Institution: The University of Manchester		
Unit of Assessment: 16 (Economics)		
Title of case study: Designing and implementing a new Kidney Exchange (DEC-K) Program in Italy		
Period when the underpinning research was undertaken: 2013-2018		
Details of staff conducting the underpinning research from the submitting unit:		
Name:	**Name:**	**Name:**
Prof. Antonio Nicolò	Professor of Economics	2012 - present
Period when the claimed impact occurred: March 2018 – December 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Professor Antonio Nicolò's research has shaped the design and implementation of a new national program in Italy for kidney transplants, combining deceased and living donor allocation mechanisms. By incorporating patient preferences into the design of allocation models and associated algorithms, the research led to a redesign of Italy's Kidney Paired Exchange (KPE) programs in order to expand membership and effectiveness. Italy is the first country in the world to implement such a program and it has already enabled an increased volume of successful donor matches and transplants. Other countries such as France are now looking to the success of the Italian system and considering adopting similar innovations.

2. Underpinning research

There is a significant gap between the demand and supply of kidneys for patients who need transplants. Living donor renal transplantation is the most promising solution for closing this gap. Despite efforts, in many European countries an expansion of living transplantation programs has not yet materialised. In many cases, a donor cannot donate the organ to a related patient due to blood or tissue incompatibility. In these cases, Kidney Paired Exchange (KPE) programs represent the best option, seeking to overcome the incompatibility of living donor-patient pairs by arranging a sequence of swaps of donors among several pairs. However, logistical complexity makes exchanges involving long chains of donor-patient pairs unfeasible and for this reason, real-life KPE programs have generally focused on maximising the number of simultaneous compatible organ exchanges between two or three donor-patient pairs, although swaps involving longer cycles can occasionally be carried out.

Ever since the seminal paper by Roth (2004) in the *Quarterly Journal of Economics*, such kidney exchange programs have been a leading illustrative example in the economic theory literature on optimal allocation mechanisms. In most of this literature however, all attributes of the good to be matched are assumed to be dichotomous – kidneys are therefore either compatible or not; i.e., there is no ranking within matching pairs. As an economic theorist working in this area, Nicolò has focused on relaxing this dichotomous quality assumption, taking into consideration the fact that compatible organs may have different quality (expected graft survival) and incorporating patient preferences into the assignment problem in order to facilitate redesigning KPE programs and expand membership and effectiveness.

Previous research by Nicolò and Rodriguez Alvarez proved an impossibility result, namely that if kidney quality is not assumed dichotomous, i.e. some matching kidneys are 'better' than others,

then it is impossible to compute an allocation mechanism using results in the previous literature. They conjectured that, in this setting, efficiency gains could also emerge since KPE programs recognising the potential quality of the matches between patients and donors would be able to enlarge the pool of participants by providing incentives to enrol.

During his time at Manchester, and starting in 2013, research by Nicolò and Rodriguez Alvarez showed that under minimal (and reasonable) additional assumptions it is possible to design and compute an allocation mechanism. They proposed a set of sequential priority rules that deliver efficiency gains as long as patients prefer kidneys from compatible younger donors to those from older donors, which is a reasonable restriction in KPE problems [1].

To have a better understanding of patients' preferences, Genie, Nicolò and Pasini elicited time and risk preferences for kidney transplantation from the entire population of patients registered at the Padua University Hospital, using a discrete choice experiment. They measured patients' willingness-to-wait to receive a kidney with a one-year longer expected graft survival, or a low risk of complication. The resulting mixed logit model provided robust evidence of heterogeneity in patients' preferences [2].

The contribution of this research [1, 2] was the design of a new allocation mechanism that builds in and recognises the costs and benefits patients incur by waiting (or not waiting) for a better match. There are two consequences of these theoretical developments for real world KPE programs. Firstly, using deceased donors to initiate a transplant chain, as proposed in the medical literature, now becomes feasible. In previous cycle programs or Samaritan-based chains there was no allowance in the allocation mechanism for the willingness of patients to accept an early transplant from a donor even though it might not be such a good match. Secondly, it creates room to increase the size of the donor pool by including compatible donor pairs who may now be optimally matched with different patients. This enlarged pool is then beneficial since the increased availability of matching organs allows individuals to expect higher quality matching kidneys given the same waiting time, or to expect a shorter waiting time given the same expected quality of the match. The research indicates that with a design that benefits more individuals, incentives to register in the program should also increase. Consequently, the pool should increase even further, thus allowing more transplants, and longer chains of transplants, to occur.

Inspired by these theoretical insights, Nicolò then put together and led an interdisciplinary team of economists, computer scientists and medical doctors, including Professors Furian and Rigotti of the Kidney and Pancreas Transplant Unit, Padua University Hospital (hereafter: Padua Kidney Transplant Centre), to design and fully specify a new and innovative program (the DECeased Kidney Paired Exchange (DEC-K) program). Development funding was obtained from a large research grant from the University of Padua (i). The program, built on the research findings above, exploits deceased donor kidneys to initiate chains of living donor kidney paired donations, and demonstrates how to compute the optimal allocation mechanism combining deceased donations with those from living donors [3, 4]. The research provided a preliminary efficacy assessment and described the development of a dedicated algorithm. The team were the first to report a successfully completed, deliberate deceased donor-initiated chain [3]. The research agenda is still ongoing and aims to analyse how to provide effective and equitable incentives to compatible pairs to enrol in the Italian Kidney Paired Donation program [5].

3. References to the research

[1] **Nicolò, A**. and Rodriguez-Alvarez, C. (2017). "Age-Based Preferences in Paired Kidney Exchange", *Games and Economic Behavior*, 102, 508–524. https://doi.org/10.1016/j.geb.2017.02.006

[2] Genie, M. G., **Nicolò, A** and Pasini, G., (2020). "The role of heterogeneity of patients' preferences in kidney transplantation", *Journal of Health Economics,* 72, 102331. https://doi.org/10.1016/j.jhealeco.2020.102331
[3] Furian, L., Cornelio, C., Silvestre, C., Rossi, F., Rigotti, P., Cozzi, E., Neri, F., **Nicolò, A**. (2019). "Deceased-donor-initiated chains: first report of a successful deliberate case and its ethical implications", *Transplantation,* 103:10, 2196-2200. doi: 10.1097/TP.0000000000002645
[4] Cornelio, C., Furian, L., **Nicolò, A**. and Rossi, F. (2019). "Using deceased-donor kidneys to initiate chains of living donor kidney paired donations: algorithm and experimentation", *Proceedings of the AAAI/ACM Conference on Artificial Intelligence, Ethics and Society (AIES),* 477-483. https://doi.org/10.1145/3306618.3314276
[5] Furian, L., **Nicolò, A**., Di Bella, C., Cardillo, M., Cozzi, E. and Rigotti, P. (2020). "Kidney exchange strategies: new aspects and applications with a focus on deceased donor-initiated chains", *Transplant International*, 33:10, 1177-1184. https://doi.org/10.1111/tri.13712

Related grants:

(i) Antonio Nicolò (PI), "Incorporating patients' preferences in kidney transplant decision protocols", University of Padova, 2013-2017, GBP300,000.

Evidence of research quality: Research outputs [1] and [2] are published in top peer-reviewed journals in Economics. Outputs [3], [4] and [5] are top interdisciplinary peer-reviewed journal papers.

4. Details of the impact

Italy had started a KPE program in 2006 and in 2015 introduced the possibility that a Samaritan (live) donor could initiate a chain of pairwise cycles/cross-over kidney transplants. But this initiative resulted in only a relatively small number of completed transplants due to very few Samaritans (typically one per year), and a difficulty in getting compatible cycles due to the small number of incompatible pairs enrolled in the program. Based on the research findings above, Nicolò worked with the Padua Kidney Transplant Centre to design an innovative program, called the DEC-K program, combining the living donor program with the standard deceased donor program [3, 4]. The new program was first adopted at the Padua Kidney Transplant Centre and is now in operation across Italy, the first country in the world where a program combining deceased and living donation has been implemented.

The contribution of Nicolò and impact of the research is noted by Dr Massimo Cardillo, current Director of the Italian National Transplant Centre (CNT), "*Prof. Antonio Nicolò has led a unique interdisciplinary team and his commitment, jointly with prof. Lucrezia Furian and prof. Paolo Rigotti of the Padua Transplant Center, has significantly contributed to the development of this successful program. He has collaborated on all stages of the implementation process: he devised the algorithm to assess the potential contribution of the program in the initial retrospective study, and contributed to the design of the protocol, including the discussion of its relevant clinical and ethical implications"* [A].

The DEC-K program at the Padua Transplant Centre

The DEC-K program aims to expand the domino effect of chains of transplants from a deceased donor organ, continuing by means of consecutive donations among pairs of incompatible donor-recipients, and ending with a transplant to a patient who is on the waiting list for a deceased organ and does not have a willing living donor. It aims to boost the number of living transplantations. Massimo Cardillo, then Director of the Transplant Coordination Polyclinic of

Milan, stated that the CNT set up a working group in December 2016, with the task of developing a single kidney allocation algorithm for all Italian Regions, the adoption of which "*will ensure equal treatment of patients, regardless of where they are registered on the list"* [B].

The project started from a retrospective study of data of biologically incompatible donor-recipient pairs, enrolled in the Padua Kidney Transplant Centre [3, 4]. The feasibility and effectiveness of the DEC-K project were then tested through a pilot phase in March 2018, at the same centre, and the first transplant under the DEC-K program was performed on 13 March 2018. The patient received a deceased donor kidney and two days later his wife donated a kidney to another patient on the waiting list [B]. Prof. Rigotti, Head of the North Italy Transplant Program (NITp) announced that *"for the first time, at the Kidney and Pancreas Transplant Center of the Hospital of the University of Padua, a chain of living kidney transplants was carried out between couples incompatible donor-recipient, triggered by a deceased donor: a unique experience not only at an Italian level but also internationally"* [B]. He added that "*In practice, the availability of a living donor allowed a patient to receive a kidney from another deceased donor, effectively shortening waiting times and allowing two lives to be saved instead of just one"* [B].

Later in 2018, Alessandro Nanni Costa, former Director of the CNT, was quoted in the national press, exclaiming that *"Among the various innovations in the activity of 2018 were the start of the program for kidney transplantation chains between incompatible couples triggered by a deceased donor, the first in the world and which is now being copied by other countries"* [C].

After five successfully completed chains, with a total of 14 kidney transplants starting from 5 deceased donors [B], the DEC-K program was approved for nationwide application in July 2019 [D].

The DEC-K program and the new Italian protocol for living donations

The DEC-K program now forms a significant part of the new Italian protocol for living donations [E]. Following nationwide implementation, three further chains were completed, involving 10 kidney transplants, in the 8 months thereafter [B]. The increase in the chance of finding a compatible kidney for recipients of incompatible pairs provides an additional incentive to enrol in the national paired donation program. Benefits of this DEC-K program increase faster relative to alternative approaches due to the multiplier effect: the donor pool enlarges, chains can get longer and quality can get better, thus increasing even further the likelihood of drawing in fresh participants; hence, one might expect even greater multiplier effects going forwards.

The DEC-K program, as of November 2020, has enabled 30 transplants (triple the number of deceased donor kidneys employed) including those undertaken during the pilot program and those since national implementation, involving 10 Italian transplant centres and 16 incompatible pairs [A]. Dr Massimo Cardillo states that to appreciate the impact of this program it is worth noting that in four years, from 2015 to 2018, only 45 transplants from living donors were performed under the standard KPE program across the whole of Italy [B]. He also notes that the COVID-19 pandemic has limited the full development of the DEC-K program in 2020, but a further increase of the transplants performed under this program is expected [A].

Emerging influence of the DEC-K program on other countries

The DEC-K program has received attention from other national agencies. Although *"the DEC-K program is a unique program worldwide…France and other European countries are moving to implement similar programs"* [A]. Simulation analysis performed by a group of French researchers of the Institute of Public Policies (IPP) in collaboration with the Agence de Biomédicine shows that allowing donation chains that begin with deceased donors, even at modest frequency, can more than triple the number of transplants in the French paired donation

program [F], [G]. Paolo Rigotti also states that the team have been contacted by members of the United Network for Organ Sharing (UNOS) for details of the program, "*because they are interested in implementing a similar program in the US"* [H].

5. Sources to corroborate the impact

[A] Testimonial letter from Director of the National Transplant Centre (17 September 2020)
[B] Preliminary report to press about the activities during 2018 of the CNT by Alessandro Nanni Costa, former Director of CNT, http://www.trapianti.salute.gov.it/imgs/C_17_primopianoCNT_430_listaFile_itemName_0_file.pdf [Italian]
[C] La Repubblica news article, "Nel 2018 boom di trapianti, calano le liste di attesa per il rene", (17 December 2018), https://bit.ly/357d0LL [Italian]
[D] Centro Nazionale Trapianti – Italian National Transplant Center (CNT) public statement (15 March 2018) [Italian]
[E] Italian Protocol for Kidney Paired Donation (CNT, this version 20 January 2020), http://www.trapianti.salute.gov.it/imgs/C_17_cntPubblicazioni_344_allegato.pdf [Italian]
[F] "Outlook on the Kidney Paired Donation Program in France", Institute de Politiques Publiques IPP brief policy report, n.41, 2019.
[G] Paired kidney donation: theory and assessment of the practice in France – Agence Nationale de la Recercher funded project. https://anr.fr/Project-ANR-17-CE36-0004
[H] Testimonial letter from Full professor of Surgery, School of Medicine, University of Padova and Head of the North Italy Transplant Program (NITp) (30 May 2019)