ESOT Fellowship 2024 – Final Technical report

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Experience

The ESOT basic science fellowship has opened multiple opportunities that have contributed to Kennedy's professional and academic development. For example, the key collaboration was with the UK National Health Service Blood and Transplant (NHS-BT) and their Cardiothoracic Advisory Group for Lung Transplantation (CTAG-L). The goal was to validate a transplant policy simulation engine, a key component of Kennedy's PhD outcome. That development relates to the evaluation of the impact of potential new UK donor-lung allocation policies on various objectives (e.g., increased post-transplant survival, lower wait-list deaths, etc.). We surveyed clinical and patient stakeholders regarding lung transplantation (i.e., lung transplant candidates, recipients, carers, physicians, surgeons, etc.) and applied methods from the field of operations research to identify which of the simulated policies aligned with the goals and values of each stakeholder group.

This collaboration has now evolved to the point where we have a prototype of a generic policy evaluation engine suitable for analysing policies across multiple organs. Moreover, the system is tuneable to the analysis of policies for several potential limited-resource allocation policies. For example, we experimented with its use during the COVID-19 pandemic to identify the best-suited ventilator allocation policies, and we performed preliminary validation of policy prediction against clinical outcomes. This implementation opened a pathway for the optimisation of donor-lung allocation in the UK. This is intended to replace the current lung allocation system in the UK.

The fellowship has also allowed closer collaboration with NHS-BT operations hub in Bristol, where we presented the research to its statisticians, the head of organ donation and transplantation (ODT) studies, and the assistant director of statistics and clinical research. Additionally, Dr. Kennedy was permitted to enter the workspace where deceased donor organ offers are coordinated nationally, observing allocation work in practice, and discussing practical limitations of potential future allocation policies. This experience was invaluable, as it validated the soundness of our methodology and ensured that the research direction was in line with NHS-BT goals and could be applied in a real-world setting.

Outcomes

The primary outcome of this fellowship comes from the collaboration with NHS-BT and CTAG-L. This research is not a theoretical exercise or data-analysis project. Instead, it lays the foundation for realistic implementation and impact on how future lung allocation could be performed in the UK.

The policy evaluation engine is composed of three independent parts:

(1) **Data Soundness and Survival Model Building**. This system receives input from transplant centres on the waiting list and post-transplant survival cohorts over time and performs several checks for consistency and adequacy. Then, a near-exhaustive analysis of input variables is conducted to identify the best survival model using a Cox proportional hazards analysis. Various statistical techniques are used to ensure the soundness of variable selection. This is then used to define a ranked risk score of each patient on both waiting and post-transplant survival lists.

(2) **Policy Simulation Engine**. This system receives input from (1) and can perform multiple statistically sound simulations over specified periods (e.g. 8 times over 20 years) according to a chosen Survival model. The engine also permits other systems to perform simulations, provided the data input is in the adequate format and the expected survival parameters and coefficients are provided. Thus far, we have implemented nine transplant policies, each with a distinct set of parameters. New policies are possible, yet require coding. We are working on a policy computer language to enable new policy exploration as a tool as well. The system generates detailed information about each simulation run, including user-chosen policy parameters and the rationale for each simulation event (e.g., wait listing, death event, transplant event, etc.). This enables a clear and precise documentation and explanation of each simulation run.

(3) **Results Visualisation**. This system receives input from (2) and performs numerous visualisations according to what users want to introspect/understand from each simulated policy run. For example, it is possible to visualise each simulated event as multiple queues (e.g. waiting, deaths, transplant, etc.), hence enabling visualisation of how each policy progresses over time. We can also visualise different policy simulations in terms of accumulated results (bar chart) over time. Other visualisations are also performed to identify how each policy performs in terms of net benefit, post-transplant survival, waiting list deaths, and other relevant criteria.

We performed a large number of simulations and confirmed that the survival analyses were of suitably high quality, documenting assumptions and evaluating each policy.

The methods developed within the engine can be applied more generally, beyond lung transplant. For example, we have performed initial experiments with UK liver waitlist data. Moreover, we also applied to the problem of ventilator allocation for COVID-19 patients. This demonstrated that the system could be applied to other organ allocation systems, as well as to other healthcare problems involving scarce resources.

Of direct relevance, we investigated the impact of preferentially allocating a single lung transplant (SLT) to candidates with Interstitial Lung Disease (ILD). Although post-transplant outcomes are not as optimal with SLT compared to both lungs, more factors at play were evaluated with the help of the simulation engine:

(1) Allocating two single lungs to two separate recipients results in a substantial decrease in waiting list mortality, with our simulations predicting a 95% reduction among the ILD population (from 45 per year to 2.2 per year).

(2) There is a secondary effect of removing two ILD candidates from the list with one donor offer: an overall reduction in demand for subsequent donor lungs. This resulted in a 10% to 30% decrease in waiting list mortality for candidates with other diagnoses.

(3) Not accepting a single lung offer in hopes of receiving a lung pair in the future results in there being a risk of dying on the waiting list before receiving another offer. For each candidate that dies on the waiting list, there is some amount of additional lifespan they could have gained but didn't – this is conceptually like "opportunity cost". When looking at the overall population survival of ILD candidates and recipients, utilising SLT resulted in an 8% increase in population-level survival.

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