, contributed to the majority of the panel (198 genes [56%]), followed by malignant neoplasm (105 genes [30%]), adult-onset immunodeficiency (39 genes [11%]), and last, thrombophilia (13 genes [4%]). In the transplant morbidity panel, 97 genes (27%) were associated with mendelian kidney and genitourinary disorders, whereas 67 genes (19%) were also part of the ACMG SF v3.2 (Figure 1).

Demographics of the study cohort

The cohort consisted of 1590 KTRs, who received first kidney transplantation between May 1970 and October 2022 and

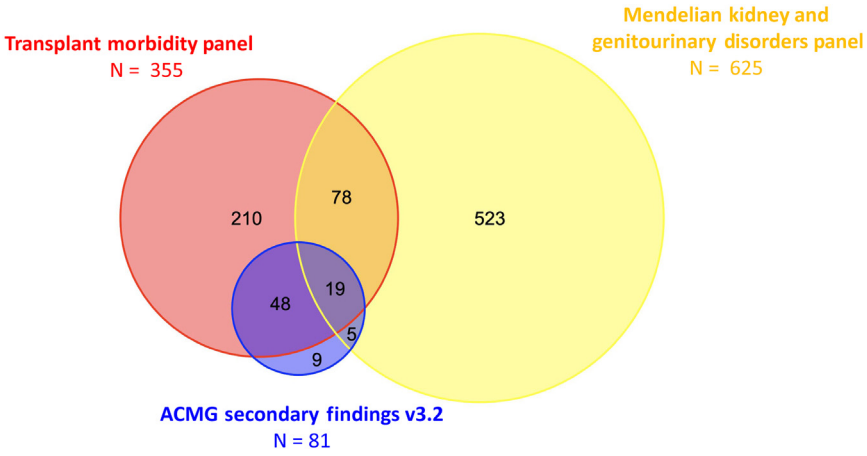

Figure 1 | Three gene lists used in the study. The total number of genes and number of overlapped genes between the transplant morbidity panel, mendelian kidney and genitourinary disorders panel, and American College of Medical Genetics and Genomics (ACMG) secondary findings gene list shown in Venn diagram.

Table 1 | Demographics of the kidney transplant cohort[a]

Characteristics	Kidney transplant cohort (N = 1590)
Age at first kidney transplant, mean ± SD, yr	43.6 ± 16.3
Biological sex	
Male	958 (60.3)
Female	632 (39.7)
Self-identified ethnic group	
White	735 (46.2)
Hispanic/Latino	426 (26.8)
Black	264 (16.6)
Asian	138 (8.7)
Unspecified	27 (1.7)
Causes of end-stage kidney disease	
Glomerulopathy	616 (38.7)
Diabetic kidney disease	266 (16.7)
Congenital/cystic kidney disease	218 (13.7)
Hypertensive nephropathy	173 (10.9)
Tubulointerstitial disease	41 (2.6)
Others	108 (6.8)
Chronic kidney disease of unknown origin	168 (10.6)

[a]All kidney transplant recipients were followed up at Columbia University Medical Center from October 2007 to January 2023 and participated in genetic biobanking studies with exome sequencing performed and with results that passed quality control metrics.
Data are presented as n (%) unless otherwise noted.

were followed up at Columbia University Medical Center, with most aged ≥18 years (98.3%). The mean age at first kidney transplant was 43.6 years, and 60.3% were males. A total of 25.3% self-identified as non-White, 26.8% as Hispanic, and 46.2% as White. All major causes of ESKD were represented in the cohort, including chronic kidney disease of unknown origin (10.6%). Among KTRs, 1010 were previously included in a study investigating the diagnostic utility of exome sequencing in patients with chronic kidney disease, and 69 of 1010 (6.8%) had a known monogenic cause of chronic kidney disease[42] (Table 1).

Diagnostic yield of the morbidity gene panel and clinical implications

Analysis of the morbidity gene panel identified 155 variants associated with 56 monogenic disorders in 144 KTRs, reaching a diagnostic yield of 9.1% (144 of 1590). Details of variants are shown in Supplementary Table S5. The diagnostic yield was 5.1% (81 of 1590 KTRs) in the cardiovascular category, 2.1% (34 of 1590 KTRs) in the malignant neoplasm category, 1.8% (29 of 1590 KTRs) in the immunodeficiency category and 0.2% (3 of 1590 KTRs) in the thrombophilia category (Figure 2). In addition, 0.5% (8 of 1590) had dual genetic diagnoses, of which 3 had genetic diagnoses under 2 different disease categories. Over half of the KTRs had diagnostic variants in 1 of the following 9 genes, listed in descending order of frequency: *TNFRSF13B*, *TTR*, *BRCA2*, *KCNQ1*, *PLIN1*, *HFE*, *HNF1A*, *TSC1*, and *MYBPC3*. Other genes with diagnostic variants are summarized in Supplementary Table S6. Most monogenic disorders were of autosomal dominant inheritance (Table 2). Most diagnostic variants had been previously reported (145 of 155 variants),

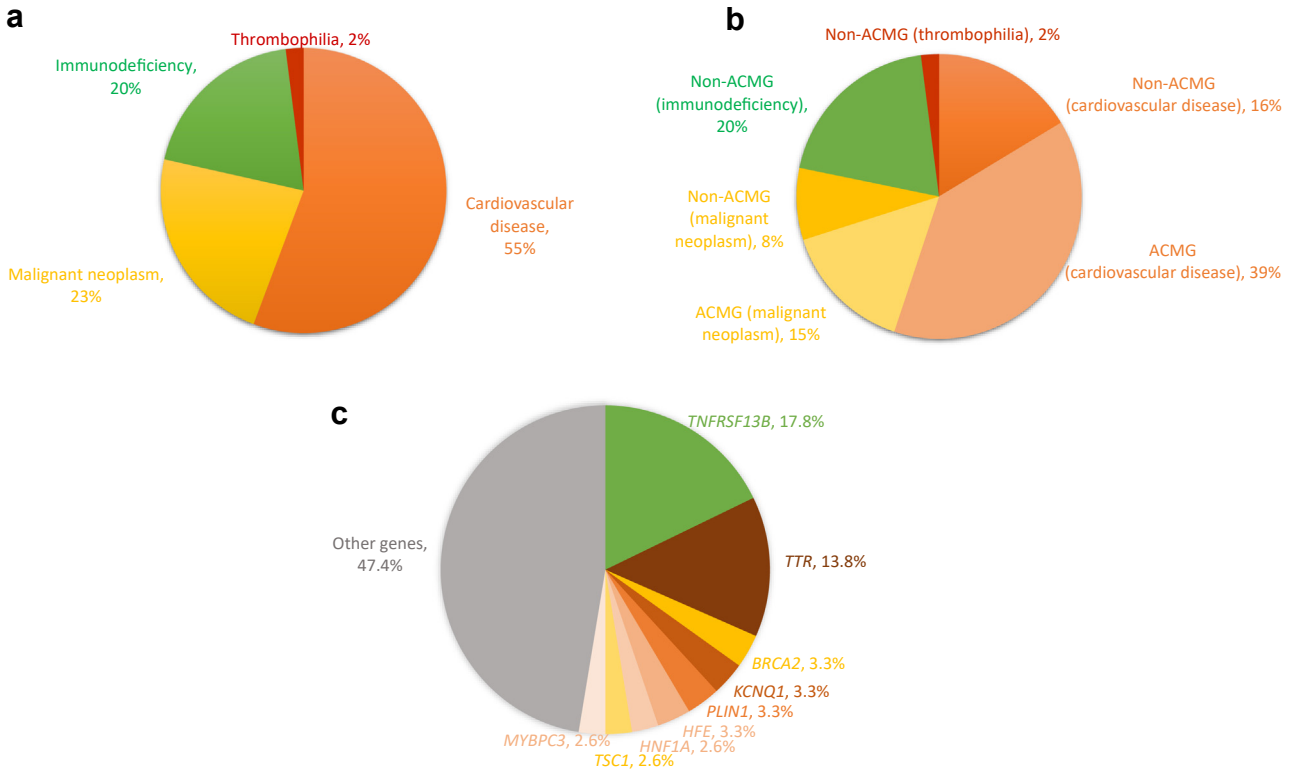

Figure 2 | Diagnostic yield of the transplant morbidity panel. (**a**) The distribution of kidney transplant recipients with diagnostic variants stratified by categories of post-transplant complications. (**b**) The proportion of kidney transplant recipients with diagnostic variants, stratified by the American College of Medical Genetics and Genomics (ACMG) secondary findings list. (**c**) The most common diagnostic genetic findings detected by the transplant morbidity panel.

Table 2 | Summary of diagnostic variants detected by the transplant morbidity panel

Patients with diagnostic variants (N = 144)		
Disease category	**No. of patients**	**Diagnostic yield, %**
Cardiovascular disease	81	5.1
Malignant neoplasm	34	2.1
Immunodeficiency	29	1.8
Thrombophilia	3	0.2
Dual[a]	3	0.2
Inheritance		**%**
Autosomal dominant	131	91.0
Autosomal recessive	8	5.6
X linked	4	2.8
Dual[b]	1	0.7
Diagnostic variants (N = 155)	**No. of variants**	**%**
ACMG classification		
Pathogenic	70	45.2
Likely pathogenic	85	54.8
Novelty		
Previously reported	145	93.5
Penetrance		
Low/reduced penetrance	62	40.0
Type of diagnostic variant		
Protein truncating	57	36.8
Frameshift	29	18.7
Nonsense	20	12.9
Splice site	8	5.2
Nontruncating	98	63.2
In-frame deletion	1	0.6
Missense	97	62.6

ACMG, American College of Medical Genetics and Genomics.
[a]Three kidney transplant recipients had diagnostic variants under 2 disease categories, which are cardiovascular disease (*KCNQ1*) and malignant neoplasm (*BARD1*), cardiovascular disease (*TTR*) and malignant neoplasm (*APC*), malignant neoplasm (*BRCA2*), and immunodeficiency (*TNFRSF13B*).
[b]One kidney transplant recipient had diagnostic genetic findings with 2 different modes of inheritance, which are autosomal dominant (*PKP2*) and autosomal recessive (*HFE*).

and there were more nontruncating variants than protein-truncating variants (98 vs. 57 variants).

Review of health records showed that 50% of patients (72 of 144) had supporting clinical features or family history of the monogenic disorders, whereas the rest had either absence or no documentation of any supporting features. Among KTRs with diagnostic variants, identification of these monogenic disorders and risk factors could allow physicians to set specific risk factor targets in 6.3% of individuals (9 of 144), arrange intensive surveillance in 97.2% (140 of 144), use preventive measures in 13.2% (19 of 144), guide disease-specific therapy in 63.9% (92 of 144), initiate specialty referral in 90.3% (130 of 144), and alter immunosuppressive regimens in 56.9% (82 of 144) (Figure 3; Supplementary Table S7).

Diagnostic yield of the mendelian kidney and genitourinary disorders gene panel

Using the mendelian kidney and genitourinary disorders gene panel, we identified 170 diagnostic variants associated with 37 monogenic disorders in 158 KTRs. The diagnostic yield reached 9.9% (Figure 4). Details of diagnostic variants are shown in Supplementary Table 8. Among KTRs with positive genetic diagnoses, 25.9% (41 of 158) did not have genetic kidney disease labeled as the primary cause of ESKD (Table 3). Among KTRs with chronic kidney disease of unknown origin, 10.1% (17 of 168) had underlying cause of ESKD revealed by genetic testing. Moreover, 1.1% of KTRs (17 of 1590) had diagnostic variants detected in genes (*HNF1A*, *HNF1B*, *GLA*, *TSC1*, *TSC2*, *TTR*, *WFS1*, and *WT1*) that not only inform the underlying cause of ESKD, but also other potential major post-transplant complications. Furthermore, 154 KTRs harbored 2 *APOL1* high-risk alleles, among which 4 KTRs harbored both the G2 and protective allele.

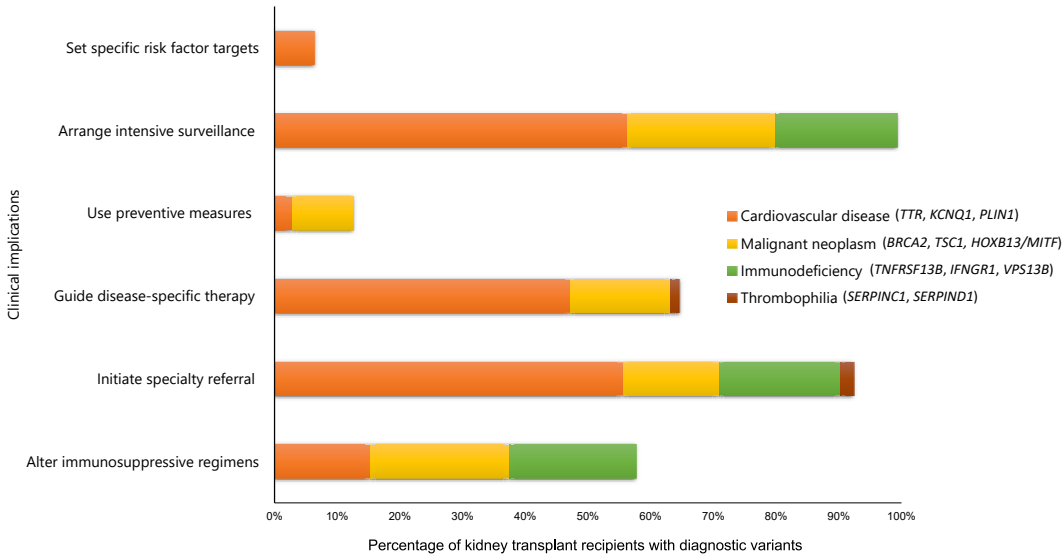

Figure 3 | Clinical implications of diagnostic variants detected by the transplant morbidity panel. Clinical implications of genetic findings in kidney transplant care, stratified by disease categories, with top 3 genes in each category listed.

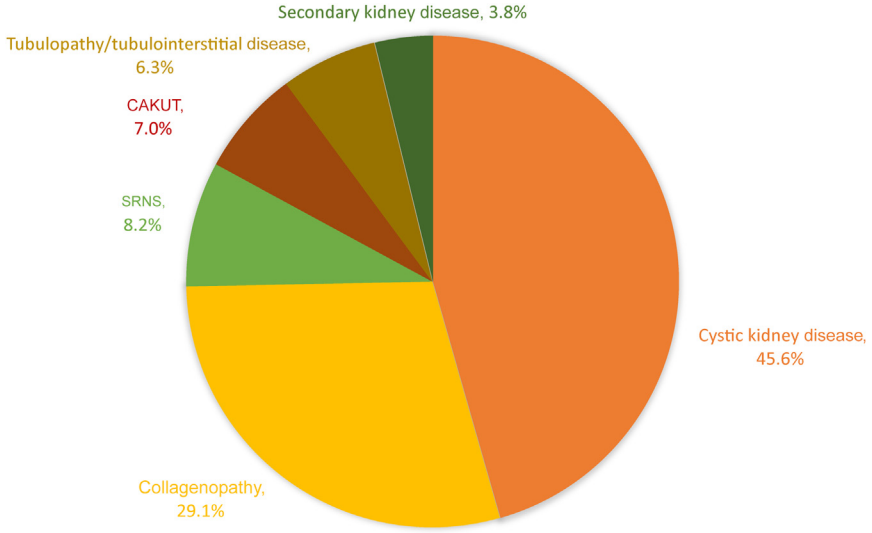

Figure 4 | Diagnostic yield of the mendelian kidney and genitourinary disorders gene panel. The proportion of kidney transplant recipients with diagnostic variants identified by the mendelian kidney and genitourinary disorders gene panel, stratified by categories of kidney disease. CAKUT, congenital anomalies of the kidney and urinary tract; SRNS, steroid-resistant nephrotic syndrome.

Table 3 | Summary of diagnostic variants detected by the mendelian kidney and genitourinary disorders gene panel

Patients with diagnostic variants (N = 158)		
Disease category	**No. of patients**	**Diagnostic yield, %**
Cystic kidney disease	72	45.6
Collagenopathy	46	29.1
Steroid-resistant nephrotic syndrome	13	8.2
Congenital or developmental kidney disease	11	7.0
Tubulopathy/tubulointerstitial kidney disease	10	6.3
Secondary kidney disease	6	3.8
Inheritance		**%**
Autosomal dominant	113	71.5
Autosomal recessive	21	13.3
X linked	24	15.2
Clinical suspicion		
Without clinical suspicion of genetic kidney disease before genetic testing	41	25.9
Diagnostic variants (N = 170)	**No. of variants**	**%**
ACMG classification		
Pathogenic	74	43.5
Likely pathogenic	96	56.5
Novelty		
Previously reported	157	91.3
Type of diagnostic variant		
Protein truncating	102	60
Frameshift	54	31.8
Nonsense	30	17.6
Splice site	18	10.6
Nontruncating	68	40
In-frame deletion	5	2.9
Missense	63	37.1

ACMG, American College of Medical Genetics and Genomics.

Detection rate of ACMG secondary findings

A total of 80 KTRs had 84 pathogenic variants identified across 32 genes on the ACMG SF v3.2, resulting in a detection rate of 5.0%. Of those 32 genes, 30 were also included in the transplant morbidity panel and accounted for 78 of the 80 KTRs (Supplementary Table S9). *TTR* harbored most of the pathogenic variants detected, followed by *BRCA2*, *KCNQ1*, and *HFE*. *OTC* and *RYR1* were the 2 genes not included in the transplant morbidity panel.

DISCUSSION

Recent studies have demonstrated great utility of exome sequencing for diagnosis of kidney disease, but the potential of genetic testing for precision nephrology has not been fully explored in the setting of kidney transplant. Patients with kidney failure who receive transplant are at increased risk for cardiometabolic, infectious, and thrombotic complications.[3–5] A recent study has shown that a polygenic score can predict the risk of post-transplant diabetes.[76] However, genetic predisposition to post-transplant complications has not been systematically studied. The ability to identify patients at risk for these complications could lead to changes in immunosuppression or improved monitoring, resulting in better clinical outcomes. For example, immunosuppressive medications (and target levels), choice of induction agents, and perioperative anticoagulation regimens could all be modified in response to evidence of increased risks.

To address this clinical need, we developed a transplant morbidity gene panel to search for monogenic disorders associated with major post-transplant complications. We focused on rare variants diagnostic of monogenic disorders because these typically confer a large risk of disease and are often clinically actionable. We detected diagnostic variants in 9.1% of all KTRs, and the genetic data had significant implications for

clinical management, such as detecting complications early, initiating preventive measures, switching to disease-specific therapy, and modifying immunosuppressive regimens. Additionally, 9.9% of our cohort had mendelian kidney and genitourinary disorders confirmed by genetic testing, among which the diagnoses would have been missed clinically in 25.9%.

We identified significant clinical implications of the diagnostic variants across cardiovascular, malignant neoplasm, immunodeficiency, and thrombophilia categories. For example, detecting pathogenic variants in genes associated with familial hypercholesterolemia would warrant physicians to set a stringent lipid profile target, rapidly intensify treatment with statins, ezetimibe, or proprotein convertase subtilisin/kexin type 9 inhibitors in suboptimally controlled cases, refer to specialized lipid clinic, and modify immunosuppressive regimen, such as to minimize corticosteroid use.[65,77–79] The same principle applies to KTRs with pathogenic variants in genes increasing the risk of diabetes, in whom a corticosteroid-sparing regimen and a less diabetogenic calcineurin inhibitor or alternatives to calcineurin inhibitor should be considered.[80,81] In another interesting example, we identified a pathogenic variant on *PPARG*, which is associated with autosomal dominant familial partial lipodystrophy type 3, in a KTR diagnosed with early-onset type 2 diabetes and hypertriglyceridemia and with a history of pancreatitis. Despite high-dose basal-bolus insulin and glucagon-like peptide-1 (GLP-1) receptor agonist, the patient did not have optimal glycemic control. Leptin replacement therapy with metreleptin has been shown to improve metabolic complications in patients with *PPARG* pathogenic variants dramatically, and it might have benefited this patient's glycemic control.[82]

In another example, we identified a pathogenic variant in the *KCNQ1* gene, which is associated with long-QT syndrome. Having this information available would alert physicians to avoid QT-prolonging medications, such as quinolones, macrolides, and azole antifungals.[83]

In the malignant neoplasm category, we identified several KTRs harboring pathogenic variants in genes associated with hereditary breast and ovarian cancer syndrome, necessitating regular surveillance imaging, overall immunosuppression reduction, consideration of prophylactic surgery or chemoprevention, and disease-specific therapy, such as poly adenosine diphosphate–ribose polymerase inhibitors.[84] These genes are also implicated in increased risk of prostate cancer with implications for male kidney recipients.

Recognizing inherited forms of immunodeficiency would empower physicians to be on guard against specific patterns of infections that are prevalent in KTRs. This would influence the choice and duration of post-transplant prophylactic antimicrobials and facilitate the design of a personalized immunosuppressive regimen. For example, knowledge of pathogenic variants in *IFNGR1,* which increase susceptibility to mycobacterial infection, would motivate intensified post-transplant surveillance and prophylaxis.[85] We also identified 27 KTRs harboring pathogenic or likely pathogenic variants in *TNFRSF13B*, among which 21 (77.8%) had clinical features compatible with those of common variable immunodeficiency, such as frequently recurrent or disseminated bacterial or viral infections, particularly sinopulmonary infections, cytopenias, organomegaly, autoimmune disorders, gastric cancer, lymphoma, or low IgG/IgM levels. Although the penetrance of primary hypogammaglobulinemia and common variable immunodeficiency in *TNFRSF13B* variant carriers is incomplete, susceptibility to infection may be exacerbated with exposure to immunosuppressive therapy. Thus, identifying individuals with pathogenic variants in *TNFRSF13B* would alert physicians to stay vigilant, reduce overall immunosuppression, and consider routine immunoglobulin replacement therapy.[86–88]

Last, recognizing KTRs at high risk of developing thromboembolism due to a *SERPINC1* or *SERPIND1* pathogenic variant would prompt prophylactic measures in the perioperative period, such either prolonged or a higher dose of perioperative anticoagulation.[89] While the study focused on rare variants (MAF $<$ 1%) with very large effects, there are also more common alleles that may augment risk of some transplant comorbidities. For example, the factor V Leiden variant (FVL), a thrombophilia risk allele, was detected in 36 individuals in the cohort. Identification of FVL by genetic testing would allow appropriate perioperative strategies such as anticoagulation to prevent thromboembolic complications.

In addition to the information in the morbidity panel, we uncovered a spectrum of monogenic causes of ESKD in KTRs in whom a genetic diagnosis was not previously considered. Many of these findings also had clinical implications for transplant care. For example, some diagnoses informed the risk of disease recurrence. In individuals with *CFH* pathogenic variants, the reported recurrence rate of atypical hemolytic uremic syndrome ranges from 30% to 100% post-transplant, and allograft outcome is generally poor, whereas individuals with *CFI*, *CFB*, and *C3* pathogenic variants have only slightly lower risk of disease recurrence. Comparatively, individuals with *CD46* or *DGKE* pathogenic variants have more favorable allograft outcome because of lower recurrence risk.[90–92] Complement genotyping will therefore stratify KTRs who are at greatest risk of recurrent disease and integrate eculizumab prophylactic therapy perioperatively.[93,94]

On the other hand, genetic forms of focal segmental glomerular sclerosis rarely recur post-transplant, except for podocin mutations.[95,96] Second, some kidney genetic diagnoses increase risk for specific post-transplant complications. For example, patients with Alport syndrome are at risk for anti-glomerular basement membrane nephritis, motivating monitoring for circulating anti-glomerular basement membrane antibodies in male patients with pathogenic truncating variants in *COL4A5* and in patients with autosomal recessive Alport syndrome during the first 12 months post-transplant.[97–99] Third, genetic diagnosis impacts transplant modality and treatment decisions. In patients with ESRD with primary hyperoxaluria type 1 due to pathogenic variants of *AGXT*, combined kidney-liver transplantation is the only curative

intervention, while pyridoxal phosphate and lumasiran are specific therapies that should be considered.[100,101] Fourth, genetic diagnosis predicts other post-transplant complications, such as diabetes in KTRs carrying *HNF1A* or *HNF1B* pathogenic variants and renal cell carcinoma in individuals carrying *TSC1*, *TSC2*, or *WT1* pathogenic variants. Of course, a diagnosis of a genetic kidney disease is helpful in guiding optimal donor selection among living relatives, obtaining workup for extrarenal complications, arranging cascade testing, and informing reproductive decisions.[102–104]

In addition, we also reported the diagnostic yield of ACMG-recommended list of medically actionable secondary findings in KTRs, which has mainly been studied in the general population. A recent study by the National Institutes of Health demonstrated that shifting from using ACMG SF v2.0 to v3.0 led to a higher frequency of returnable pathogenic variants, from 3.4% to 4.1%.[105] By using the latest ACMG SF v3.2, we observed a diagnostic yield of 5.0%. In contrast to most previous studies that found pathogenic variants most often in genes under the malignant neoplasm category, we demonstrated a higher diagnostic yield in genes associated with cardiovascular diseases. The discrepancy may be explained by the shift to include a greater proportion of genes related to cardiovascular phenotype in the latest version of ACMG SF gene list, the stringent exclusion criteria from transplantation in patients with a history of malignant neoplasm, faster progression of kidney disease in patients with cardiovascular risk factors, and clear guidelines available on the minimum waiting time needed before being rewaitlisted for transplant.[106–109]

Although genetic testing paves the way for personalized medicine in kidney transplantation, there are limitations. Our gene panel did not include mitochondrial diseases, such as mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), which may have renal manifestations and clinical implications for peritransplant management. Despite the fact that incorporating the transplant morbidity gene panel as part of pretransplant workup would potentially enable personalized management in both pretransplant and post-transplant care, further prospective studies are needed to demonstrate the cost-effectiveness and long-term benefits of such implementation. Current management guidance for unexpected genetic findings is designed for the general population. For example, in women with *BRCA1*-associated hereditary breast and ovarian cancer, breast cancer screening relies on a combination of monthly self-examination, annual clinical breast examination, annual mammography, and breast magnetic resonance imaging. However, are these surveillance measures adequate for our KTRs? Guidelines specific to the transplant population are needed to address the cohort-specific risks and needs.

The strengths of our study include its large sample size, and >50% of the cohort members are from populations underrepresented in human genetic research. These should be balanced with its limitations, which include the retrospective nature, where manual reverse phenotyping of pathogenic variants using electronic health records may not fully reflect individual's phenotype spectrum, and there is a relatively greater proportion of patients with glomerular disease compared with diabetic kidney disease as the cause of ESKD. For these reasons, multicenter prospective studies are needed in the future. Last, as novel gene-disease associations are constantly being updated, the gene lists in our study are by no means exhaustive of all up-to-date monogenic disorders associated with kidney diseases and categories of major post-transplant complications.

Altogether, our findings illustrate the clinical utility of the morbidity gene panel in kidney transplantation and should be applicable to any solid organ transplantation. By integrating genetic testing early in transplant evaluation, a management plan can be individually tailored, aiming to reduce complications. Although there are still many barriers to overcome to implement genetic testing widely in transplant practice, our study lays the foundation for future research in the field of genetic testing in solid organ transplantation. Studies to longitudinally evaluate the impact of both monogenic and polygenic risk on transplant treatment decisions, allograft survival, overall morbidity and mortality are needed. Development of specific guidelines for better management of transplant recipients with monogenic disorders is called for. Return of meaningful genetic results to research participants in a timely and sensitive manner requires close collaboration among researchers, genetic counselors, and transplant physicians so that actionable genetic findings would bring about the maximum clinical benefits. Subsequent genetic counseling visits should be available to address further questions and concerns from the patients. Ethical issues surrounding genetic testing in transplantation, such as transplant eligibility, donor selection, cost-benefit analysis, and health care use, also need to be addressed. Potential utility of an integrated genomic assessment of individual transplant recipients on risk of allograft loss, rejection, primary disease recurrence, post-transplant complications, and pharmacogenomics awaits further exploration.

DISCLOSURE

This study was partly funded by an investigator-initiated grant by Natera, Inc. The sponsor did not participate in the study design, the collection, analysis, and interpretation of data, the writing of the report, and the decision to submit the article for publication. AGG has served on advisory boards for Natera through a service agreement with Columbia University. All the other authors declared no competing interests.

DATA STATEMENT

The summary statistics are publicly available. Researchers interested in using more detailed patient-level data may contact the corresponding author.

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Table S1. Gene selection criteria for the transplant morbidity panel.

Supplementary Table S2. Exome capture kits used in the study.

Supplementary Table S3. The transplant morbidity panel gene list by disease category.

Supplementary Table S6. Diagnostic yield of the transplant morbidity panel.

Supplementary File (Excel)

Supplementary Table S4. The 355 genes in the transplant morbidity panel.

Supplementary Table S5. Diagnostic genetic findings by the transplant morbidity panel.

Supplementary Table S7. Clinical implications of individual genetic finding.

Supplementary Table S8. Diagnostic genetic findings by the mendelian kidney and genitourinary disorders gene panel.

Supplementary Table S9. Diagnostic genetic findings identified only by the American College of Medical Genetics and Genomics secondary findings v3.2.

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