In silico evaluation of the impact of allogenomics kidney graft Donor/Recipient matching strategy

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CONTEXT

Kidney diseases represent one of the major raising causes of disability in western countries, and transplantation is the best replacement therapy available for most patients with end-stage kidney disease. Despite the refinement of the HLA matching strategies in the last 20 years, still 40% of kidney allografts failed within 10 years of transplantation. The main cause is chronic graft rejection, an immune reaction mounted by the (R) against the Donor (D) graft.

Current method and variables for graft allocation are based on D/R HLA typing and matching, Age difference across possible D/R pairs, time spend on the awaiting list by the putative (R) as well as identification of preformed antibodies against the putative (D) graft in the Recipient. In particular, preformed antibodies that can lead to a positive crossmatch test blocking the access to transplantation.

Recent studies from us and other groups demonstrate that the entire genome, and not only the HLA locus, can influence as well the R's immune response to the (D) graft.[1] Making use of this additional information for graft allocation can have a significant impact on long term graft function. Centralizing D/R DNA information appears instrumental in at least two respects: (1) genomic based diagnostic of the original kidney disease for (R), (2) the comparison of (D) and (R) genomes for risk stratification and better graft allocation.[2]

Here, the PhD candidate will join the "Allogenomics" team for 3 years to work on improving our understanding of the genomic and epidemiological factors that can influence the long-term outcome of the transplantation. The Allogenomics team develops since 2018 new matching strategies and risk stratification methods for kidney transplantation based on exome sequencing data from (D) and (R). The team implemented a bioinformatics pipeline (alloPipe), that can be used both as a command line tool and as a webserver. Starting from exome sequencing data, Allopipe compares of the proteomes and immunopeptidomes of D and R to compute two scores of graft compatibility (AMS and afAMS).

The PhD candidate will develop and improve the current allogenomics computational methods for graft allocation on a larger retrospective kidney transplant cohort from Sorbonne University. He/She will develop different modeling strategies that can evaluate the impact of standard method for graft allocation (Current French Biomedicine Agency Allocation ranking FBAAR) and compare it to the allogenomics method based on AMS/afAMS. In order to validate prospectively the clinical applicability of the allogenomics allocation strategy, we wish to use statistical and machine learning models that can predict possible outcome according to the graft allocation strategies. Such methods, in line with personalized medicine approach, have already been applied successfully for predicting the impact of treatment effect. We will use it to emulate digitally a clinical trial comparing the different strategies.

METHODS

Purpose. To evaluate the potential impact on post-transplantation outcomes of an allogenomics-based donor/recipient matching using methods based on predictor of treatment effect.

Co-primary outcomes. Death of any cause following kidney transplantation; loss of graft function (i.e., following transplantation, need for dialysis or for another transplantation).

In the first stage, baseline survival functions will be adjusted to the two retrospective cohorts that have been collected at SU and the relative merit of the two scoring strategies will be assessed. We will then make in step 2 use of this knowledge to sample according to expected outcome that different allocation strategies would imply.

Study population. All adult recipients of a first kidney-only allograft obtained from a deceased donor who had surgery performed in Sorbonne University hospital between 2017 and 2023 (N=700). This cohort will be complemented by a rich baseline consisting of all other patient sequenced in the Nephrology department of SU (N=1600). All corresponding donors have results for HLA typing as DNA available for Exome Sequencing.

Analysis. As a first step for all patients, we will compute both (1) the "FBAAR" reference score, using information already collected (e.g., time spent in waitlist, in dialysis, HLA mismatching, etc…), and the new allocation score, which substitute the "HLA-mismatch" component with an "allogenomics" component using exome sequences. We will then estimate survival functions (time-to-death and time-to-graft loss) as a function of the reference allocation score, the allogenomics-based allocation score, together with other covariates (HLA antibodies, donor age...) We will be able to evaluate the relative effect of the different scoring strategies Time horizon will be set to 5 years.

In a second step, we will use the estimated relationship between a patient profile, its genomic background and the outcome of the transplant, to perform an in-depth analysis of alternative strategies for graft allocation. In particular we will perform a cost-utility analysis by combining knowledge from the literature with treatment costs as documented by the *Assurance maladie*

The successful PhD candidate has the potential to impact the allocation strategy for kidney allograft at the national level, beyond benefiting to the patient at the individual level.

REQUIRED SKILLS, PROJECT TEAM

The candidate will have to integrate and automate clinical data and genomic data generated from clinical care and generated virtual D/R pair generated by the allocation strategies.

The candidate should have a solid grasp in using computational method and manipulating large datasets (ten thousand of samples with genomic data). An understanding of genomics and/or previous experience in simulation studies (Markov models, discrete event simulation) would be appreciated.

Team: Dr Hugues Richard (Statistics and Computer Science), Dr Yannis Lombardi (Data Science), Prof Laurent Mesnard (Nephrogenomics, Transplantation). ISCD/SCAI: Are institutes from Sorbonne university see more on https://iscd.sorbonne-universite.fr and https://scai.sorbonne-universite.fr/

REFERENCES

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