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OUTLOOK ON THE KIDNEY PAIRED DONATION PROGRAM IN FRANCE

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Many countries, including France, have seen a sharp increase in the number of renal disease patients waiting for a transplant. The shortage of kidney transplants has led some countries to develop "paired donation" programmes, which allow patients who can only find incompatible living donors to "swap" donors in order to receive a compatible transplant. In France, the number of additional transplants obtained through this programme is very limited, due in large part to the strict legal framework governing paired donations. For example, the law stipulates that an exchange can only take place between two patient / donor pairs.

In its June 2018 summary report, the French National Consultative Ethics Committee (CCNE) lays out avenues to reform the paired donation programme. The French government is expected to present a draft law on revision of the bioethics law in the coming months. It therefore struck us as important to assess the potential effect on transplant numbers if the law were changed to authorise more flexible practices in the paired donation programme.

On the face of things, increasing the number of patient / donor pairs allowed to take part in an exchange seems like a good way of generating more transplants, but we show that this measure has only a modest impact. A different approach, which has proven effective in other countries, is to allow "donation chains". We show that allowing donation chains that begin with deceased donors, even at modest frequency, can more than triple the number of transplants.

- Deceased donor-initiated donation chains can increase the number of patients receiving transplants in the paired donation programme by up to 279%.
- With the constraint that a donation chain can only begin with a "high-quality" deceased donor, the increase is 214%.
- Patients without a willing and able living donor, and thus waiting for a deceased donor transplant, are not penalised by this reform.
- The hope is that the new Bioethics law will allow these donations chains so that the number of transplants can be significantly increased. This would involve lifting the current obligation requiring the surgeries associated with paired donations to be performed at the same time.

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Paired donation programmes: context

Around the world, the number of renal disease patients waiting for a transplant continues to rise. In France, the number jumped from 8,475 in 2011 to 13,431 in 2017, an almost 60% increase.[1] Since the number of deceased donors (see Box 1) is fairly stable, transplant shortage represents a major challenge for the years to come. Transplants from living donors do help fill this gap, but for a patient, the chances of finding a compatible living donor are still relatively slim. In response to this situation, in recent years, alternatives have been developed for patients who have a willing but biologically incompatible kidney donor. One such alternative, i.e. paired donation programmes, "pools" incompatible patient / donor pairs so that patients can swap donors in order to receive a compatible transplant.[2]

The first paired donation programmes emerged in South Korea in 1991 and in the United States in 2001. A paired donation programme was authorised in France with the Bioethics law of 2011 and has been implemented since 2013. However, this French programme remains small in scale and is far from producing the hoped-for number of transplants. A cumulative total of 78 patient / donor pairs have taken part in the programme, and only 6 paired exchanges (12 transplants) took place between December 2013 and February 2018. The initial estimates by the French Agence de la Biomédecine were of 50 to 100 transplants per year.[3] This makes France's paired donation programme one of the least effective in Europe.[4] One of the main reasons for this poor performance is the strict legal framework governing paired donations. In substance, the law stipulates that an exchange can only take place between two pairs (of patients and donors) and that the surgeries for the two pairs must be done at the same time. The draft law on revision of the bioethics law expected from the government in the coming months may relax this legal framework. Of course, exchanges involving more than two patient / donor pairs could increase the number of patients receiving transplants. In practice, however, the logistical constraints are such that these exchanges must be limited in size.[5]

An alternative approach, which has proven effective in other countries, is to allow a "donation chain" that starts with a kidney from an "unpaired donor", i.e. a donor not associated with a specific patient. In practice, an unpaired donor can be an "altruistic" living donor who donates their kidney for the benefit of patients in a paired donation programme (as in the United States, the United Kingdom, Spain, etc.). An unpaired donor can also be a deceased donor (as in Italy, for example).[6] Our analysis is focused on this second case[7].

The aim of this brief is two-fold. First, we show the impact that deceased donor-initiated donation chains can have on the proportion of patients receiving transplants. We find a significant impact, even if the frequency of these chains remains modest (one per trimester). Second, we explain why this reform is of primary importance, more so than allowing exchanges involving more pairs.

Paired donations: current practices and alternative practices

A paired donation programme pools pairs made up of a patient and donor who are immunologically incompatible with each other. The goal is to allow a patient in the programme to find a compatible donor in exchange for the kidney from their donor (i.e. their family member or friend), which can be allocated to another patient in the programme. Here we outline the two main practices in use in the world: exchanges between pairs, and donation chains. Box 2 provides further information for a more in-depth understanding of these practices.

Exchanges between pairs. This type of exchange allows patient / donor pairs to swap donors. As explained in Box 2, for logistical reasons, most paired donation programmes limit the maximum number of pairs that can swap donors. Currently in France, only two-pair exchanges are allowed in the paired donation programme. Many countries allow exchanges between a larger number of pairs, generally 3 or 4.

Donation chain. Donation chains begin with a deceased donor (UD in the figure in Box 2) whose kidney is transplanted to a patient in the paired donation programme (P1). This first transplant triggers a chain of donations: the living donor (D1) paired with the patient who receives the kidney from the deceased donor can then give their kidney to another patient in the programme (P2). In turn, this patient's donor (D2) can then give their kidney to another patient, and so on. As illustrated in Box 2, a do-

[1] https://www.agence-biomedecine.fr/annexes/bilan2016/donnees/organes/06-rein/synthese.htm.

[2] For some patients, there is also the possibility of receiving the incompatible transplant from their own donor after undergoing desensitisation treatment. In many cases, however, incompatible transplants are not only costly, but the results in terms of the organ's post-transplantation lifespan are not as good as with compatible transplants.

[3] https://www.agence-biomedecine.fr/Le-don-croise.

[4] See Biró and al., 2019.

[5] Most countries also require the surgeries to be performed at the same time, which generally limits exchanges to a maximum of three or four pairs.

[6] Furian and al., forthcoming.

[7] This choice is justified by the relative abundance of deceased donors in France compared to other countries (in Europe, only Spain has a higher deceased donor rate per inhabitant than France, according to *Newsletter Transplant 2016*), whereas there is no assurance that being an "altruistic" donor is an accepted practice in France, at least in the short term.

Box 1 : Glossary.

Patient. Person with chronic renal disease who is in need of a kidney transplant.

Hyperimmunised patient. Patient presenting tissular incompatibility with a large proportion of the population. More specifically, a hyperimmunised patient presents tissular incompatibility with more than 85% of the deceased donors with the same blood type as the patient and from whom transplants have been taken over the past 5 years.

Deceased donor. A person in a state of brain death (or after circulatory arrest) and from whom one kidney (or both kidneys) can be removed and given to patients waiting for a transplant.

Living donor. A living person with close ties to a patient to whom they wish to give one of their kidneys. This person can be the patient's father or mother, or, by special request, a son or daughter, brother or sister, spouse, grandparent, aunt or uncle, first cousin, or spouse of the patient's father or mother. The living donor can also be any person providing evidence of at least two years of conjugal life with the recipient or evidence of having a close and stable emotional relationship with the recipient for at least two years.

Pair. A pair is made up of a patient and the living donor willing to give the patient a kidney. The patient / donor pairs in the paired donation programme are immunologically incompatible. For a patient and donor to be immunologically incompatible, they must be incompatible in terms of blood type (ABO compatibility) or in tissular terms (HLA compatibility).

Paired donation programme. Programme that can allow each participating patient to swap their incompatible living donor for a different living donor who is a compatible match.

Transplant. A transplant is a body part that is removed in order to be transplanted. In this case, it is a kidney removed for transplantation.

nation chain does away with the need for the surgeries to be performed simultaneously, allowing a larger number of patients to be involved.

With the implementation of donation chains come three main challenges. First, it is known that the quality (measured as the post-transplantation lifespan of the transplant) of a kidney from a deceased donor is inferior to that of a kidney from a compatible living donor. Second, using kidneys from deceased donors can reduce the pool of potential kidneys for patients without living donors–who are thus waiting for a kidney from a deceased donor–in favour of patients who do have living donors, raising a fairness problem. Lastly, introducing donation chains can raise incitement problems: patient / donor pairs may want to join the paired donation programme so that the patients can receive a kidney from a deceased donor, without the donors truly intending to give their kidney. In Box 3, we outline the donation chain system we propose, taking into account these three challenges.

Impact of introducing new practices

Methodology. The impact of introducing new practices into the paired donation programme has been assessed on the basis of counterfactual analysis. For this analysis, the main source of data used pertains to the paired donation programme. For each quarter from December 2013 to February 2018, we know all the pairs that took part in the programme. We have the data on each donor's immunological compatibility with each patient in the programme. Thus, we have all the information needed to study the rates of transplants for patients in the programme that would have occurred if other policies had been adopted (exchanges between more than two pairs, or chains) when the paired donation programme was launched in 2013. The reference situation we take as our point of comparison is that only two-pair exchanges are allowed.[8]

Increasing the maximum number of pairs in an exchange. Box 1 shows the percentage of additional transplants made possible by introducing exchanges between 3 and then 4 pairs. Exchanges between 3 pairs would have increased the number of transplants by slightly more than 20% (bringing the total number of transplants to 17), while allowing exchanges between 4 pairs would have had a marginal additional effect (a total of 18 transplants). There is no change to the number of hyperimmunised patients[9] receiving transplants, which remains 2. The increase in access to transplants is therefore real but still modest.

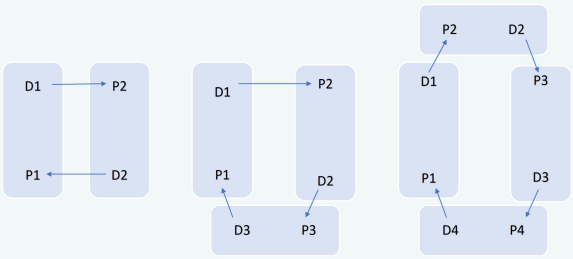
Introducing deceased donor-initiated donation chains. To evaluate the impact of introducing this new practice,

[8] In this reference situation, we obtain a total of 14 transplants (7 exchanges). In reality, only 12 of these transplants were successfully completed, as one exchange had to be abandoned for medical reasons.

[9] Hyperimmunised patients are the most difficult to find transplants for because of the very high probability that they will have tissular incompatibility with a random donor from the population.

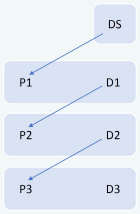
Box 2 Exchanges between pairs and donation chains.

Exchanges between pairs. Exchanges between 2, 3 and 4 pairs are illustrated in the figure below. Each rectangle represents an incompatible pair, and an arrow from a donor D_i to a patient P_j indicates that P_j is compatible with D_i.



In practice, the surgeries for an exchange between pairs must be performed at the same time. This requirement protects against the repercussions if a donor involved in an exchange were to fail to follow through. For example, taking the case of an exchange between two pairs in the figure above, let us imagine that the transplants are not done at the same time. If the transplant between D1 and P2 was done before the transplant between D2 and P1, then D2 failing to follow through after P2 had been transplanted would cause a major problem: patient P1 would not receive a transplant even though they had "lost" their donor when the kidney was taken from D1. Performing the surgeries simultaneously avoids this type of situation; logistically, however, it imposes significant constraints. Consequently, in practice, the maximum number of pairs in an exchange is often limited, usually to three (United Kingdom, United States, Spain, etc.) or two (France, Italy), and more rarely, to four (Netherlands).

Donation chains. The following figure represents a donation chain. A donation chain has to start with an unpaired donor, i.e. a donor not associated with a specific recipient for their organ. There are two types of donors in this category: "altruistic" donors and deceased donors. In this brief, we focus on this second type of unpaired donor. In the donation chain presented in the figure below, the unpaired donor (UD) gives their kidney to patient P1; in turn, D1 then gives their kidney to patient P2... The chain continues until it reaches a donor for whom there is no compatible patient in the paired exchange programme (as is the case for D3 in the figure below).



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[a]Non-simultaneous surgeries in a donation chain proceed according to two systems. In the first, used in most countries, chains end with a transplant to a patient on the wait-list for a deceased-donor kidney (thus, a patient not in the paired donation programme). In this case, a period of 2 to 3 days between two operations may be necessary for chains involving more than 4 pairs (these short interval periods are allowed in Spain, for example). With the second system, some countries allow "never ending" chains in which, each day, the donor paired with the last patient to have received a transplant waits for a compatible patient to enter the programme, in order to continue the chain. In the United States, for example, where never ending chains are allowed, the longest chain led to more than 100 transplants. In this case, the interval period between two operations may be much longer.

Box 3: Donation chain implementation in detail.

Challenge 1. In a deceased donor-initiated donation chain, one patient will receive the transplant from the deceased donor in "exchange" for their living donor's transplant. As the quality (measured as the post-transplantation lifespan of the transplant) of a kidney from a deceased donor is on average inferior to that of a kidney from a compatible living donor, we can naturally ask whether the system is unfair to this patient. Moreover, if the quality of the kidney obtained is too low, there is the question of whether the patient will want to accept the transplant. Thus the goal as we see it is to start donation chains with deceased-donor kidneys of comparable quality to kidneys from compatible living donors.

Solution. We only initiate a donation chain with transplants of "sufficient" quality, comparable to that of a transplant from a compatible living donor.

Challenge 2. Initiating a donation chain with a kidney from a deceased donor raises a question of fairness. Using transplants from deceased donors can lead to fewer kidneys being offered to patients who are waiting for a deceased-donor kidney because they do not have a willing and able living donor (and therefore are not in the paired donation programme).

Solution. The living donor at the end of the donation chain (who does not match any patient in the paired donation programme) gives their kidney to a patient who is not in the paired donation programme. This way, every time a kidney from a deceased donor is "used up" in the paired donation programme, a kidney from a living donor is "given back" to the patients on the wait-list for a deceased-donor transplant.

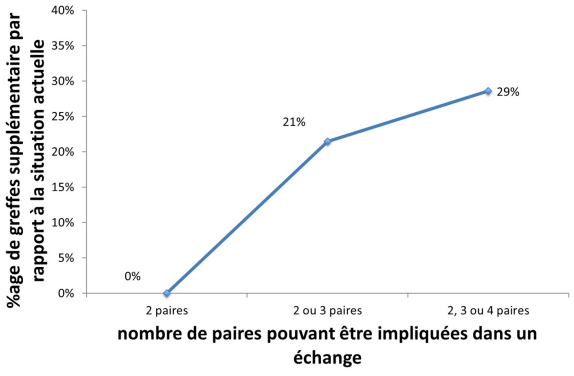
Challenge 3. It can be difficult to perform the first transplant in the chain (i.e. from the deceased donor to the first patient) and the second transplant (i.e. from the first patient's donor to the second patient) at the same time.[a] Thus, it is possible that the first patient could receive a transplant from a deceased donor and their donor could then refuse to give their kidney. Certain patients could thus enrol in the programme with a " false donor"–i.e. who does not truly intend to give their kidney–in order to obtain a transplant from a deceased donor, as wait times can be long for patients not in the paired donation programme.

Solution. We identify a patient to receive a high-quality deceased-donor kidney within a very short period.[b] The donor paired with this patient gives their organ to start a chain. In exchange, the patient is given high priority on the wait-list for a deceased-donor kidney.

[a] Because the first transplant comes from a deceased donor, it cannot be planned, whereas the second transplant needs to be taken from a living donor, which requires a minimum of advance planning.

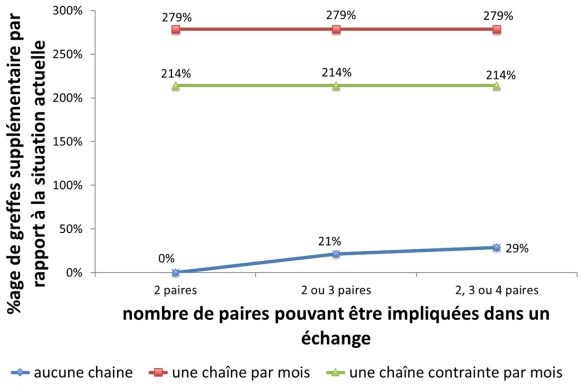
[b] More specifically, to ensure that this patient receives a sufficiently high quality kidney within a relatively short period, we calculate the number (annual average) of "high-quality" transplants that each patient in the paired donation programme would have received if the patient had been placed at the top of the wait list for deceased-donor kidneys. By "high-quality" transplants, we mean transplants of higher quality than the average (compatible) living donor transplant. We use the *Kidney Donor Risk Index* (Rao and al., 2009) as the measure of quality.

Figure 1: Quantification of the effect of increased exchange size on number of transplants.



y axis: percentage of additional transplants relative to the current situation. *x axis*: Number of pairs that can be involved in an exchange.

Figure 2: Quantification of the effect of introducing deceased donor-initiated donation chains.



y axis: percentage of additional transplants relative to the current situation. *x axis*: Number of pairs that can be involved in an exchange. Blue line: no chain; Green line: one constrained chain per month; Red line: one chain per month.

we consider that one chain (as described in Box 3) per quarter can be initiated. Figure 2 summarises the results obtained (noting that, in this figure, the blue curve represents the case in which chains are not allowed, thus corresponding to the curve shown in Figure 1).

Even if only two-pair exchanges are allowed, one donation chain per quarter could increase the total number of

patients receiving transplants in the programme by more than 279% (red curve in Figure 2). If the first patient in our chain can receive a transplant from a deceased donor of comparable quality to that of a compatible living donor (see Box 3) with an average wait time set to one month, then the percentage of patients receiving a transplant increases by 215% (green curve in Figure 2).[10]

It should be noted that when chains are introduced, increasing the maximum number of patients per exchange no longer affects the number of patients receiving transplants. It is also important to note that donation chains allow more hyperimmunised patients to receive transplants, increasing from 2 to 10.

Conclusion

Even at fairly low frequency, deceased donor-initiated donation chains can significantly increase access to transplants for patients enrolled in the paired donation programme. These donation chains also realise all the gains that can be expected from raising the maximum number of patients per exchange.

It is essential to note that our simulations surely underestimate the number of transplants that these donation chains could make possible. Indeed, by increasing the probability of receiving a transplant through the paired donation programme, there is a good chance that more patients would decide to take part in the programme, which would likely create a ripple effect and help further increase the proportion of patients obtaining a transplant. With this in mind, we also evaluated the impact of an increase in the number of participants. Our simulations confirm that allowing deceased donor-initiated donation chains significantly increases access to transplants.

In conclusion, for the paired donation programme to operate optimally, the Bioethics law should ideally allow donation chains (starting with deceased donors) without requiring them to be simultaneous (the authorised interval period between operations could be 3 days).

Reference study

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[10] In this last case, a chain leads to transplants for an average of 3 patients, and the longest chains lead to transplants for 6 patients. As the 1st transplant, from the deceased donor to the patient in pair 1, may be done later (see Box 3), these chains involve a maximum 5 transplants. We can imagine them being performed in two segments (2 transplants, then 3 transplants) with the surgeries for each segment being simultaneous and a short interval period between the two segments (up to 3 days).

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