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## **Trajectories of glomerular filtration rate and progression to end stage kidney disease after kidney transplantation.**

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## ABSTRACT

Although the gold standard of monitoring kidney transplant function relies on glomerular filtration rate (GFR), little is known about GFR trajectories after transplantation, their determinants, and their association with outcomes. To evaluate these parameters we examined kidney transplant recipients receiving care at 15 academic centers. Patients underwent prospective monitoring of estimated GFR (eGFR) measurements, with assessment of clinical, functional, histological and immunological parameters. Additional validation took place in seven randomized controlled trials that included a total of 14,132 patients with 403,497 eGFR measurements. After a median follow-up of 6.5 years, 1,688 patients developed end-stage kidney disease. Using unsupervised latent class mixed models, we identified eight distinct eGFR trajectories. Multinomial regression models identified seven significant determinants of eGFR trajectories including donor age, eGFR, proteinuria, and several significant histological features: graft scarring, graft interstitial inflammation and tubulitis, microcirculation inflammation, and circulating anti-HLA donor specific antibodies. The eGFR trajectories were associated with progression to end stage kidney disease. These trajectories, their determinants and respective associations with end stage kidney disease were similar across cohorts, as well as in diverse clinical scenarios, therapeutic eras and in the seven randomized control trials. Thus, our results provide the basis for a trajectory-based assessment of kidney transplant patients for risk stratification and monitoring.

**Keywords:** End stage renal disease, kidney transplantation, mortality, kidney function, trajectories, glomerular filtration rate.

## INTRODUCTION

End stage renal disease (ESRD) places a heavy and growing burden on health systems, now affecting 7.4 million individuals worldwide<sup>1</sup>. This number is driven by the high prevalence of chronic kidney disease (CKD). Indeed, 850 million individuals suffer from CKD,<sup>1-3</sup> while diabetes, cancer, and HIV/AIDS affect 422, 42, and 37 million individuals, respectively.<sup>4-6</sup>

The estimated GFR (eGFR), fundamental to define CKD<sup>7,8</sup>, is used worldwide for patient monitoring and decision-making. According to a systematic review we conducted (Table S1), current approaches for investigating the relationship between eGFR course and outcomes such as ESRD and mortality have been limited by registry data, including convenience clinical samples and a limited number of eGFR measurements for a single patient.<sup>9</sup> Importantly, no study to date has been primarily designed towards a prospective protocol-based and standardized assessment of eGFR together with thorough patient characterization, including immunological and biological profiling, histological phenotyping and information about treatments. An integrated approach to determine at an early stage post-transplant patient eGFR trajectories over 10 years may bring an original perspective to the traditional clinical interpretation of kidney function based on cross-sectional or short-term eGFR measurements.

To avoid making any prior assumptions on the evolution of eGFR, we used a contemporary unsupervised approach known as latent class mixed modeling<sup>3</sup>. This approach has already demonstrated its clinical relevance in diverse medical settings such as depression,<sup>9</sup> atherosclerosis,<sup>10</sup> or disability<sup>11,12</sup> by unraveling unrecognized profiles of patients. The identification of trajectories of renal function might be useful to provide a more nuanced picture of disease progression, which may ultimately contribute to guiding CKD care.

We present here the results from a longitudinal prospective study that comprises consecutive kidney recipients from 15 cohorts and 7 randomized controlled trials (RCTs).

Using the information gathered by protocol-driven, repeated eGFR assessments performed alongside clinical, biological, histological and immunological phenotyping, we determined whether a trajectory-based approach could identify universal prototypes of eGFR trajectories. We also investigated the determinants of these trajectories and their time to progression to ESRD and all-cause mortality.

## **RESULTS**

### ***Characteristics of the derivation and validation cohorts***

Overall, 14,132 patients were included in the study. The derivation cohort (n=4,140), the European validation cohort (n=5,155) and the North American cohort (n=2,328) included a total of 11,623 patients receiving care from 15 transplant centers between January 1, 2000, and December 31, 2016, corresponding to 74,826 patient-years. The median follow-up post-transplantation was 6.5 years (IQR 4.0-8.6). The total number of eGFR measurements was 403,497 (34.7±10.2 measurements per patient, Figure S1). The additional validation cohorts comprised a total of 2,509 patients recruited in 7 already published RCTs.<sup>13-19</sup> Baseline characteristics stratified by center are displayed in Tables S2-5. The baseline characteristics, allocation systems and induction therapy of the derivation and validation cohorts are detailed in Table 1, Table S6 and S7.

### ***Identification of eGFR trajectories in the various cohorts and RTCs***

#### *Derivation cohort*

At 1 year post-transplantation (i.e., the baseline of the study), the mean eGFR was 51.1±18.7 mL/min/1.73 m<sup>2</sup>. 8 mutually exclusive eGFR trajectories over 10 years after transplantation were identified (Figure 1A). The model showed a good discrimination of 0.73, meaning that the model adequately assigned patients to specific trajectories (details regarding the model selection in supplementary methods S1 and Table S8).

### *External validation cohorts*

Latent class mixed models were independently applied to the external validation cohorts from Europe and the US. At baseline, the mean eGFR was  $49.1 \pm 17.5$  ml/min/1.73 m<sup>2</sup> in Europe and  $54.7 \pm 19.4$  ml/min/1.73 m<sup>2</sup> in the US.

In these geographically distinct cohorts, the best fitting models identified again 8 distinct profiles of eGFR trajectories and confirmed the consistency of the 8 profiles previously identified in the derivation cohort (Figure 1B and C). Both models showed good discrimination (0.73 in Europe and 0.71 in the US). The distribution of each center per trajectory is displayed in Table S9.

### *Randomized controlled trials*

Latent class mixed models were also applied to patients enrolled in 7 randomized controlled trials (n=2,509 patients). At baseline (the time of randomization), the mean eGFR was  $53.8 \pm 19.3$  ml/min/1.73 m<sup>2</sup>. The best model identified 8 eGFR trajectories that were very similar to those previously identified (Figure S2), with a good discrimination of 0.77.

### ***Clinical, functional, structural and immunological determinants of eGFR trajectories***

Thirty clinical, functional, structural and immunological factors of eGFR trajectories were investigated (Figure S3). The results of the univariate analysis conducted in the derivation cohort are reported in Table 2. After multivariable analysis, the following independent determinants measured at 1 year post-transplantation were identified: i) donor age ( $p < 0.001$ ); ii) allograft functional parameters including eGFR ( $p < 0.001$ ) and proteinuria (g/g of creatininuria, log-transformed) ( $p < 0.001$ ); iii) allograft histological parameters,<sup>20</sup> including interstitial fibrosis and tubular atrophy (IFTA Banff score) ( $p < 0.001$ ), microcirculation inflammation defined by glomerulitis and peritubular capillaritis (g+ptc Banff scores) ( $p < 0.001$ ), interstitial inflammation and tubulitis (i+t Banff scores) ( $p = 0.033$ ); and iv)

recipient immunological profile as defined by the presence of circulating anti-HLA donor-specific antibodies ( $p=0.026$ ) (Figure 2 and Table S10).

When investigated in the external validation cohorts, these 7 determinants remained independently associated with eGFR trajectories with similar magnitudes as in the derivation cohorts (Figure S4).

### ***Progression to ESRD according to eGFR trajectories***

During the follow-up, a total of 1,688 patients reached ESRD (defined by return to dialysis or repeated transplantation). Figure 3 and Figure S5 depict the progression to ESRD for each eGFR trajectory. We found that eGFR trajectories #3, #5, #7 and #8 were associated with decreased long-term graft survival, defined by 8-year death-censored graft survival of 62.43%, 42.61%, 55.17% and 0%, respectively, while trajectories #1, #2, #4, and #6 were characterized by 8-year death-censored graft survival of 99.17%, 96.27%, 99.50%, and 94.26%, respectively (log-rank test:  $p<0.001$ ).

### ***Association between eGFR trajectories and mortality***

The trajectories were also associated with mortality. During the follow-up, a total of 1,240 patients died. We found that eGFR trajectories #3, #5, #7 and #8 were associated with higher mortality (8-year patient survival of 84.30%, 73.62%, 72.31% and 40.51%, respectively) than trajectories #1, #2, #4, and #6, which were characterized by 8-year patient survival of 94.37%, 94.31%, 93.02%, and 87.71%, respectively (log-rank test:  $p<0.001$ , Figure S6).

### ***Prediction of eGFR trajectories based on determinants assessed at 1 year***

Based on the determinants identified, we built an online interface to provide clinicians with a ready-to-use tool that predicts the eGFR trajectories (developed with the *Shiny* package on R: <https://transplant-prediction->

system.shinyapps.io/personalized\_eGFR\_trajectories\_prediction/). Clinicians can enter the individual parameters of one patient, and 8 likelihoods of belonging to each trajectory are provided, corresponding to the personalized likely future kidney function of the patient, as well as the allograft survival and the mean slope of eGFR of the predominant eGFR trajectory (clinical application with real-life patients in supplementary methods S2).

### ***Sensitivity analysis***

#### *Validation of eGFR trajectories in different subpopulations and clinical scenarios*

We confirmed that the 8 eGFR trajectories were consistent in different subpopulations and clinical scenarios (Table S11 for statistical performances), including for i) living or deceased donor kidney recipients (Figure S7), ii) African American and non-African-American recipients (Figure S8); and iii) patients treated by calcineurin inhibitor-based regimens versus mTOR-inhibitor-based regimens (Figure S9).

#### *eGFR trajectories and center effect*

To take into account a possible center effect in the assessment of the determinants of the eGFR trajectories, the center was also forced in the final multivariable model of the derivation cohort (Table S12). The 7 determinants previously identified remained the same.

#### *eGFR trajectories with CKD-EPI formula*

To test whether the use of the CKD-EPI equation may change the primary identification of eGFR trajectories based on the MDRD formula, we have performed additional latent class mixed models with GFR estimated with the CKD-EPI equation. The trajectories remained the same (Figure S10).

#### *Consistency of eGFR trajectories according to the timing of baseline eGFR assessment*

We confirmed the 8 eGFR trajectories when the GFR evaluation started before 1 year post-transplantation. This included eGFR assessed at 3 months and 6 months post-transplantation (Figure S11). We also confirmed the 8 trajectories when the GFR evaluation started at 2 years post-transplantation.

#### *Determinants of eGFR trajectories and timing of biopsy*

We confirmed the determinants of eGFR trajectories when including only patients with a biopsy performed at 1 year more or less one month (N=3,536 patients out of 4,140) (Table S13). The distribution of the time of biopsy is depicted in Figure S12.

#### *Determinants of eGFR trajectories and albuminuria*

When using albuminuria instead of proteinuria, the determinants previously identified remained the same. The associations of albuminuria with eGFR trajectories were comparable to those of proteinuria (Table S14).

#### *Relationship between eGFR trajectories and eGFR change*

We finally confirmed the ability of the trajectories to stratify the risk of ESRD as compared to 2-years eGFR change, a common way of assessing ESRD risk.<sup>21,22</sup> While eGFR change demonstrated consistency with previous studies, we also showed that 28.9% of the patients were reclassified at early-stage by the trajectory-based assessment : with the 2-years eGFR change, 16.8% of the patients had an overestimated risk and 12.1% had an underestimated risk of progression to ESRD (supplementary methods S3).

## **DISCUSSION**

In this international study of 14,132 kidney transplant recipients of whom 2,509 were retrieved from 7 already-published RCTs and 11,623 were carefully phenotyped patients from European and US transplant centers with protocol-based repeated measurements of

renal function and histology and immune profiling, we used an unsupervised approach to identify for the first time eight distinct trajectories of long-term allograft function. We found that these trajectories were quite varied for several different conditions related to donor and recipient characteristics, ongoing disease processes and immunological profiles that can be determined at an early stage after transplantation. We also characterized the associations of these trajectories with long-term ESRD and mortality outcomes. Interestingly, we demonstrated that the 8 trajectories and their determinants were consistent in 15 geographically distinct cohorts from Europe and the US, which is remarkable given their distinct allocation systems, patient characteristics and management practices.<sup>23,24</sup> Finally, we demonstrated that the 8 trajectories were consistent among participants in 7 randomized controlled trials.

Despite the importance of functional evaluation in any kidney disease,<sup>25</sup> no study has characterized long-term trajectories using large unselected transplant cohorts with prespecified longitudinal eGFR monitoring together with deep-level patient phenotyping, including donor and recipient characteristics, histology, immunology and treatment. Beyond the novel study design, the advantage of our original trajectory approach over traditional analysis is its ability to map the eGFR course and classify individuals into distinct, mutually exclusive groups.<sup>26</sup> Hence, this approach not only helps to conceptualize the long-term trajectories of eGFR but also allows to probe the population heterogeneity. Furthermore, we believe that identifying the profiles of the evolution of a chronic disease without any preconceived ideas and investigating whether these profiles manifest consistently across centers and countries may provide important guidance on the potential universality of the disease, its determinants, and its associations with outcomes.

The profiles of patients who presented with high eGFR at one year after transplantation and remained stable over time (trajectories 1 and 2) were characterized by having organs from young donors, low immunological risk, an absence of ongoing allograft injury (immune and non-immune), and fewer histological lesions related to allograft damage.

The analysis also revealed two other profiles consisting of patients presenting with middle/high eGFR at 1 year but substantial declines in renal function later (trajectories 3 and 8). This result highlights the limitation of considering eGFR values during a limited period of time: those patients who start with a high eGFR might nonetheless have ongoing inflammation or other risk factors that will drive a trajectory of deterioration. On the other hand, while the anticipated prognosis in recipients with a low eGFR at one year may appear poor at that moment, the actual long-term survival may be excellent when the trajectory is stable (trajectory 6).

This study also emphasizes the interplay between kidney transplant donor and recipient characteristics, the allograft immune profile, allograft injury and the eGFR trajectories. The associations between these characteristics and the trajectories of allograft function suggest mechanistic explanations for why some eGFR profiles are low at baseline yet show little evidence of deterioration; such eGFR profiles are mainly associated with donor parameters that are not expected to worsen.<sup>20</sup> Hence, in the absence of an ongoing inflammatory process or additional injury, the allograft function of such patients may not decline. On the other hand, the presence of anti-HLA DSA, active antibody-mediated rejection or T-cell mediated rejection were associated with trajectories characterized by declining renal function.

Remarkably, despite unsupervised identification of 8 eGFR trajectories in the derivation cohort, very similar trajectories were independently detected in North American and European cohorts and several RCT covering distinct clinical scenarios. This validation of the same set of trajectories for patients in different healthcare systems promotes the idea that the same fundamental factors drive the evolution of renal allograft functional outcomes throughout the world, which we further supported by identifying the determinants of eGFR trajectories in the derivation cohort and confirming them in the external validation cohort. However, the proportions of patients in each trajectory differed somewhat between the three

cohorts, perhaps reflecting intrinsic variability in the demographics and causes of renal diseases across nations.

### ***Clinical implications of the present research***

In this study, we also identified the same 8 trajectories in the setting of 7 clinical trials covering different clinical scenarios.<sup>13-19</sup> This finding reinforces the potential of trajectory-based patient assessment at an early stage after transplantation to predict long-term eGFR course and ESRD in clinical trials. Indeed, in CKD clinical trials, a change in kidney function is the only alternative outcome to death or allograft failure that has been proposed as a meaningful surrogate endpoint by the FDA.<sup>27</sup> Consequently, to make trajectory-based monitoring of patients feasible in contemporary transplant practice, we developed an easy-to-use online interface that allows clinicians to predict the personalized likely future kidney function trajectory of any given patient and the related risk of future allograft failure ([https://transplant-prediction-system.shinyapps.io/personalized\\_eGFR\\_trajectories\\_prediction/](https://transplant-prediction-system.shinyapps.io/personalized_eGFR_trajectories_prediction/)). Hence, complementing graft survival prediction systems based on conventional Cox models that have been recently developed<sup>28</sup>, clinicians will be able to continuously assess at any time during patient follow-up how the patient deviates from his/her anticipated trajectory. This will only require assessments of kidney function that are noninvasive and will help to better manage and monitor the patient.

### ***Limitations***

Some limitations should be noted. First, eGFR is subject to measurement error.<sup>29</sup> However, given our prospective design, any error would probably have attenuated the identification of 8 distinct trajectories, whereas we were able to consistently identify the trajectories across different cohorts. In addition, in the derivation cohort, all eGFRs were assessed using the same institutional center. Second, one of the trajectories identified (trajectory 7) has relatively high inter-patient variability. This trajectory is composed of patients with low eGFR at baseline and a pattern of stability afterwards, as well as patients

with low eGFR at baseline with some subsequent decrease. Third, there are unmeasured characteristics of the recipients and allografts, such as the genetic basis of kidney function,<sup>30,31</sup> that may well affect allograft outcomes and could be explored in future studies. Last, for reasons of statistical power, we binarized the MFI of anti-HLA DSA. This may represent a slight loss of information.

In conclusion, this analysis takes an original and unsupervised approach to analyzing and characterizing trajectories of long-term eGFR and their determinants after kidney transplantation associated with the development of ESRD and mortality. On the basis of independent analysis, we also found that the eGFR trajectories and their determinants manifested similarly across centers on different continents and in the setting of clinical trials. Our results provide an important new addition to the existing scheme of kidney function monitoring and patient individual risk stratification, potentially paving the way towards therapeutic interventions.

## **METHODS**

### ***Study design and participants***

#### *Derivation cohort*

The derivation cohort consisted of 4,140 consecutive patients over 18 years of age who were prospectively enrolled at the time of kidney transplantation at Necker Hospital (n=1,596), Saint-Louis Hospital (n=965), Toulouse Hospital (n=784), and Foch Hospital (n=795) in France, between 2000 and 2014. Data were anonymized and entered at transplant, at 3 months, 6 months, 1 year post-transplantation, and yearly thereafter using a standardized protocol. Data were submitted for an annual audit to ensure quality (supplementary methods S4 to S6 for detailed data collection procedures). Data were retrieved from the Paris Transplant Group database on June 2019. The institutional review

board of the Paris Transplant Group (<https://www.paristransplantgroup.org>) approved the study.

#### *Validation cohorts*

External validation was conducted on 7,483 kidney transplant recipients over 18 years of age from 11 cohorts in Europe and North America between 2003 and 2016. Datasets from the validation centers were collected as part of routine clinical practice and entered into the centers' databases in compliance with local and national regulatory requirements and sent anonymized to the Paris Transplant Group (see details on allocation system in each center in supplementary methods S4, S5 and Table S6).

#### *Additional external validation cohort*

Additional external validation was conducted in 2,509 kidney transplant recipients previously recruited in 7 registered and published phase II and III clinical trials: *Certitem*,<sup>13</sup> *NCT01079143*; *Rituxerah*,<sup>14</sup> *Eudra CT 2007-003213-13*; *Borteject*,<sup>15</sup> *NCT01873157*; *Spiesser*<sup>16</sup>; *Concept*,<sup>17</sup> *Eudra CT 2004-002987-62*; *Kainz et al.*<sup>18</sup> *study, ISRCTN78828338*; and *Transform*,<sup>19</sup> *NCT01950819*. The details of the clinical trials depicting the population characteristics, study design, inclusion criteria and interventions are provided in Table S7.

#### ***Procedures and clinical protocols***

Creatinine measurements were prospectively recorded per the center protocol after transplantation. eGFR was calculated with the Modification of Diet in Renal Disease (MDRD) study equation.<sup>32</sup> The choice of MDRD formula was motivated by its superior performance as compared with the CKD-EPI formula, when estimating the measured GFR, available at 1 year in the derivation cohort (Figure S13). Center protocols for follow-up data included eGFR measurement at 1 year after transplantation and every 6 months thereafter as well as at the time of any biopsies. Patients were followed from 1 year post-transplantation (the index date

of the analyses) until preemptive retransplantation, death, return to dialysis, or the date of final data extraction. The list of parameters assessed in the derivation cohort is displayed in supplementary methods S6.

We defined the baseline period at 1 year after transplantation where the recipients underwent concomitant evaluation of the proteinuria/creatininuria ratio<sup>33,34</sup>, allograft surveillance biopsy (including elementary lesion scores and diagnoses according to the Banff international classification<sup>20</sup>, see supplementary methods S7) and circulating anti-HLA-A, B, Cw, DR, DQ, DP antibody (assessed using single-antigen flow bead assays in the derivation and validation cohorts<sup>35</sup>, supplementary methods S8) according to a prespecified protocol.

### ***Outcome measures***

The main outcome measure was eGFR trajectory. The secondary outcomes were 1) progression to end stage renal disease (ESRD), defined as a kidney recipient's definitive return to dialysis or preemptive kidney retransplantation, and 2) all-cause mortality. The outcomes were prospectively assessed at each transplantation anniversary, up to June 30, 2019.

### ***Statistical analysis***

Continuous variables were described using means and standard deviations (SDs) or medians and interquartile ranges, as appropriate. We compared means and proportions between groups using Student's t-test, analysis of variance (ANOVA) (Mann-Whitney U test for DSA mean fluorescent intensity) or the chi-squared test (or Fisher's exact test if appropriate).

### ***Derivation of post-transplantation eGFR trajectories***

eGFR trajectories were identified over 10 years after transplantation using latent class mixed models.<sup>26</sup> This approach characterizes trajectories in repeated measurements,

with the assumption that several underlying subpopulations (i.e., the latent classes) can be detected.<sup>36</sup> It does not require the same number of measurements per patient or the same timepoints of measurement (details and illustration in supplementary methods S9). We considered for each patient all the eGFR measurements until ESRD, death, or date of last follow-up. We compared the linear trajectory models with nonlinear models, including quadratic ( $t^2$  effect) and splines, and confirmed the suitability of linear models used for trajectory identification. Furthermore, we tested different link functions to identify the best fitting model (Table S8).

At model convergence, each patient was assigned posterior likelihoods of belonging to each eGFR trajectory. Patients were assigned to the class to which they had the highest likelihood of belonging. eGFR trajectories were independently investigated in the derivation cohort and the validation cohorts.

#### *Definition of the optimal number of eGFR trajectories*

The number of eGFR trajectories was defined according to *i*) the Bayesian Information Criterion (BIC) and the Akaike Information Criterion (AIC), *ii*) the discrimination (i.e., the ability of the model to specifically classify patients in the eGFR trajectories), *iii*) the entropy (i.e., the ability of the model to identify distinct eGFR trajectories) and *iv*) the interpretability of the model, as previously published<sup>10,11,37,38</sup> (supplementary methods S8).

#### *Determinants of eGFR trajectories*

In the derivation cohort, the associations between eGFR trajectories and clinical, histological, functional, and immunological parameters at the time of transplantation and at 1 year post-transplantation were assessed using multinomial logistic regressions. Parameters associated with trajectories in the univariate analysis with a p-value < 0.10 were thereafter included in the multivariable model. Stepwise backward elimination was performed to obtain the final multivariable model.

#### *Missing data and imputation*

A total of 226 patients (5.46%) in the derivation cohort had at least one missing data element for the final multinomial model. Multiple imputation using chained equations were used (*Mice* R package, using 20 sets of imputations); continuous parameters were imputed with random forests, and categorical parameters were imputed with polynomial regressions.

#### *eGFR trajectories and association with ESRD and all-cause mortality*

Kaplan-Meier curves were used to report progression to ESRD and all-cause mortality according to the identified eGFR trajectories. For patients who died with a functioning allograft, allograft survival was censored at the time of death as a functional allograft.<sup>39</sup> A co-primary outcome was death from any cause.

We used R (version 3.2.1, R Foundation for Statistical Computing) and STATA (version 14, Data Analysis and Statistical Software) software for the descriptive and survival analyses. Values of  $p < 0.05$  were considered statistically significant, and all tests were 2-tailed. Specific additional computational resources were used to obtain model convergence in a reasonable amount of time.<sup>40</sup> Details regarding the interpretation of important statistical concepts are given in supplementary methods S1.

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## **DISCLOSURE**

We report no relationships or activities that could appear to have influenced the present work.

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## **INFORMED CONSENT**

The institutional review boards of the Paris Transplant Group participating centers approved the study. All patients provided written informed consent at the time of transplantation.

## **Supplementary Material**

**Methods S1.** Criteria used for the selection of the latent class mixed models

**Methods S2.** Practical application for predicting allograft function trajectories

**Methods S3.** eGFR trajectories and eGFR change

**Methods S4.** Data collection procedures

**Methods S5.** Independent validation cohorts

**Methods S6.** Transplant parameters prospectively collected in the derivation cohort

**Methods S7.** Kidney allograft phenotypes at time of risk assessment

**Methods S8.** Detection and characterization of donor-specific anti-HLA antibodies

**Methods S9.** Latent class mixed models: Synopsis of the analysis

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**Figure S13:** MDRD vs CKD-EPI equations to estimate measured GFR

Supplementary information is available at Kidney International's website

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## FIGURE LEGENDS

**Figure 1A. eGFR profiles and their individual trajectories in kidney recipients in the derivation cohort:** This figure represents the main profiles of kidney function identified with latent class mixed models. Each patient, represented by an individual eGFR trajectory, is assigned to the profile for which the membership probability is the highest. eGFR trajectory<sup>#1</sup> was composed of patients with high baseline renal function (71.6 mL/min/1.73 m<sup>2</sup>) that remained stable (eGFR slope per year = -0.7 mL/min/1.73 m<sup>2</sup>). eGFR trajectory<sup>#2</sup> was composed of patients with very high baseline function (91.6 mL/min/1.73 m<sup>2</sup>) with slightly decreasing function over time (eGFR slope per year = of -1.0 mL/min/1.73 m<sup>2</sup>). eGFR trajectory<sup>#3</sup> was composed of patients with high baseline kidney function (70.1 mL/min/1.73 m<sup>2</sup>) and fast decline over time (eGFR slope per year = -8.9 mL/min/1.73 m<sup>2</sup>). Patients from eGFR trajectory<sup>#4</sup> presented with a pattern of intermediate baseline eGFR (55.6 mL/min/1.73 m<sup>2</sup>) and stability over time (eGFR slope per year = -0.1 mL/min/1.73 m<sup>2</sup>). eGFR trajectory<sup>#5</sup> was defined by a middle/low baseline eGFR (48.2 mL/min/1.73 m<sup>2</sup>) with decreasing function over time (eGFR slope per year = -5.4 mL/min/1.73 m<sup>2</sup>). eGFR trajectory<sup>#6</sup> was composed of patients with low baseline eGFR (41.0 mL/min/1.73 m<sup>2</sup>) but with stability over time (eGFR slope per year = 0.1 mL/min/1.73 m<sup>2</sup>). eGFR trajectory<sup>#7</sup> was composed of patients with very low baseline eGFR (28.4 mL/min/1.73 m<sup>2</sup>) and mildly declining function over time (eGFR slope per year = -3.0 mL/min/1.73 m<sup>2</sup>). Finally, eGFR trajectory<sup>#8</sup> was characterized by recipients with intermediate baseline eGFR (58.0 mL/min/1.73 m<sup>2</sup>) but a very fast subsequent decline in eGFR (eGFR slope per year = -26.6 mL/min/1.73 m<sup>2</sup>). Table S15 provides further details on eGFR category and slope for each eGFR trajectory.

**Figure 1B and 1C. eGFR profiles and their individual trajectories in kidney recipients in the external European and North American validation cohorts:** Latent class mixed models were applied to the European and the North American validation cohorts. In these independent analyses, the eGFR profiles identified were similar to those identified in the derivation cohort.

**Figure 2. Independent determinants of eGFR trajectories in the derivation cohort: multivariable analysis:** After investigating 30 clinical, functional, structural and immunological parameters, 7 determinants of eGFR trajectories were identified. The trajectory of reference was trajectory 1 (i.e.,

patients with high and stable kidney function over time). Multinomial regressions were used to conduct this analysis.

Abbreviations: OR, odds ratio; HLA, human leukocyte antigen; DSA, donor-specific antibody

**Figure 3. eGFR trajectories and progression to ESRD in the overall population (derivation and validation cohorts combined, n=11,623):** We pooled the French, European and North American validation cohorts according to their identified eGFR trajectories to obtain the broad picture of allograft function after kidney transplantation. For each eGFR trajectory, Kaplan-Meier curves were used to present the corresponding allograft survival.

**Table 1: Baseline characteristics of the derivation and validation cohorts**

**Table 2: Determinants of eGFR trajectories in the derivation cohort:** This table shows the eGFR trajectories in the univariate multinomial regression analysis. The trajectory of reference was trajectory #1, including patients with a high and stable kidney function over time.

# Trajectories of glomerular filtration rate and progression to end stage kidney disease after kidney transplantation

Population: kidney recipients



European and US cohorts



Randomized controlled trials

-14,132 highly phenotyped patients  
 -403,497 eGFR measurements  
 -15 transplant centers  
 -7 RCTs

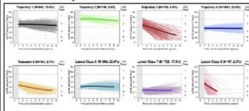


Latent class mixed modeling

$$Y_{ij} = X_{ij}(t_{ij})^T \beta + Z_i(t_{ij})^T \gamma_i + \epsilon_{ij}(t_{ij})$$

$$\gamma_i = P(\gamma) = g(X_{ij}) = \sum_{k=1}^K \rho_k \gamma_k + \epsilon_{ij}(t_{ij})$$

Identification of 8 eGFR trajectories



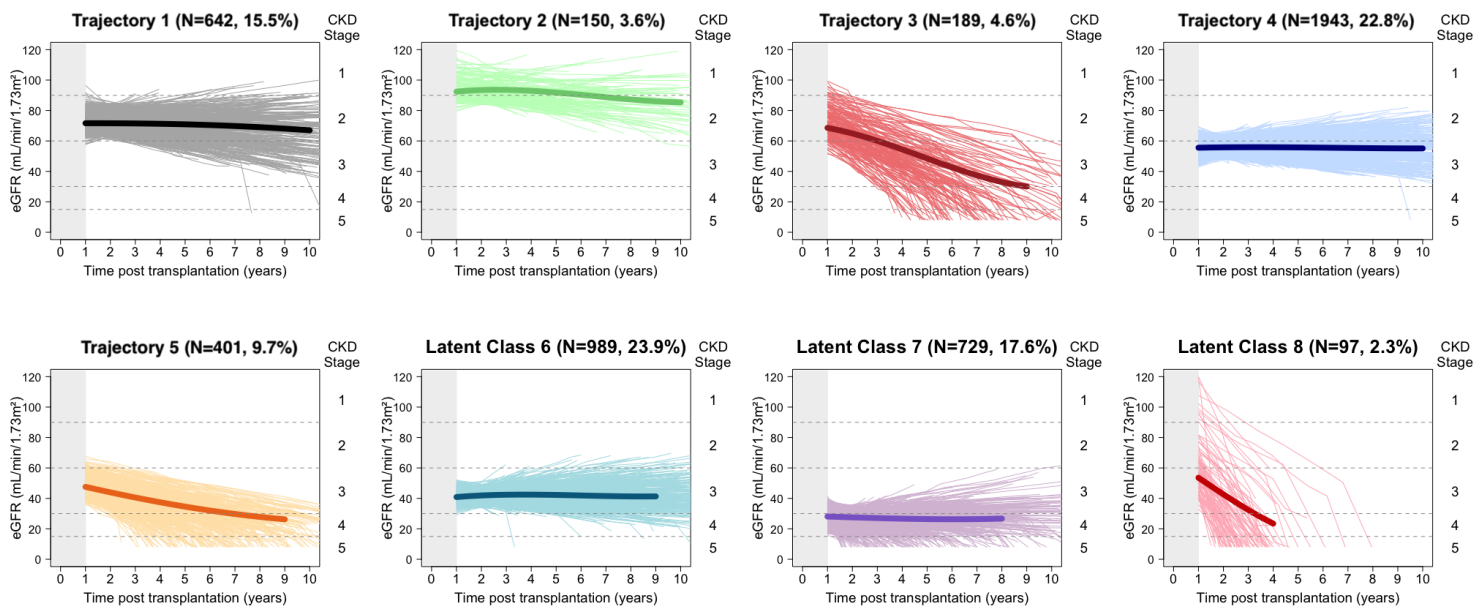
- 1 The eGFR trajectories were highly associated with ESRD and all-cause mortality
- 2 Clinical, immunological and histological determinants of the eGFR trajectories were identified
- 3 The eGFR trajectories and their determinants were validated in Europe, the US and in the RCTs
- 4 Based on the results, we built an eGFR trajectories prediction system adapted to the patient monitoring

## CONCLUSION:

We identified and validated universal eGFR trajectories and their determinants, associated with ESRD. Our results provide the basis for a trajectory-based monitoring after kidney transplantation.

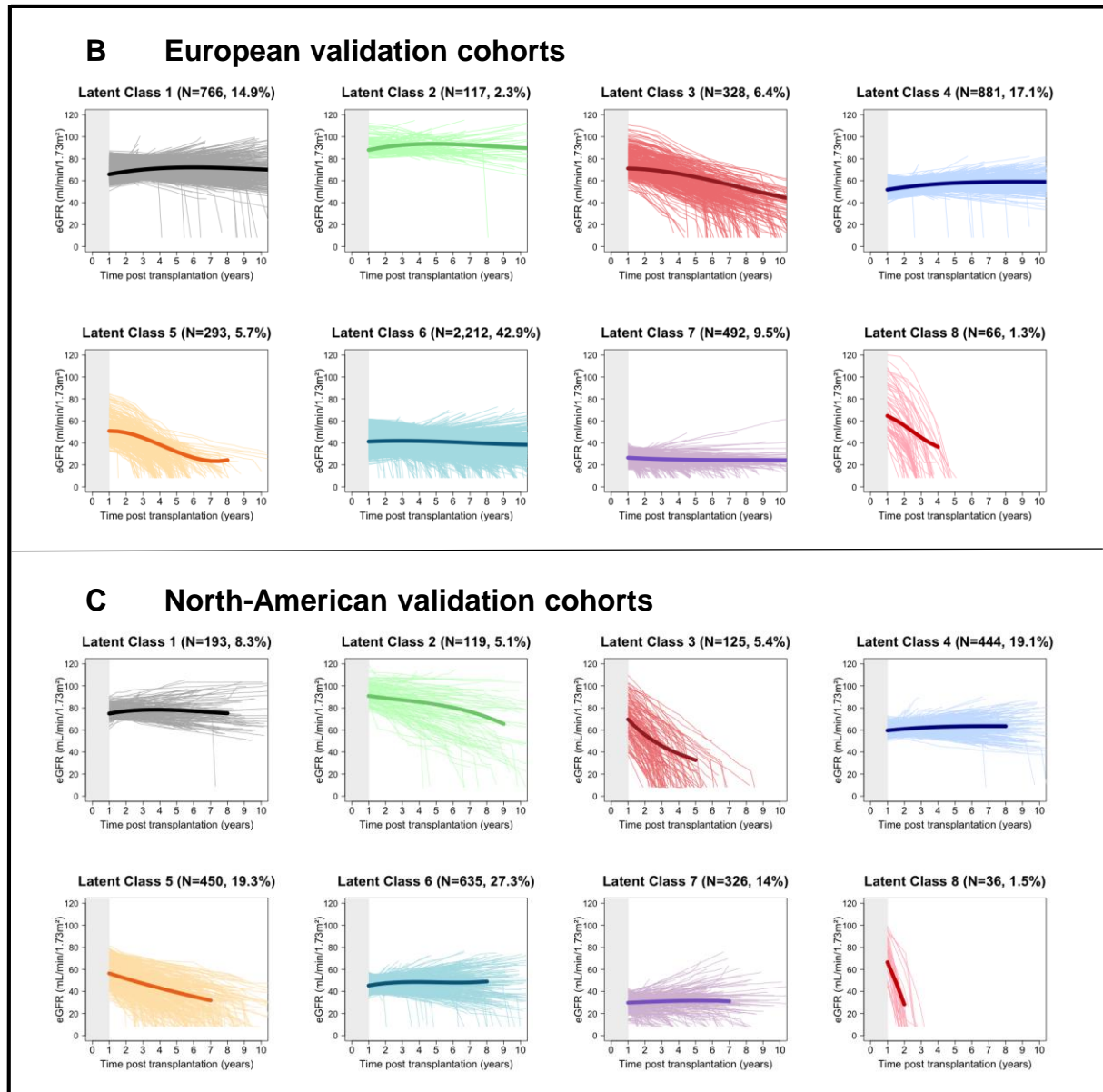
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This figure represents the main profiles of kidney function identified with latent class mixed models. Each patient, represented by an individual eGFR trajectory, is assigned to the profile for which the membership probability is the highest. This figure represents the main profiles of kidney function identified with latent class mixed models. Each patient, represented by an individual eGFR trajectory, is assigned to the profile for which the membership probability is the highest. eGFR trajectory<sup>#1</sup> was composed of patients with high baseline renal function (71.6 mL/min/1.73 m<sup>2</sup>) that remained stable (eGFR slope per year = -0.7 mL/min/1.73 m<sup>2</sup>). eGFR trajectory<sup>#2</sup> was composed of patients with very high baseline function (91.6 mL/min/1.73 m<sup>2</sup>) with slightly decreasing function over time (eGFR slope per year = of -1.0 mL/min/1.73 m<sup>2</sup>). eGFR trajectory<sup>#3</sup> was composed of patients with high baseline kidney function (70.1 mL/min/1.73 m<sup>2</sup>) and fast decline over time (eGFR slope per year = -8.9 mL/min/1.73 m<sup>2</sup>). Patients from eGFR trajectory<sup>#4</sup> presented with a pattern of intermediate baseline eGFR (55.6 mL/min/1.73 m<sup>2</sup>) and stability over time (eGFR slope per year = -0.1 mL/min/1.73 m<sup>2</sup>). eGFR trajectory<sup>#5</sup> was defined by a middle/low baseline eGFR (48.2 mL/min/1.73 m<sup>2</sup>) with decreasing function over time (eGFR slope per year = -5.4 mL/min/1.73 m<sup>2</sup>). eGFR trajectory<sup>#6</sup> was composed of patients with low baseline eGFR (41.0 mL/min/1.73 m<sup>2</sup>) but with stability over time (eGFR slope per year = 0.1 mL/min/1.73 m<sup>2</sup>). eGFR trajectory<sup>#7</sup> was composed of patients with very low baseline eGFR (28.4 mL/min/1.73 m<sup>2</sup>) and mildly declining function over time (eGFR slope per year = -3.0 mL/min/1.73 m<sup>2</sup>). Finally, eGFR trajectory<sup>#8</sup> was characterized by recipients with intermediate baseline eGFR (58.0 mL/min/1.73 m<sup>2</sup>) but a very fast subsequent decline in eGFR (eGFR slope per year = -26.6 mL/min/1.73 m<sup>2</sup>). **Table S15** provides further details on eGFR category and slope for each eGFR trajectory.

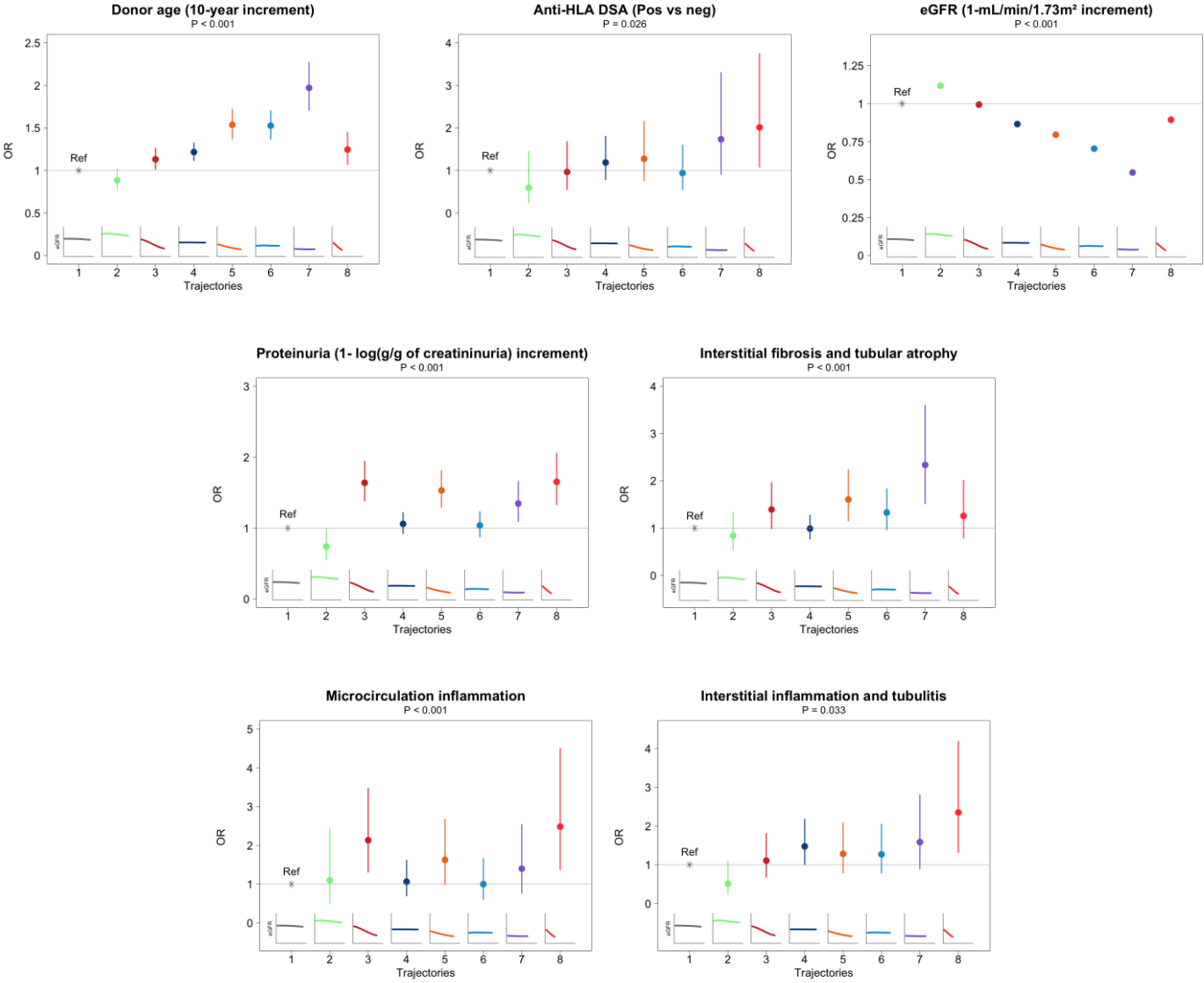


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Latent class mixed models were applied to the European and the North American validation cohorts. In these independent analyses, the eGFR profiles identified were similar to those identified in the derivation cohort.

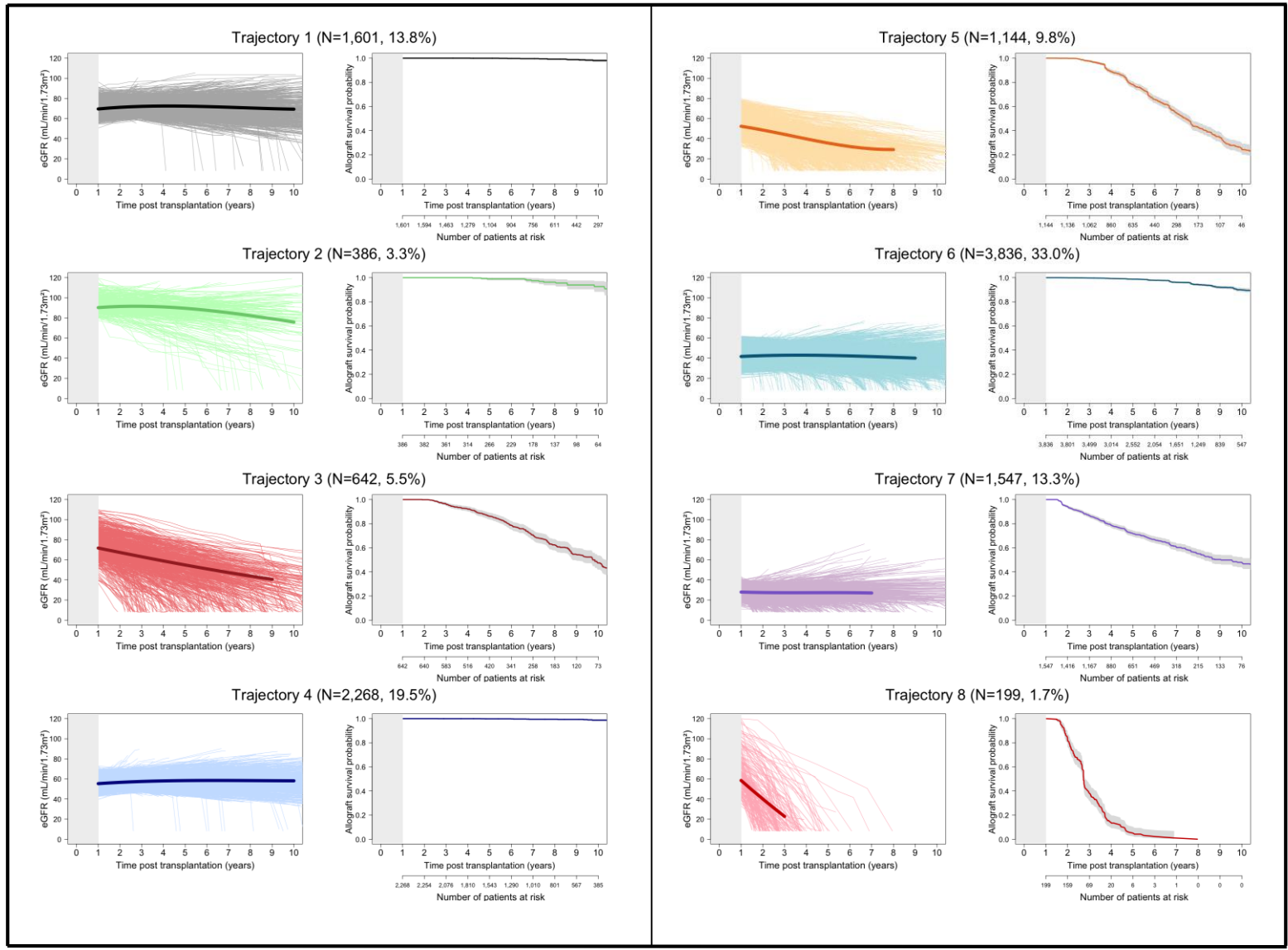


**Figure 2: Independent determinants of eGFR trajectories in the derivation cohort: multivariable analysis.** After investigating 30 clinical, functional, structural and immunological parameters, 7 determinants of eGFR trajectories were identified. The trajectory of reference was trajectory 1 (i.e., patients with high and stable kidney function over time). Multinomial regressions were used to conduct this analysis.



**Figure 3: eGFR trajectories and progression to ESRD in the overall population (derivation and validation cohorts combined, n=11,623)**

We pooled the French, European and North American validation cohorts according to their identified eGFR trajectories to obtain the broad picture of allograft function after kidney transplantation. For each eGFR trajectory, Kaplan-Meier curves were used to present the corresponding allograft survival.



**Table 1: Baseline characteristics of the derivation and validation cohorts**

	French derivation cohort (4 centers, n=4,140)		European validation cohort (6 centers, n=5,155)		North American validation cohort (5 centers n=2,328)		p <sup>a</sup>
	N		N		N		
<b>Recipient characteristics</b>							
Age (years), mean (SD)	4,140	49.69 (13.57)	5,155	51.98 (13.58)	2,328	49.99 (14.07)	<0.001
Gender male, No. (%)	4,140	2,570 (62.08)	5,155	3,238 (62.81)	2,314	1,411 (60.98)	0.313
<b>End stage renal disease causes</b>	4,140		5,153		2,008		
Glomerulonephritis, No. (%)		1,098 (26.52)		1,454 (28.22)		524 (26.10)	
Diabetes, No. (%)		482 (11.64)		420 (8.15)		402 (20.02)	<0.001
Vascular, No. (%)		280 (6.76)		423 (8.21)		202 (10.06)	
Other, No. (%)		2,280 (55.07)		2,856 (55.42)		866 (43.13)	
Preformed anti-HLA DSA, No. (%)	4,140	570 (13.77)	5,155	180 (3.49)	2,328	278 (11.94)	<0.001
Calculated PRA (cPRA) > 85%, No. (%)	4,140	560 (13.53)	5,155	440 (8.54)	2,328	185 (7.95)	<0.001
<b>Donor characteristics</b>							
Age (years), mean (SD)	4,137	51.63 (16.01)	5,147	51.47 (15.06)	2,325	42.23 (14.66)	<0.001
Male gender, No. (%)	4,140	2,246 (54.25)	5,150	2,884 (56.00)	2,312	1,155 (49.96)	<0.001
Hypertension, No. (%)	4,060	1,055 (25.99)	4,625	1,492 (32.26)	1,508	339 (22.48)	<0.001
Diabetes mellitus, No. (%)	3,782	225 (5.95)	3,569	261 (7.31)	1,539	34 (2.21)	<0.001
Creatinine > 1.5mg/dL, No. (%)	4,111	462 (11.24)	4,857	412 (8.48)	1,516	230 (15.17)	<0.001
Positive HCV serology, No. (%)	4,100	8 (0.20)	4,448	18 (0.40)	2,311	49 (2.12)	<0.001
<b>Donor type</b>							
Deceased donor, No. (%)	4,140	3,502 (84.59)	4,773	4,312 (90.34)	2,328	1,182 (50.77)	<0.001
Death from cerebrovascular disease, No. (%)	3,502	1,880 (53.68)	4,299	2,729 (63.48)	1,181	469 (39.71)	<0.001
Cardiac death, No. (%)	3,500	42 (1.20)	4,100	78 (1.90)	1,181	113 (9.57)	<0.001
Expanded criteria donor, No. (%)	4,076	1,467 (35.99)	5,035	2,021 (40.14)	2,318	172 (7.42)	<0.001
<b>Transplant baseline characteristics</b>							
Prior kidney transplant No. (%)	3,741	593 (15.85)	4,756	725 (15.24)	2,322	457 (19.68)	< 0.001
Cold ischemia time (hours), mean (SD)	4,124	16.37 (8.86)	5,086	16.21 (7.68)	2,125	11.52 (12.53)	<0.001
Delayed graft function <sup>b</sup> No. (%)	4,062	1,116 (27.47)	5,125	1,151 (22.46)	2,326	431 (18.53)	<0.001
HLA-A/B/DR mismatch number mean (SD)	4,137	3.72 (1.38)	5,044	3.18 (1.40)	2,166	3.79 (1.70)	<0.001

Abbreviations: HLA: human leucocyte antigen. DSA: donor-specific antibodies. PRA: panel reactive antibody.

<sup>a</sup> p-values were calculated for comparisons between the three cohorts.

<sup>b</sup> Delayed graft function is the use of dialysis in the first week post-transplantation.

**Table 2: Determinants of eGFR trajectories in the derivation cohort:** This table shows the eGFR trajectories in the univariate multinomial regression analysis. The trajectory of reference was trajectory #1, including patients with a high and stable kidney function over time.

	N	Trajectory 1(Ref) (N=642)	Trajectory 2 (N=150)	Trajectory 3 (N=189)	Trajectory 4 (N=943)	Trajectory 5 (N=401)	Trajectory 6 (N=989)	Trajectory 7 (N=729)	Trajectory 8 (N=97)	p <sup>a</sup>
<b>Recipient parameters</b>										
Age (10-year increment)	4,140	-	0.92 (0.80-1.05)	1.06 (0.94-1.20)	1.23 (1.14-1.32)	1.46 (1.32-1.60)	1.57 (1.46-1.70)	1.81 (1.66-1.97)	1.14 (0.97-1.33)	<0.001
Gender (ref=male)	4,140	-	1.48 (1.03-2.13)	1.31 (0.94-1.84)	1.17 (0.95-1.44)	1.43 (1.10-1.85)	1.25 (1.01-1.54)	1.54 (1.23-1.92)	0.75 (0.46-1.21)	0.001
<b>Donor parameters</b>										
Age (10-year increment)	4,137	-	0.76 (0.67-0.85)	1.19 (1.07-1.33)	1.40 (1.30-1.50)	1.93 (1.76-2.11)	1.91 (1.78-2.05)	2.38 (2.19-2.58)	1.41 (1.22-1.64)	<0.001
Gender (ref=male)	4,140	-	2.11 (1.41-3.18)	1.09 (0.78-1.52)	0.73 (0.59-0.89)	0.74 (0.57-0.95)	0.65 (0.54-0.80)	0.75 (0.60-0.93)	0.94 (0.61-1.45)	<0.001
Hypertension	4,060	-	0.62 (0.33-1.18)	1.45 (0.93-2.27)	1.51 (1.13-2.02)	3.08 (2.24-4.23)	3.07 (2.34-4.03)	5.88 (4.45-7.76)	2.20 (1.30-3.71)	<0.001
Diabetes mellitus	3,782	-	1.49 (0.53-4.19)	2.19 (0.94-5.09)	1.34 (0.71-2.51)	3.00 (1.57-5.72)	3.00 (1.70-5.31)	4.32 (2.45-7.65)	1.30 (0.37-4.58)	<0.001
Creatinine (ref < 1.5mg/dL)	4,111	-	1.17 (0.65-2.10)	1.23 (0.73-2.09)	1.08 (0.77-1.53)	1.06 (0.69-1.63)	1.37 (0.98-1.90)	1.59 (1.13-2.24)	1.52 (0.80-2.89)	0.110
Donor type (ref=living)	4,140	-	1.38 (0.86-2.21)	1.52 (0.98-2.36)	0.99 (0.77-1.26)	1.90 (1.34-2.69)	1.83 (1.40-2.38)	4.30 (3.01-6.15)	1.64 (0.90-2.97)	<0.001
Expanded criteria donor	4,076	-	0.60 (0.32-1.11)	2.10 (1.41-3.14)	1.94 (1.47-2.54)	5.70 (4.21-7.71)	5.11 (3.95-6.64)	10.5 (8.00-13.80)	3.06 (1.88-4.97)	<0.001
<b>Transplant baseline parameters</b>										
Prior kidney transplant (ref=No)	3,741	-	1.08 (0.66-1.77)	1.21 (0.78-1.88)	0.96 (0.72-1.28)	1.14 (0.80-1.61)	0.79 (0.58-1.06)	1.13 (0.83-1.52)	1.43 (0.82-2.49)	0.131
Cold ischemia time (1-hour increment)	4,124	-	1.01 (0.99-1.03)	1.04 (1.02-1.06)	1.02 (1.00-1.03)	1.04 (1.03-1.06)	1.04 (1.02-1.05)	1.07 (1.05-1.08)	1.02 (0.99-1.04)	<0.001
Delayed graft function <sup>b</sup>	4,062	-	0.73 (0.43-1.25)	2.06 (1.40-3.03)	1.44 (1.11-1.88)	2.37 (1.75-3.20)	2.18 (1.69-2.81)	3.81 (2.94-4.94)	2.28 (1.41-3.71)	<0.001
<b>Immunological parameters*</b>										
HLA-A/B/DR mismatch number (1-mismatch increment)	4,137	-	0.92 (0.81-1.04)	0.92 (0.82-1.03)	0.96 (0.89-1.03)	1.00 (0.91-1.09)	0.99 (0.92-1.06)	1.00 (0.93-1.08)	1.08 (0.93-1.27)	0.471
Anti-HLA donor-specific antibody, mean fluorescence intensity (ref=negative)	4,090	-	0.81 (0.60-1.09)	1.12 (1.02-1.22)	0.97 (0.89-1.06)	1.09 (1.01-1.19)	1.00 (0.92-1.08)	1.14 (1.06-1.22)	1.16 (1.05-1.27)	<0.001
<b>Functional parameters*</b>										
eGFR at evaluation (1-mL/min/1.73 m <sup>2</sup> increment)	4,140	-	1.11 (1.10-1.13)	0.99 (0.98-1.00)	0.86 (0.85-0.87)	0.78 (0.77-0.80)	0.70 (0.68-0.71)	0.54 (0.52-0.56)	0.89 (0.87-0.91)	<0.001
Proteinuria (1- log (g/g of creatinuria) increment)	4,137	-	0.27 (0.08-0.88)	6.09 (4.01-9.25)	2.86 (1.88-4.37)	5.84 (3.88-8.80)	4.10 (2.73-6.17)	6.47 (4.32-9.68)	6.08 (3.93-9.39)	<0.001
<b>Structural histopathology parameters*</b>										
Antibody-mediated rejection	4,140	-	1.32 (0.69-2.53)	1.93 (1.13-3.29)	1.42 (0.97-2.07)	2.60 (1.72-3.91)	1.62 (1.11-2.35)	3.11 (2.16-4.46)	5.94 (3.48-10.13)	<0.001
T-cell mediated rejection	4,106	-	0.50 (0.11-2.17)	1.41 (0.58-3.46)	1.21 (0.66-2.21)	1.93 (1.00-3.73)	1.47 (0.82-2.63)	2.08 (1.16-3.71)	2.86 (1.15-7.09)	0.035

<b>Interstitial fibrosis and tubular atrophy</b> (ci+ct,ref=0-1)	4,094	-	0.62 (0.43-0.91)	1.33 (0.96-1.85)	1.25 (1.02-1.53)	2.73 (2.10-3.56)	2.51 (2.04-3.08)	5.37 (4.20-6.87)	1.77 (1.15-2.74)	<b>&lt;0.001</b>
<b>Microcirculation inflammation</b> (g+ptc,ref=0-1)	4,063	-	1.04 (0.67-1.62)	1.93 (1.35-2.78)	1.38 (1.08-1.75)	2.45 (1.85-3.24)	1.52 (1.20-1.94)	2.67 (2.09-3.41)	3.21 (2.06-5.02)	<b>&lt;0.001</b>
<b>Transplant glomerulopathy</b> (ref=0)	4,075	-	0.32 (0.04-2.49)	1.32 (0.47-3.76)	1.71 (0.89-3.28)	4.35 (2.26-8.37)	2.00 (1.06-3.78)	4.63 (2.52-8.50)	3.81 (1.48-9.80)	<b>&lt;0.001</b>
<b>C4d graft deposition</b> (ref=0)	4,016	-	0.83 (0.38-1.81)	1.70 (0.96-3.00)	1.64 (1.12-2.41)	2.02 (1.31-3.13)	1.28 (0.86-1.89)	2.40 (1.64-3.51)	3.48 (1.90-6.36)	<b>&lt;0.001</b>
<b>Interstitial inflammation and tubulitis</b> (i+t,ref=0-1)	4,102	-	0.65 (0.40-1.06)	1.54 (1.06-2.23)	1.35 (1.06-1.72)	1.55 (1.16-2.07)	1.36 (1.07-1.73)	2.30 (1.80-2.94)	2.71 (1.73-4.24)	<b>&lt;0.001</b>
<b>Arteriosclerosis</b> (ref=0)	3,868	-	0.81 (0.47-1.37)	1.39 (0.91-2.13)	1.61 (1.23-2.10)	2.58 (1.90-3.50)	2.91 (2.25-3.76)	4.94 (3.79-6.44)	1.54 (0.90-2.62)	<b>&lt;0.001</b>
<b>Vasculitis</b> (ref=0)	4,008	-	1.41 (0.15-13.65)	5.89 (1.39-24.88)	3.43 (0.99-11.93)	7.17 (2.03-25.31)	3.07 (0.88-10.73)	5.84 (1.72-19.84)	11.65 (2.74-49.57)	<b>0.001</b>
<b>Arteriolar hyalinosis</b> (ref=0)	4,044	-	0.89 (0.49-1.63)	2.07 (1.33-3.21)	1.40 (1.03-1.91)	2.29 (1.62-3.24)	2.37 (1.77-3.18)	4.00 (2.97-5.38)	1.45 (0.78-2.69)	<b>&lt;0.001</b>

Abbreviations: HLA: human leucocyte antigen.

<sup>a</sup> P-values were calculated as p for trend with analysis of variance.

<sup>b</sup> Delayed graft function is the use of dialysis in the first week post-transplantation.

\* Parameters measured at 1 year after transplantation, the starting point of our study.

# Trajectories of glomerular filtration rate and progression to end stage kidney disease after kidney transplantation

## Population: kidney recipients



## European and US cohorts

Spieser



Certitem



Concept



Transform



Kainz Study



Rituxerah

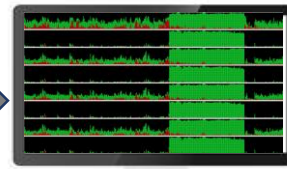


Borteject



## Randomized controlled trials

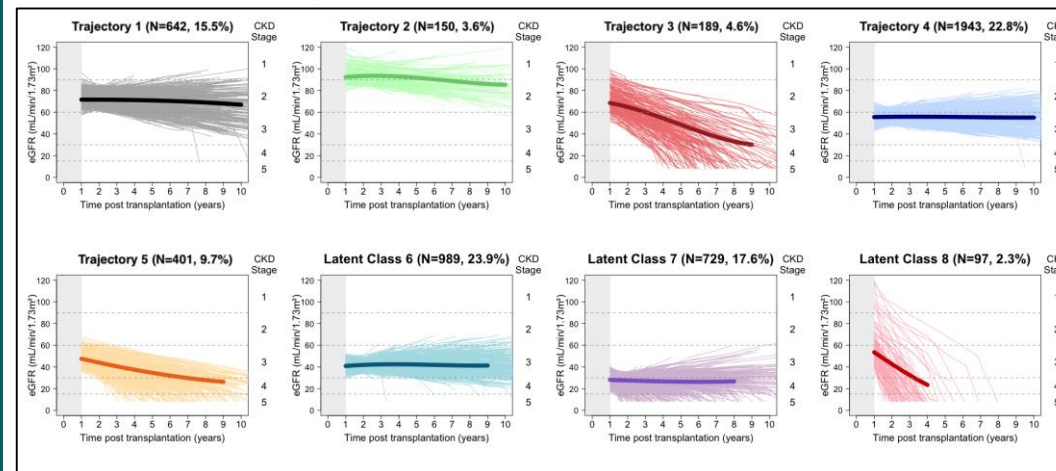
- 14,132 highly phenotyped patients
- 403,497 eGFR measurements
- 15 transplant centers
- 7 RCTs



$Y_{ij} = X_{Li}(t_{ij})^T \beta + Z_i(t_{ij})^T u_i + w_i(t_{ij})$   
 Latent class mixed modeling

$$\pi_{ig} = P(c_i = g | X_{ci}) = \frac{e^{\xi_{0g} + X_{ci}^T \xi_{1g}}}{\sum_{l=1}^G e^{\xi_{0l} + X_{ci}^T \xi_{1l}}}$$

## Identification of 8 eGFR trajectories



- 1 The eGFR trajectories were highly associated with ESRD and all-cause mortality
- 2 Clinical, immunological and histological determinants of the eGFR trajectories were identified
- 3 The eGFR trajectories and their determinants were validated in Europe, the US and in the RCTs
- 4 Based on the results, we built an eGFR trajectories prediction system adapted to the patient monitoring

**CONCLUSION:**  
 We identified and validated universal eGFR trajectories and their determinants, associated with ESRD. Our results provide the basis for a trajectory-based monitoring after kidney transplantation.