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The impact of donor and recipient common clinical and genetic variation on estimated glomerular filtration rate in a European renal transplant population.

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Abbreviations

Cub and Sushi Multiple domains 1 gene (CSMD1)

Deterioration of Kidney Allograft Function Genomics (DeKAF)

Estimated glomerular filtration rate (eGFR)

Genetics & Translational Research in Transplantation Network (iGeneTRiN)

Genome-wide association studies (GWAS)

Genomics of Kidney Transplantation (GEN03)

Human Genome Diversity project (HGDP)

Oxysterol-binding protein 2 gene (OSBP2)

Polygenic risk scores (PRS)

Principal component (PC)

Principal components analysis (PCA)

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Abstract

Genetic variation across the HLA is known to influence renal-transplant outcome. However, the impact of genetic variation beyond the HLA is less clear. We tested the association of common genetic variation and clinical characteristics, from both the donor and recipient, with post-transplant eGFR at different time-points, out to 5-years post-transplantation.

We conducted GWAS meta-analyses across 10,844 donors and recipients from five European ancestry cohorts. We also analysed the impact of polygenic risk scores (PRS), calculated using genetic variants associated with non-transplant eGFR, on post-transplant eGFR.

PRS calculated using the recipient genotype alone, as well as combined donor and recipient genotypes were significantly associated with eGFR at 1-year post-transplant. 32% of the variability in eGFR at 1-year post-transplant was explained by our model containing clinical covariates (including weights for death/graft-failure), principal components and combined donor-recipient PRS, with 0.3% contributed by the PRS. No individual genetic variant was significantly associated with eGFR post-transplant in the GWAS.

This is the first study to examine PRS, composed of variants that impact kidney function in the general population, in a post-transplant context. Despite PRS being a significant predictor of eGFR post-transplant, the effect size of common genetic factors is limited compared to clinical variables.

1. Introduction

Since the discovery of the HLA in the 1950s, it has been clear that genetic factors are important in kidney transplant outcomes¹. A number of studies have examined candidate genes or variants beyond the HLA and their impact on graft function²⁻⁴, however, few have been replicated⁵. To date, only a small number of genome-wide association studies (GWAS) have analysed medium/long-term

allograft outcome⁶⁻⁸. A study from 2013 identified recipient genotype loci on chromosomes 14 and 18 which significantly associated with 5 years serum creatinine and long-term graft survival⁶.

However, this study was limited by its sample size (n=326) and an independent effort failed to replicate the findings⁹. This highlights the need for larger, robust GWAS of allograft outcome to determine the extent to which common variation affects the outcome of kidney transplantation.

Kidney transplants are a relatively rare phenotype and collaborative efforts such as the UK and Ireland Renal Transplant Consortium (UKIRTC⁷) and International Genetics & Translational Research in Transplantation Network (iGeneTRaiN¹⁰) facilitate well-powered studies of transplant related phenotypes. Recently the UKIRTC published a GWAS of kidney transplant outcomes which examined graft survival and acute rejection in the first twelve months post-transplant, in a deceased donor cohort of 2,094 transplant pairs⁷. Although much better powered than earlier efforts, no significant associations were found beyond the previously known effect of the HLA. A GWAS involving pooled DNA from 4,127 renal transplant recipients identified signals of association with T-cell mediated acute rejection at the *PTPRO* and *CCDC67* loci. The finding was replicated, but not as part of an independent study⁸. Neither the *PTPRO* or *CCDC67* signal replicated in the UKIRTC GWAS of acute rejection, however the definition of acute rejection in the UKIRTC study¹¹ was not specific to T-cell mediated rejection which may explain the discordance. Here, we hypothesise that a continuous variable of outcome (i.e. eGFR) would provide additional power to detect the impact of genetic variation on markers of graft outcome.

In non-transplant populations, there has been a number of large well-powered GWAS that have identified genetic variants that associate robustly with kidney function¹²⁻¹⁵, the largest of which (n=133,814) was carried out by Pattaro et al¹³. However, despite the identification of a number of risk loci, univariate effect sizes were small (OR of 0.93 to 1.06 for the 23 novel loci identified).

Common genetic variants typically have small effects on complex human traits, and thus are usually not of clinical relevance. Polygenic risk scores (PRS) quantify the cumulative effects of a number of

loci, which may individually have a small predictive ability. By doing so, PRS's may be more clinically relevant than looking at common genetic variants independently. One study, by Gorski et al¹², used summary statistics from their GWAS of estimated glomerular filtration rate (eGFR) to create a polygenic risk score (PRS) which was then tested against eGFR in an independent cohort of 1,017 individuals. They found the PRS to explain 2.2% of the trait variance compared to 1.3% when just considering genome-wide significant loci.

In this study, we set out to test the hypothesis that common variation from donor or recipient genotype is associated with short and medium term allograft kidney function, using 1-year, 5-year and Δ (change between 1 and 5 year) eGFR as measures of kidney function. Involving 10,844 transplant donors and recipients, and delivered through the iGeneTRaiN consortium, this study is the largest GWAS of allograft function to date. In addition to studying the association of individual SNPs with eGFR, we also set out to test the hypothesis that higher polygenic load for increased eGFR in the donor, recipient and combined (donor and recipient) genomes is associated with increased graft function. To do this, we tested if PRS estimated using alleles from a GWAS of kidney function (using eGFR as a proxy) in a non-transplant population¹³ is predictive of kidney function in a number of renal transplant cohorts.

2. Materials and Methods

2.1. Cohorts

We assembled five cohorts via the iGeneTRaiN consortium¹⁰. They are 1) 'Transplant Lines' (the Netherlands), 2) the Vienna/Prague cohort (Austria), 3) the Deterioration of Kidney Allograft Function Genomics (DeKAF) cohort (United States, NCT00270712), 4) the Genomics of Kidney Transplantation (GEN03) cohort (United States, NCT01714440) and 5) the United Kingdom and Ireland Renal Transplant Consortium (UKIRTC) cohort. See Table 1 for cohort descriptions and

supplementary methods for genotyping and imputation information. The appropriate ethics committees at each site approved the protocol for this study.

Notably, GEN03 and DeKAF Genomics cohorts were entirely living donor transplants whereas UKIRTC, TransplantLines and Vienna/Prague cohort was predominantly deceased donor transplants. In TransplantLines, the year of transplant ranged from 1993-2008. In the UKIRTC, the year of transplant ranged from 1981-2007. In DEKAF Genomics, transplants were performed between 2005-2011 and in the GEN03 study from 2012-2016. In the Vienna/Prague cohort, the year of transplant ranged from 2005 to 2015.

2.2. Phenotype

We set out to analyse three phenotypes in each of these cohorts: eGFR at one-year post-renal transplant, eGFR at five years post-transplant and the change in eGFR from one to five years (Δ) post-transplant (see supplementary methods for details on calculating eGFR).

The following inclusion/exclusion criteria were applied: Participants must 1) be of European ancestry, 2) have donated/received a renal transplant and 3) be unrelated to level of 3rd degree relative.

To identify individuals of European ancestry, all patient cohorts were merged with samples from the Human Genome Diversity project (representing seven different global populations) or the 1000 Genomes Project and analysed using principal components analysis (PCA). Principal component (PC) 1 was plotted against PC2 and individuals in the patient cohorts that did not overlap with the European individuals in the HGDP were removed. To identify individuals unrelated beyond 3rd degree, we used PLINK's --genome function to calculate identity-by-descent (PIHAT) scores¹⁶. One individual from each pair of related individuals (i.e. 3rd degree, or closer relatives) was excluded from the analysis¹⁶.

2.3. Clinical analyses

We first assessed a number of available clinical predictors of allograft function (see supplementary table 1 for list and definitions of clinical variables tested). These clinical variables were tested on a dataset of over 1,400 renal transplant recipients from TransplantLines and Dublin (subset of UKIRTC cohort). Significant clinical variables identified in the univariate linear regression analysis (see Table 2) were then tested in a stepwise regression model (see Supplementary Tables 2-7). Collinear variables were removed and the remaining clinical variables were included as covariates in our genetic analyses. See supplementary methods for further details.

2.4. Genome-wide association study

Genome-wide association studies were carried out at each site independently for each available outcome variable (\log_{10} 1-year eGFR, \log_{10} 5-year eGFR and Δ eGFR) with PCs (to correct for population-specific allelic differences), and available clinical variables with weights for death and failure in the \log_{10} 1-year eGFR and \log_{10} 5-year eGFR GWAS included as covariates (see supplementary methods section). GWAS were conducted separately for donor and recipient genotypes. See supplementary methods section 4 for further details.

The results from each site were then combined using a meta-analysis approach (see supplementary methods for further details). The meta-analysis approach utilised in this study has previously been applied in a number of other genome-wide analyses of common genetic variation including analyses of kidney function^{13,17-19}. Genome-wide level of significance was set at 5×10^{-8} for the GWAS meta-analysis.

Retrospective power calculations were carried out using a combination of R's `pchisq` and `qchisq` functions. In the recipient full model (significant clinical covariates (including weights for death/failure for the \log_{10} 1-year eGFR and \log_{10} 5-year eGFR analyses – see supplementary methods), principal components and given genetic variant) we had 80% power to detect a variant

which explains 0.75%, 1.87% and 2.20% of outcome variance in the one-year, five-year and Δ recipient analysis respectively. In the donor full model GWAS, we had 80% power to detect a variant which explains 1.12%, 2.13% and 2.49% of outcome variance in the one-year, five-year and Δ donor analysis respectively.

In the recipient baseline model (just PCs, failure and death as covariates), we had 80% power to detect a genetic variant which explains 0.67%, 1.39% and 1.78% of outcome variance in the one-year, five-year and Δ recipient analysis respectively. In the donor baseline GWAS, we had 80% power to detect a variant which explains 0.98%, 1.58% and 2.01% of outcome variance in the one-year, five-year and Δ donor analysis respectively.

2.5. Polygenic risk analysis

For the PRS analysis, we employed the same clinical covariates and outcome measures as the GWAS analysis. We defined PRS as the sum of the alleles associated with a given trait weighted by the effect size of that allele as determined by a previous GWAS²⁰. PRSs were calculated using results of a previous GWAS of eGFR in a non-transplant population¹³. We calculated the PRS at multiple p-value thresholds to enable us to examine at different sets of SNPs (for example, is the top 1,000 or top 10,000 most significant SNPs associated with eGFR in the general population a better predictor of eGFR post-transplant). See supplementary methods for further details on how we calculated these scores. PRSs were then tested as predictors of each outcome variable correcting for available significant clinical covariates (as discussed previously) and PCs using in a linear regression model (see supplementary methods for further details). Linear regressions were carried out separately at each site and then combined using a meta-analysis approach in line with previously published meta-analyses of PRS²¹. See supplementary methods for further details.

3. Results

This study involved 10,844 transplant donors and recipients recruited from UKIRTC (n=4,108), TransplantLines (n=1,806), GEN03 (n=1,039), DeKAF (n=2,666) and Vienna/Prague (n=1,225). The mean age of recipients and other clinical variables are reported in Table 1. Subjects had a mean eGFR of 52.43ml/min at 1 year and 51.39ml/min at 5 years post-transplant. The mean Δ eGFR was -1.01ml/min. Distributions of eGFR in each of the five cohorts can be seen in Supplementary Figures 1 to 4.

3.1. Clinical analysis

Clinical covariates were tested in a combined cohort comprising over 1,400 renal transplant recipients from TransplantLines and the Dublin subset of the UKIRTC (see supplementary methods for further details). After correcting for multiple testing and collinearity (see Supplementary Table 2-7), we identified donor age, donor type, donor sex, recipient age, delayed graft function and acute rejection as significant predictors of \log_{10} eGFR at 1-year. These variables explained 22% of the outcome variance.

Donor age, mycophenolate mofetil exposure, delayed graft function, acute rejection and donor type were identified as significant predictors of \log_{10} eGFR at 5-years. These variables explained 21% of the variance in eGFR at 5 years post-transplant.

Recipient age at time of transplantation, mycophenolate mofetil exposure and acute rejection were identified as significant predictors of Δ eGFR. These variables explained 4% of the variance in delta eGFR. These clinical predictors of eGFR were brought forward for the following GWAS and polygenic risk score analyses.

3.2. Genome-wide association study

To test the hypothesis that, in a univariate model, common donor or recipient genotype is associated with graft function, imputed genotype data was tested against \log_{10} eGFR at 1-year and 5-years post-transplant and Δ eGFR between 1 and 5 years taking a GWAS approach.

No genome-wide significant signals were detected in the donor or recipient GWAS in either the baseline or full model for \log_{10} eGFR at 1-year or 5-year post-transplant or Δ eGFR (see Figure 1 and Supplementary Figures 5-16). The top ten most significant variants for each GWAS are described in Supplementary Tables 8-13. The genomic inflation for each of the GWASs was minimal and the GWASs appeared to behave normally when the expected versus observed p-values were plotted (see Supplementary Figures 5-16).

3.3. Polygenic risk analysis

Having assessed the donor and recipient genotype in a univariate model, we next examined common genetic variation in a multivariate polygenic risk model. Using linear regression models, we tested the hypothesis that a polygenic load for increased eGFR (calculated using alleles from non-transplant populations, see methods section 2.5) in the kidney donor, recipient or combined (donor and recipient) genotype, is associated with increased post-transplant eGFR (see Table 3). The PRS at $p < 0.0001$ calculated using the recipient genotype and the combined donor-recipient genotype significantly predicted \log_{10} eGFR at 1-year post-transplant (see Figure 2 and 3). These figures illustrate that the effect size was consistent across sites with an increased PRS leading to a higher eGFR post-transplant - i.e. increased number of alleles that predict higher eGFR in non-transplant populations correlates with higher eGFR post-transplant.

The amount of variance explained by the full model (significant clinical covariates including weights for death/failure, principal components and polygenic risk score at $p < 0.0001$) for the combined donor-recipient PRS was 32% with 0.3% contributed by the PRS. The amount of variance explained

by the full model for the recipient PRS was 30% with 0.2% contributed by the PRS (see Supplementary Table 14). Notably, approximately 9% of the variance explained by clinical variables is attributed to the death/failure weights (see Supplementary Table 14).

None of the PRS (at any pT) significantly predicted \log_{10} eGFR 5 years or Δ eGFR when calculated using the donor, recipient, or combined (sum of the donor and recipient alleles) genotype. Also, none of the PRS calculated using solely the donor alleles were significant predictors of any of the outcomes tested. Low heterogeneity was found across sites (see Table 3).

4. Discussion

In this study, we set out to test the impact of clinical variables and common genetic variation from both the donor and recipient on eGFR post-transplant using both univariate and polygenic methods.

Although both clinical variables and polygenic risk scores were found to be predictive of eGFR post-transplant, clinical variables explained several orders of magnitude more of trait variance.

We identified a number of significant clinical predictors of eGFR at 1 and 5 years including donor age, donor type (living/deceased), donor sex, recipient age, delayed graft function, acute rejection and mycophenolate mofetil exposure. Collectively, these variables explained over 20% of the variance in eGFR at 1 and 5 years post-transplant. We also found that recipient age at time of transplantation, mycophenolate mofetil exposure and acute rejection predicted change in renal function over the first 5 years post-transplant. These findings and the direction of effect of these variables are in line with the literature and have all been previously implicated in eGFR post-transplant²²⁻²⁴. Notably, mismatches at HLA A, B and DR and the total number of mismatches across these three loci (calculated using serological testing) were not found to be significant in our clinical analysis (see Table 2). This likely due to advancements in immunosuppression as well as most donors and recipients being matched based on preferential HLA typing, which in combination are masking the effects of the HLA.

We did not find any donor or recipient SNP that associated (post-correction for multiple testing) with eGFR at 1 year, 5 years or Δ eGFR post-renal transplantation. However, in the top SNPs from a number of the GWAS there were some interesting and potentially biologically relevant signals – although we stress these were not significant and so their role in graft function remains uncertain. For example, in our donor \log_{10} 5-year eGFR full model GWAS, the most significant SNP was found in the fifth intron of the Cub and Sushi Multiple domains 1 gene (*CSMD1*). *CSMD1* has been implicated in a variety of diseases including schizophrenia and colorectal cancer^{25,26}. *CSMD1* has also been proposed as a regulator of the complement pathway – a pathway essential for inflammation and immune regulation²⁷. Over the past decade, evidence has emerged which implicates the complement pathway in allograft ischemia-reperfusion as well as alloimmunity that results in graft injury thereby affecting the life-span of the graft²⁸. Further work is required to decipher if common variants in this gene play a role in allograft function.

For our donor GWAS of delta eGFR, in both the baseline and full models, the most significantly associated variant with delta eGFR was rs136237 (full model $p = 7.89 \times 10^{-7}$, baseline model $p = 7.04 \times 10^{-7}$), a SNP in the third intron of the oxysterol-binding protein 2 gene (*OSBP2*). This gene encodes a protein that binds some oxygenated forms of cholesterol called oxysterols and inhibits their functions²⁹. Oxysterols are involved in a vast range of important biological processes including apoptosis and platelet aggregation³⁰. *OSBP2* is expressed at low levels in the kidney^{31,32}. Further work is required to validate this finding.

Despite some interesting signals towards the tail of the distribution, none reached statistical significance and so our findings indicate that no single common genetic variant, in either the donor or recipient genome, explains a clinically relevant proportion (>2%) of the variation in eGFR post-kidney transplantation. It is probable that there are SNPs explaining a smaller proportion of eGFR post-transplant, but we were underpowered to detect these under a univariate model. This study focused specifically on common genetic variation, it is possible that rare variation in the donor

and/or recipient genotype is influencing allograft function, but further work is required to clarify this.

We demonstrated that both recipient PRS and our combined PRS model significantly associated with \log_{10} eGFR at 1-year post-transplant. We found that the recipient and combined PRS at pT 0.0001 was significantly associated with \log_{10} 1-year eGFR, indicating that common sub-genome-wide significance threshold (5×10^{-8}) genetic variants influence graft outcome. This PRS was not found to associate with Δ eGFR or \log_{10} 5-year GFR. This may indicate that the genetic variation that influences graft outcome is different for short-term outcome than that for medium-term or long-term graft function. This is consistent with our clinical findings, where concordance between the clinical variables that predict 1-year eGFR and 5-year eGFR is incomplete, indicating that different factors affect early stage vs medium stage graft function. However, we had more samples in our 1-year eGFR, than in our 5-year eGFR analysis and so potentially with larger numbers in the 5-year analysis this PRS may become significant as the same effect size and direction was seen.

Approximately 30% of the variance in \log_{10} 1-year eGFR was explained by our full model (clinical covariates including weights for death/graft-failure, PC and PRS) in both the recipient PRS and combined PRS analysis. The majority of this variation was explained by the clinical covariates and less than $\sim 0.3\%$ of the variance is explained by either PRS. Interestingly, Gorski et al¹² found that a PRS based on eGFR associated variants calculated at the same p-value threshold (pT 0.0001) explained 1.7% of the outcome variance in non-transplant populations indicating that although the genetic basis for GFR post-transplant overlaps with that in non-transplant individuals, there are differences. However, our PRS was based off a different set of GWAS results¹³ than that in Gorski et al and their paper used a different method for calculating the PRS which may account for differences between the variance explained. The PRS, albeit not clinically relevant, does highlight that the recipient genotype, as well as the donor genotype, is associated with early-stage graft function. Notably, the donor genotype is only significant in the context of the recipient genotype (i.e. in our combined model).

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Our study had a number of limitations. Firstly, although we had relatively comprehensive phenotypic data and corrected for clinical covariates, we likely did not have sufficient data to account for all clinical heterogeneity within and between our cohorts. In particular, our cohorts had different eras of transplantations and therefore different immunosuppression protocols which may have led to additional heterogeneity between cohorts. Potentially, through analysis of more similar cohorts we may have had more significant findings. However, in the PRS analyses, we did test for heterogeneity between our cohorts and found it to be minimal and any SNPs with high levels of heterogeneity in our GWAS were removed.

Secondly, these meta-analyses were carried out on European ancestry populations and therefore further work is needed to investigate single variant and polygenic effects in other non-European populations.

In conclusion, we found that polygenic effects of common genetics variants influence short-term allograft function but did not find any significant associations in our univariate model. This study is the first of its kind to look at the impact of polygenic effects of variants that impact kidney function in the general population in a post-transplant context. Our finding suggests that although common genetic variation does impact graft outcome, the effect size is limited compared to clinical variables.

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Deterioration of Kidney Allograft Function Genomics and Genomics of Kidney Transplantation

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The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Figure legends

Figure 1. Manhattan plots of recipient and donor \log_{10} 1-year, \log_{10} 5-year and Δ eGFR – full model

The red line indicates the genome-wide significance threshold (5×10^{-8}), the blue line indicates suggestive significance threshold (1×10^{-5}). A = recipient \log_{10} 1-year eGFR – full model (λ (genomic inflation factor) = 1.01). The top SNP was an intergenic variant on chr17p13.3. N SNPs = 3,673,881. B= donor \log_{10} 1-year eGFR – full model (λ = 1.01). N SNPs = 3,641,041. The most significant SNP was found in an intergenic region on chr12p13.1. C= recipient \log_{10} 5-year eGFR – full model (λ = 0.99). The top SNP was an intergenic variant on chr17q22. N SNPs = 3,924,633. D= donor \log_{10} 5-year eGFR – full model (λ = 1.01). N SNPs = 3,938,549. The most significant SNP was found on chromosome 8 in an intron of *CSMD1*. E= recipient Δ eGFR – full model (λ = 1.01). The top SNP was found in the gene *ZNF551* on chromosome 19. N SNPs = 3,915,961. F= donor delta eGFR – full model (λ = 1.01). N SNPs = 3,927,634. The most significant SNP was found on chromosome 22 in an intron of *OSBP2*.

Figure 2. Recipient PRS at pT 0.0001 as a predictor of \log_{10} eGFR at 1-year post-transplant

Site = study cohort. TxLines= TransplantLines. Vienna = Vienna/Prague cohort. Weight= proportion of data the given site contributed to overall model; coef [95% CI] = effect size with lower and upper 95% confidence intervals. PRS_pT_0.0001 = normalized recipient PRS of eGFR at p-value threshold 0.0001, RE model = Random-effects model. Model was adjusted for significant clinical covariates and the first eight principal components at each site (see section 3.1).

Figure 3. Combined PRS at pT 0.0001 as a predictor of \log_{10} eGFR at 1-year post-transplant

Site = study cohort. TxLines= TransplantLines. Vienna = Vienna/Prague cohort. Weight= proportion of data the given site contributed to overall model; coef [95% CI] = effect size with lower and upper 95% confidence intervals. Combo_PRS_pT_0.0001 = normalized combined PRS of eGFR at p-value threshold 0.0001. RE model = Random-effects model. The model was adjusted for significant clinical covariates and the first eight principal components at each site (see section 3.1).

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Tables

Table 1. Descriptive statistics for each cohort of significant clinical predictors and eGFR measures

		UKIRTC	TxLines	GEN03	DeKAF	Vienna/ Prague
Recipients	N	2233	983	673	1864	616
	Range of year of transplant	1981- 2007	1993- 2008	2012- 2016	2005- 2011	2005-2015
	% male	64%	57%	62%	63%	63%
	Average length of follow-up post-transplant - years	8.47 (4)	9.77 (5)	1.90 (0.8)	2.25 (1)	4.75(3)
	Average age at transplant	46.32 (13)	48.26 (13)	50.25 (15)	50.46 (14)	52 (14)
	% with failure by year 1	1%	4%	0%	0%	5%
	% with death by year 1	0.3%	2%	0%	1%	3%
	% with failure by year 5	8%	10%	1%	3%	10%
	% with death by year 5	4%	8%	1%	3%	8%
	% on mycophenolate mofetil	37%*	72%	100%	95%	99%
	% with delayed graft function	NA	30%	6%	7%	30%
	% Acute rejection episode by year 1	20.57%*	30%	15%	14%	36%
% Acute rejection episode by year 5	NA	33%	16%	18%	40%	
Donors	N	1875	823	366	802	609
	% male	57%	52%	43%	41%	56%
	Average age	43.1 (16)	43.02 (15)	45.50 (12)	44.31 (11)	50 (14)
	% Living	0%	17%	100%	100%	15%
eGFR at 1 year	N observations	1905	937	673	1864	556
	Mean	48.1	45.6	61.9	58.1	52.5
	Median	47.1	44.6	59.2	55.9	50.8
	Max	120.5	108.7	201.2	217.6	109.8
	Min	4.5	2.5	15.0	4.0	2.0
	Stdev	17.8	18.8	21.8	20.8	18.8
eGFR at 5 year	N observations	1700	906	NA	NA	315
	Mean	46.4	46.2	NA	NA	51.5
	Median	44.9	45.9	NA	NA	50.8
	Max	122	181	NA	NA	105
	Min	4.1	2.5	NA	NA	9.4
	Stdev	19.4	22.5	NA	NA	19.9
Δ eGFR	N observations	1283	719	NA	NA	296
	Mean	-1.8	2.0	NA	NA	-2.5
	Median	-1.8	2.7	NA	NA	-2.9
	Max	65.6	73.3	NA	NA	45.9
	Min	-57.3	-60.4	NA	NA	-45.4
	Stdev	13.4	16.1	NA	NA	12.3

The above table provides descriptive statistics for the UK and Ireland Renal Transplant consortium cohort (UKIRTC), TransplantLines cohort (TxLines), GEN03, DeKAF and Vienna/Prague cohort. N = number of individuals, % = Percentage, % with failure by year 1/5 = Percentage with a failure event within 1/5 years post-transplant, % with death by year 1/5 = Percentage who died within 1/5 years post-transplant, % on mycophenolate mofetil = percentage of patients who received mycophenolate mofetil at the start of their transplant (intention to treat), % living = percentage of living donors, stdev = standard deviation, min = minimum value observed, max = maximum value observed. Delayed graft function status was unavailable for the UKIRTC cohort. Acute rejection status for the

UKIRTC cohort was only available for the first twelve months post-transplant. Δ eGFR and 5-year eGFR were unavailable for the GEN03 and DeKAF cohorts.

* A large number of the UKIRTC patients had missing information for MMF and AR status and so these percentages were calculated from those who had yes/no status for MMF and individuals with missingness were excluded. MMF % was calculated as follows: 1045 N – not exposed to MMF, 604 – were exposed, 584 = missing. $(604 / (1045 + 604)) * 100 / 1 = 36.62\%$. For acute rejection at 1 year, 1093 – did not experience an AR episode in the first twelve months, 283 did have an AR episode and 857 were missing. AR % was calculated as follows: $(283 / (1093 + 283)) * 100 / 1 = 20.57\%$.

Clinical Variable	Log 1-year eGFR				Log 5-year eGFR				Δ eGFR			
	Coef.	SE	Pbon	N	Coef.	SE	Pbon	N	Coef.	SE	Pbon	N
<i>Acute Rejection</i>	-0.07	0.01	1.53x10 ⁻⁸	1407	-0.09	0.01	3.48x10 ⁻¹¹	1399	-4.57	0.99	8.08x10 ⁻⁵	1108
<i>Azathioprine</i>	0.02	0.01	1	1406	-0.01	0.01	1	1399	-3.61	1.09	0.02	1108
<i>Cold Ischemic Time</i>	-0.00004	0.00001	0.001	1400	-0.00004	0.00001	0.0009	1392	-0.001	0.001	1	1108
<i>CMV</i>	-0.04	0.01	0.0004	1407	-0.04	0.01	0.06	1340	-1.54	0.97	1	1108
<i>Corticosteroids</i>	0.09	0.03	0.02	1402	0.08	0.03	0.24	1399	-3.89	2.65	1	1108
<i>Cyclosporin</i>	0.04	0.02	0.48	1355	0.03	0.02	1	1399	1.34	1.48	1	1108
<i>Delayed graft function</i>	-0.09	0.01	2.42x10 ⁻¹³	1407	-0.09	0.01	1.39x10 ⁻⁸	1398	0.86	1.15	1	1103
<i>Donor age</i>	-0.004	0.0003	3.84x10 ⁻³⁰	1407	-0.004	0.0004	1.41x10 ⁻²⁰	1399	-0.02	0.03	1	1063
<i>Donor sex</i>	-0.04	0.01	0.001	1407	-0.03	0.01	0.08	1399	0.47	0.93	1	1108
<i>Donor Type</i>	-0.07	0.01	3.54x10 ⁻⁷	1407	-0.05	0.02	0.006	1399	-0.39	1.16	1	937
<i>HLA-mismatch A</i>	0.00	0.01	1	1407	-0.01	0.01	1	1196	-1.11	0.78	1	1108
<i>HLA-mismatch B</i>	-0.01	0.01	1	1407	0.00	0.01	1	1196	0.40	0.74	1	936
<i>HLA-mismatch DR</i>	0.01	0.01	1	1407	0.003	0.01	1	1195	-0.72	0.84	1	937
<i>Mycophenolate</i>	0.02	0.01	1	1196	0.05	0.01	0.003	1399	3.52	0.94	0.004	1107
<i>Recipient age</i>	-0.003	0.0004	1.3x10 ⁻⁹	1195	-0.0005	0.0004	1	1399	0.17	0.04	2.68x10 ⁻⁵	1108
<i>Recipient sex</i>	-0.01	0.01	1	1196	-0.03	0.01	0.44	1399	-0.20	0.94	1	937
<i>Sirolimus</i>	-0.09	0.03	0.14	1407	-0.03	0.04	1	1399	5.64	2.86	0.96	1108
<i>Site</i>	0.01	0.01	1	1407	0.001	0.02	1	1399	-2.92	1.15	0.22	1108
<i>Tacrolimus</i>	-0.01	0.02	1	1196	-0.02	0.02	1	1399	-2.25	1.82	1	1108
<i>Total MM</i>	0.00	0.00	1	1407	-0.003	0.005	1	1196	-0.27	0.36	1	1108

Table 2. Linear regression results for clinical variables associated with eGFR at 1 year, 5 years and Δ eGFR from 1 to 5 years

Coef. = regression coefficient; SE=standard error; Pbon = Bonferroni corrected p value (unadjusted p value*20); N = number of individuals tested (i.e. who had the measure available); Site = cohort associated with given individual where Dublin =one and TransplantLines =zero. Graft failure and death with a functioning graft were adjusted for in the log₁₀ 1-year and 5 year eGFR analyses. Acute Rejection = acute rejection within 1 year post-transplant for log₁₀ 1-year eGFR analysis and within 5 years for Δ eGFR and log₁₀ 5-year eGFR analysis. Azathioprine = azathioprine - intention to treat at start of transplant. Cold Ischemic Time = cold ischemic time in minutes. CMV = cytomegalovirus infection in recipient post-transplant. Corticosteroids = intention to treat at start of transplant. Cyclosporin = intention to treat at start of transplant. Delayed graft function = yes/no. Donor age = donor age at time of transplant. Donor sex = male = 0, female = 1. Donor Type = Living/deceased = living = 1, deceased = 0. HLA-mismatch A = Number of HLA mismatches between donor and recipient at A locus. HLA-mismatch B = Number of HLA mismatches between donor and recipient at B locus. HLA-mismatch DR = Number of HLA mismatches between donor and recipient at DR locus. Mycophenolate = Mycophenolate - intention to treat at start of transplant. Recipient age = recipient age at time of transplant. Recipient sex = recipient sex - male=0, female=1. Sirolimus = Sirolimus - intention to treat at start of transplant. Site = Dublin/TransplantLines, Dublin = 1, TransplantLines = 0. Tacrolimus = Tacrolimus - intention to treat at start of transplant. Total MM = Total number of HLA mismatches across A, B and DR locus.

D/R	pT	eGFR	Estimate	SE	Pun	Padj	I ²	N	N SNPs
combined	0.0001	1year	0.011	0.003	4.35x10 ⁻⁵	0.001	0.0%	3234	6229
recipient	0.0001	1year	0.008	0.002	8.68x10 ⁻⁵	0.005	6.2%	5295	6229
donor	0.0001	1year	0.006	0.003	0.01	0.755	2.7%	3564	6229
donor	0.1	5year	0.011	0.005	0.05	1	35.0%	2152	287016
recipient	0.0001	5year	0.008	0.004	0.06	1	0.0%	2494	6229
combined	0.0001	5year	0.008	0.005	0.11	1	0.0%	1930	6229
recipient	0.0001	Δ	0.668	0.367	0.07	1	0.0%	2191	6229
donor	0.001	Δ	-0.348	0.358	0.33	1	0.0%	1904	14097
combined	0.001	Δ	-0.513	0.413	0.21	1	0.0%	1722	14097

Table 3. Most significantly associated polygenic risk scores with eGFR post-transplant

Meta-analysis results for linear regression of polygenic risk scores vs. eGFR measures. 1/5 year = \log_{10} eGFR at 1/5 year post-transplant. Δ = change in eGFR between 1 and 5 years post-transplant. Model was adjusted for all available significant clinical covariates and the first eight principal components at each site (see section 2.5 and 3.1). D/R = indicates whether the test was carried out on the recipient, donor or combined donor-recipient genotype. pT = p-value threshold of the calculated polygenic risk score. Estimate = estimated effect size. SE = standard error of the estimate. Pun = uncorrected p-value. Padj=approximate adjusted p-value. I² = the proportion of total variation in study estimates that is due to heterogeneity. N = number of individuals tested. N SNPs = number of SNPs at the given p-value threshold (prior to pruning for linkage disequilibrium).





