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Kidney Exchange Programs: Incentives for Compatible Couples

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Firma dello studente

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Introduction

Kidneys are fundamental organs for every human being and the preservation of their efficient and correct functioning is crucial for a healthy life. Nowadays, the kidney diseases affect almost the 10% of the whole population worldwide and this data is increasing (National Kidney Foundation, 2021).

There are several factors that may facilitate the occurrence of the problem: genetic predisposition, unhealthy habits like smoking, wrong diet and many more. Once that a kidney is damaged, most of the time it is impossible to restore its functions, especially if it is in advanced stage of deterioration. Through specific medical examinations, it is possible to detect the working percentage of the kidneys.

Although some habits may help to prevent kidney problems, most of diseases are unavoidable and it is crucial to understand how to take care of them. The patients with kidney diseases need to be medically treated as soon as possible in order to increase the possibilities of successful rehabilitation. Currently, the available options are mainly two: the dialysis and the kidney transplantation. In most of the cases, they are not alternatives, but they represent steps of the same path towards a final treat. The final aim of a treated patient is to obtain a compatible kidney for the transplantation.

The dialysis procedures can be divided into two types: the hemodialysis and the peritoneal dialysis (Mazzucchi et al., 2000). They have different characteristics, but they do not present any significant difference of their outcome in term of success rate. They differ in the frequency and invasiveness. Thus, the nephrologist indicates the best therapy according to the specific case to each patient.

Kidney transplantation is a medical procedure that is taking more place in the last decades and nowadays the kidney is the most transplanted organ worldwide (Statista, 2021), especially due to the fact that, usually, every human being was born with two kidneys and just one of them is sufficient to survive. Moreover, the greater awareness of the related problems and consequences, has increased the frequency of the medical visits finalized in finding out the kidney diseases promptly.

Kidney transplantation represents the optimal choice for any patient and consist in the replacement of a damaged kidney with another donated one.

Not every kidney can be transplanted to any potential recipient. In fact, there are some criteria to keep into consideration while allocating the organs. The incompatibilities may determine a graft rejection or failure. Logically, this is a solution that must be avoided. The main factors to analyze for a transplantation is the blood group (ABO incompatibility) and the Human Leukocyte Antigens (HLA incompatibility). Nowadays, there are some medical treatments that allow the transplantation also for some incompatible couples, but they are not regarded as the best solution in the long term. Furthermore, the cost associated with these practices are extremely high.

The transplanted organ may come both from living and deceased donor. The kidney transplantation from living donor is widely considered the most efficient therapy to solve the kidney disease by countless authors that conducted studies and research about the topic in the last decades. People waiting for an organ from deceased donor are on dedicated waiting list until a suitable kidney is available.

For people receiving the organ from a living donor the situation is more articulated. The donor can be a relative, a partner or a friend or even a stranger. Often a familiar offers their organ in order to avoid that the relative could spend years in the waiting list, but unfortunately not always they are compatible. Consequentially, there is the need to find an efficient re-allocation of the incompatible couples for the kidney transplantations. Kidney exchange programs have exactly this goal. In fact, not every compatible organ gives the same expected result in term of quality of life for the transplanted patient. The reject of an organ represents definitely a failure, both under the health and economic points of view, because the patient would need either to undergo again the dialysis or to be transplanted one more time. Moreover, it is crucial to underline that, after every failed transplantation, the likelihood to find another compatible kidney decreases significantly.

There are several models trying to decree the best solution with different rules like the exchange between incompatible and compatible pairs, longer exchange chains, vouchers for future kidney transplantations and the inclusion of kidneys coming from deceased donors. The larger the pool is, the easier it will be to find an optimal donor for every recipient. To assist the classification of the amount of the available kidney, Massie et al. (2016) developed the so-called "Living Kidney Donor Profile Index (LKDPI)" that tries to classify the kidney according to their expected outcome for the transplantation taking into consideration several parameters such as the age, the estimated glomerular filtration rate (eGFR), the systolic blood pressure, and the Body Mass Index (BMI).

If a couple is incompatible, the only choice for them is to join a kidney exchange program, hoping for a compatible partner from another couples. The aim of the thesis is to understand when it makes sense also for a so-defined "compatible couples" or "half-compatible couples" to participate to such programs. They are the couples that would be able to undergo the transplantation, but the expected outcome suggests that there either is room of improvement or the possibility to avoid desensitization.

This thesis will try to address the following research question: “what are the incentives for compatible and half-compatible couples to join a kidney exchange programs?”.

Through a counterfactual exercise on the couples that have been transplanted in the hospital of Padua between year 2010 and year 2019, it has been possible to test the effectiveness of many models. Several characteristics, like the maximum waiting time and the LKDPI improvement threshold, are inserted in the models in order to shape them in different ways to select the one that better fits the real-life situation.

Kidney Diseases and Possible Therapies

The Kidneys

The kidneys are fundamental organs for every human being. They are part of the urinary system, which also includes other organs: renal pelvis, ureters, bladder, and urethra (John Hopkins Medicine, 2021). People were usually born with two kidneys, located one on each side of the spine, on the back of the abdomen, below the ribs. They are not perfectly symmetrical: the presence of the liver tends to create asymmetry between the location of the two kidneys, with the result that the right kidney is slightly lower than the left one, while the left one is usually placed slightly in a more medial position in comparison to the right one. A single healthy kidney contains around one million nephrons, which are microscopic units responsible for many functions: filtering, reabsorption, secretion, and excretion of substances.
They are bean-shaped and they measure, in average, roughly 10/11 centimeters with a weight of 150-170 grams each one. Although normally people were born with two working kidneys, it is sufficient that only one performs efficiently to guarantee a healthy life (Hoffman, 2021). As we age, all the organs, tend to work less efficiently and to present more problems that must be taken care of. The kidneys do not represent an exception. Erfanpoor et al. (2021) conducted a study about the kidneys and state that people aged 65 or older are more likely to present kidney diseases.

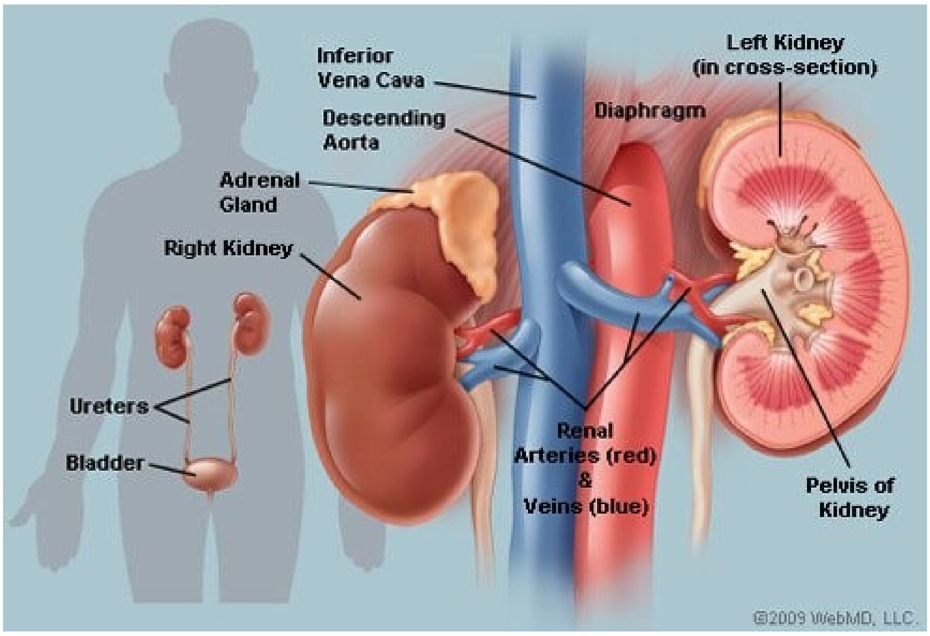

Figure 1: Picture of Kidneys.
Source: MediceNet (2021)

Kidneys perform many fundamental functions that guarantee a healthy body for the human being. They are responsible for several tasks: for example, the right balance of many factors, such as blood, liquids, and hormones. Lerma et al. (2015) have identified and classified them into six main roles:

- Removal of waste products: the main functions of the kidneys is the blood purification and the separation of unhealthy components, such as the residuals of proteins consumed for the normal body functions.
- Removal of excess fluid: regulating the amount of liquids, such as water and urine, the kidneys allow the correct functioning of the body, which otherwise would be prone to swelling.
- Balance minerals and chemicals: among the substances regulated by the kidneys, we can mention sodium, potassium, hydrogen, calcium, phosphorus, and many others. All these components play a pivotal role in the wealth being of the person under several points of view, from the regular heartbeat to the right functioning of the muscles.
- Control of blood pressure: through the production of hormones to keep under control the level of waters and salt and the blood pressure.
- Red blood cells production: the kidneys produce erythropoietin, which plays a pivotal role in the production of red blood cells (RBC). It follows that, if the kidneys fail to work efficiently, the production of red blood cells will not be enough, and the person will suffer of anemia (low hemoglobin).
- To maintain healthy bones: in fact, kidneys maintain healthy and strong bones and teeth through the transformation of vitamin D into its active form. This fact allows the proper and correct absorption of elements like calcium from the food.

All these functions are carried by kidneys and for this reason it is important that they work in the right way. They play the role of regulators of many substances for every human being, and nobody can live healthily without any of them. A kidney disease or a kidney failure may have several negative consequences for the person. For this reason, it is crucial that the required actions are taken as soon as possible, in order to prevent more complicated problems, or, ultimately, to treat them promptly.

The branch of internal medicine that studies, treats and manages the kidney disease is called “nephrology”. The specialized doctors, called nephrologists, deal with the preservation of kidney health, the prevention, and the treatment of any related disease. The word “renal” refers to any aspect related to the kidney.

Symptoms of Kidney Diseases

The proper functioning of the kidneys is vital for the human being. If the kidney functions are not carried on properly, the life of the person will be negatively affected. Lerma et al. (2015) listed some of the most common ones:

- Excessive swelling of the face, abdomen, feet or even below the eyelids (the so-called periorbital edema). Obviously, excessive swelling may be caused by several factors, but it does not automatically imply kidney problems.
- Loss of appetite, abnormal taste, nausea, and vomiting. The last two are more common for severe kidney diseases.
- High blood pressure/Hypertensions: especially at young age these symptoms are important red flags to detect kidney problems and should not be ignored.
- Anemia and weakness: fatigue, concentration issues and face pallor are consequences of low hemoglobin level, which may be one of the first stages of kidneys diseases and possibly future failures.
- Nonspecific complaints such as body aches, itching, and leg cramps. During childhood, even the late or retarded growth may be a symptom.
- Several urinary complaints such as reduction in urine volume, burning sensation, uncommon high frequency of urination need and difficulties in the normal urination process are some of the main problems caused.

Factors that increase the risk of kidney diseases

Unfortunately, kidney diseases are very common, and everybody may be affected by them. Since the diseases have several possible causes, there is not a way to be completely sure to be able to prevent them. It has been proved that some subjects are more likely to suffer of kidneys diseases in comparison to others.

James et al. (2010) for instance, highlight the fact that people with diabetes, hypertension or cardiovascular diseases are more prone to have kidneys problems than people without these other concomitant illnesses. The presence of both diabetes and hypertension in the same person, amplifies not only the risk of suffering of kidney disease, but also the consequential complications that they would manifest (Erfanpoor et al. 2021). Hypertension is the second most common cause of kidney diseases (Kidney National Foundation, 2021). Moreover, people with a family history which presents kidney disease, diabetes or hypertension are more likely to develop problems although they do not present these illnesses. Other factors that increase the risk of kidney diseases are the tobacco consumption in high frequency and the regular intake of pain killer pills. Some factors related to the person influence the risk as well: for example, people suffering of obesity or elderly ones often present health problems that lead to an unproper functioning of these organs. Obesity is measured by the Body Mass Index (BMI) which is the result of the body weight divided by the square of heigh (in meters) of the person. BMI should be between 18,5 and 24,9; if the index is over 25, the person is considered overweight, while if it is over 30, the person is considered obese (World Health Organization, 2021). Furthermore, people with congenital defect of urinary tract tend to be more inclined to suffer kidney diseases (Lerma et al. 2015).

Recently, Xu et al. (2018) analyzed the possible linkage between pollution and kidney diseases. The idea behind the research is that kidneys are responsible for the filtration of toxins, also the environmental ones inhaled through the breath, and in polluted areas the concentration of toxins is higher. Therefore, the kidneys need to work more to filter them. The authors demonstrate how air pollution, heavy metal pollution, and industrial and agricultural chemicals increase the risk of kidney problems.

Diagnosis of Kidney Diseases

It is highly recommended to everyone to regularly undergo tests that can identify the potential risk of kidney diseases. It is vital to find them out as soon as possible to be able to treat them promptly. The National Kidney Foundation (NKF), based in the United States of America, identify three main tests to investigate the eventual presence of kidney diseases or any harbinger of them:

- Blood analysis: hypertensions represent both a possible cause and one of the consequences of kidney diseases. High blood pressure values are 140/90, which represent the values for systolic blood pressure (pressure of the blood during the heartbeats) and diastolic blood pressure (pressure of the heart in the resting time between heartbeats). Keeping the blood pressure under control is important to prevent kidney diseases. Moreover, the presence in the blood of creatine and urea, two by-products supposed to be removed by the kidneys, would indicate the abnormal functioning of the filtering process (Lerma et al., 2015).
- Urinalysis: through the analysis of a urine sample, it is possible to see the presence of protein, red blood cell, white blood cells and other substances. In particular, the presence

of proteins, called “proteinuria”, in the urine is a first sign that the there is a high risk of kidney diseases, especially in diabetic people. Several tests such as the “protein to creatinine ratio test” or the “albumin to creatinine ratio test” are available and useful to detect potential disfunctions.

- Glomerular Filtration Rate (GFR) outlines how efficiently the kidneys are removing the wastes from the blood; for this reason, it is maybe the most proper test to verify the correct functioning. The results are taken from a serum (or blood) creatinine test. The values depend also on personal factors such as age and gender, due to the fact that younger people tend to present higher values. Normally, a GFR is supposed to be over 60. Consequentially, below this threshold there is the concrete risk of kidney disease, while a GFR of 15 or lower may indicate the complete kidney failure.

Lerma et al. (2015) underline that there are other tests available to investigate the state of the kidneys. In fact, there a few radiological tests that can perform the function. Ultrasounds can detect the presence of cysts, stones or tumors that hinder their correct functioning. Other possible tests are X-ray of the abdomen, Intra Venous Urography (IVU) or voiding cystourethrogram (VCUG), which is used especially for children. Moreover, kidney biopsy, cystoscopy and urodynamics are specific tests needed for the diagnosis of particular kidney problems.

Glomerular Filtration Rate (GFR) and Chronic Kidney Disease (CKD)

Chronic Kidney Diseases (CKD) have been widely debated in the last decades and often the definition has been changed according to the most recent scientific discoveries. When the organ is structural damaged, it results in a chronic reduction of the efficiency of its functioning. Webster et al. (2017), according to the international guidelines, define the CKD as “condition as decreased kidney function shown by glomerular filtration rate (GFR) of less than 60 mL/min per 1,73 m2, or markers of kidney damage, or both, of at least 3 months duration, regardless of the underlying cause”. The GFR exactly measures the number of milliliters (mL) filtered every minute (min) per 1,73 squared meters (m2), which is the mean body surface for adults. Values should be adjusted based on the individual characteristics such as weight, height, and age (National Kidney Foundation, 2014). The lowest the GFR is, the worst are the kidneys working. Moreover, Webster et al. (2017) underline that it is five to ten times more likely for patients suffering CKD to pass away than to reach the end stage of kidney disease.

STAGES OF CHRONIC KIDNEY DISEASE		GFR*	% OF KIDNEY FUNCTION
Stage 1	Kidney damage with **normal** kidney function	90 or higher	90-100%
Stage 2	Kidney damage with **mild loss** of kidney function	89 to 60	89-60%
Stage 3a	**Mild to moderate** loss of kidney function	59 to 45	59-45%
Stage 3b	**Moderate to severe** loss of kidney function	44 to 30	44-30%
Stage 4	**Severe** loss of kidney function	29 to 15	29-15%
Stage 5	Kidney **failure**	Less than 15	Less than 15%

Figure 2: Stages of Chronic Kidney Disease.
Source: National Kidney Foundation (2021)

There are several stages to classify the chronic kidney diseases, depending on the GFR results and, consequentially, on the percentage of functioning of the organs. When the GFR is 90 or higher (stage 1 of chronic kidney disease), the organ in perfectly working. The lower the GFR is, the higher is the stage of the chart and consequentially the less is the organ performing. From stage 1 to stage 4 of CKD the organ is working, but the efficiency should be kept under control. When the GFR is lower than 15 mL/min per 1,73 m2, there is the kidney failure (identified with the stage 5 of chronic kidney disease).

Abu Jawdeh et al. (2014) state that more than 27 million people only in the United States, suffer from chronic kidney diseases. In year 2017, the cases of people suffering from chronic kidney diseases was around 700 million worldwide and the estimation is that 1,2 million people died for complications related to kidney problems (GBD Global Kidney Disease Collaboration, 2017).

Kidney Failure (KF), End-Stage Kidney Disease (ESKD) or End-Stage Renal Disease (ESRD)

When an extreme low level has been reached, there is a kidney failure. Kidney Failure (KF), End-Stage Kidney Disease (ESKD) or End-Stage Renal Disease (ESRD) is the last stage of a chronic kidney disease, in which the GFR is lower than 15 mL/min per 1,73 m2. In this case, the kidney is unable to fulfill the minimum required task for a long-term life (Webster et al., 2017). In this case, it is essential to have clear the situation and to proceed to the possible solutions, since doing nothing would probably determine the death of the patient. Kidneys in fact, are vital organs for the human beings.

Kidney failure is becoming always more common: only in the United States, in 1985 the number of treated patients was 113.000, in 1995 it was 287.000 and in 2005 the number was around 500.000 treated patients (Coresh et al., 2008). These numbers may depend also on the fact that the medicine is improving year by year and nowadays it is easier to detect a problem that in the past may have stayed hidden for longer time or even never been found out. Other factors, like the higher level of pollutions (Xu et al., 2018), have been taken into consideration as explanation for the increasing trend.

Daugirdas et al. (2015) consider severe stages both stages 4 and 5 for CKD. Even if the kidney is currently in stage 4, where the GFR is lower than 30 mL/min per 1,73 m2, the patient should be taken into nephrologist care. According to their research, the filtering capacity at this stage is considered not sufficient and it is just a matter of time before it deteriorates even more, reaching worrying values of GFR.

Once that the failure of the kidney has been detected, it is important to know how to proceed. There are three main Renal Replace Therapies (RRT): hemodialysis (HD), peritoneal dialysis (PD) and renal transplantation (RT) (Mazzucchi et al., 2000). The alternatives have different characteristics, with both positive and negative sides, and should be carefully analyzed before choosing. The analysis should take into consideration several factors, especially the one regarding the health of the patient that may lead to one specific choice.

Abu Jawdeh et al. (2014) state that more than half a million people only in the United States, suffer from end-stage kidney diseases and need a kidney replacement.

Dialysis

Dialysis is a procedure used to perform the tasks that a failed kidney cannot perform anymore by itself. When there is a kidney failure, the dialysis is needed to remove the waste products and filter the fluids from the blood. This process is usually carried on by some high-specialized machineries. Without the dialysis, the unwanted substance would continue to stay in the body, and this would not allow a correct continuation of the normal life causing severe symptoms that hinder the correct functions of the body.

The duration of the treatment is not stated: in some cases, the dialysis is needed when the kidneys are temporarily unable to work in a proper way, while in other cases it is required to be done constantly and for the rest of the life. Dialysis is not an optimal or a final solution, which is represented by the kidney transplantation, but it is often used as a complementary praxis for the organ replacement. When a patient needs a transplantation, not always a compatible donor with a compatible organ is available: in this case, the dialysis is necessary in the meanwhile. Moreover, if kidney transplantation is not possible due to several reason, for instance the incompatibility or the impossibility to find a suitable donor or the poor health conditions that would lead to a too risky operation, dialysis is needed for the rest of the life of the patient (National Health Service, 2021). The number of people needing dialysis is continuously increasing (Hsu et al., 2013).

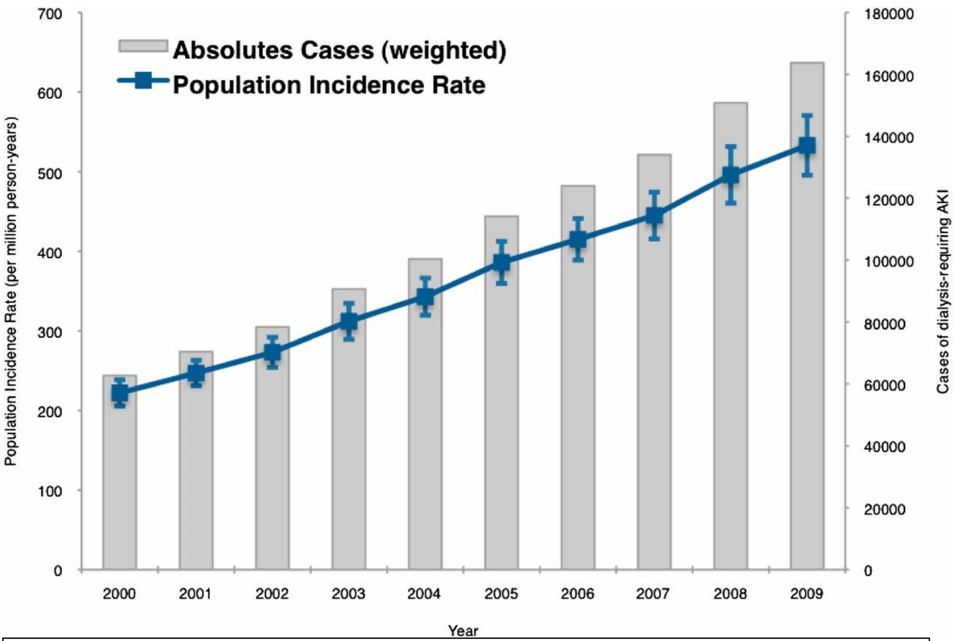

Figure 3: Temporal Changes in Incidence of Dialysis 2000-2009.
Source: Hsu et al. (2013).

There are two main types of dialysis: hemodialysis (HD) and peritoneal dialysis (PT). Mazzucchi et al. (2000) underline how there are contrasting opinion about the best option. According to several research, the best option is not common, but hinges on the single patient according to several factors such as age, general health condition, presence of other diseases etc. According to the authors, patients that undergo hemodialysis have a higher rate of success in the first year, while patients that underwent peritoneal dialysis seem to have higher survival percentages and better life conditions in the long term. Karopadi et al. (2013) states that "it is not unreasonable to consider hemodialysis and peritoneal dialysis as clinically equivalent modalities" for treating end-stages renal diseases.

The costs for dialysis are extremely high. It is often difficult to bear them even for developed countries, while for the emerging ones they represent an almost insurmountable obstacle for most of the people: in fact, the great majority of the people either pass away or give up the treatment after three months because of the unbearable expenses that the dialysis process requires (Garcia Garcia et al. 2012).

Hemodialysis

The hemodialysis the most used one (National Health Service, 2021). In this process, people receive the treatment through a tube attached to a needle in the arm. The aim of this tool is to extract the blood, to purify it, to filter it and remove the pernicious and unwanted wasted before passing the blood back to the patient.

The National Health Service (2021) explain the required time for a successful hemodialysis process. At a specialized center, there is the need of three session of four hours each one to obtain a satisfactory result.

There is also the option to carry on the hemodialysis at home, with different frequency and last of the sessions (Mazzucchi et al., 2000). The National Health Service (2021) indicates the most popular schedules for the home hemodialysis: 4 days a week for 4 hours, 5 days a week for 3 hours or 6 days a week for 8 hours, usually carried overnight. The decision about the frequency should be carefully taken by the nephrologists according to the damages of the kidneys and the general health conditions of the patient.

Peritoneal Dialysis

Between the two dialysis options, the peritoneal one is probably the less popular one, although the results are almost the same as the hemodialysis. Peritoneal dialysis does not use external machineries but utilizes the lining inside the abdomen as a filter. Some weeks before the beginning of the therapy, it is necessarily required an intervention aimed at inserting a medical tool called "catheter", which is a soft tube that can perform several activities essential for a successful outcome of the medical treatment (National Institute of Diabetes and Digestive and Kidney Diseases, 2021). The therapy can also be done at home, but it is more common that it

takes place in hospitals. In this case, it is called Continuous Ambulatory Peritoneal Dialysis, whose acronym is CAPD (Baboolal et al., 2008).
There is a fluid, called "dialysis solution", that must be connected with the catheter with a tube. It contains water with salt and other additives (for instance: sodium, chloride, calcium, magnesium, and others). The catheter allows the interchange of fluids, purifying the body ones. In this way, the unwanted substances are removed artificially since the kidneys are not able to do anymore. This process lasts usually 30 to 40 minutes and must be repeated 3 or 4 times a day or can be done by a machine overnight (National Health Service, 2021). It is less invasive in comparison to hemodialysis since it allows the patient to go to work or go to school counting on the self-management of the patient (Jain et al., 2019).
Gokal and Mallick (1999) list the advantages and disadvantages of this therapy, in comparison to hemodialysis. Some of the advantages are related to the fact that there is not the need of complex machineries, it is easier to do and can be done in different places, allows a more liberal diet and, in average, it is cheaper. Some of the disadvantages are a higher risk of infections or complications, the psychological aversion that people have towards the use of tools like the catheter and the higher frequency of the therapy, that may disturb the daily routine of the patients, causing anxiety especially in the elderly people.

Average cost for peritoneal dialysis and hemodialysis around the world

Identifying an average cost for the dialysis is a complex task because of the enormous difference among the countries worldwide. Karopadi et al. (2013) analyze the costs of these practices collecting the data of 78 articles and research from 46 countries divided into six regions: North America, Latin America, Asia and Middle East, Africa, Europe, and Pacific area. In detail, the countries taken into consideration were 20 developed and 26 developing. There are several results that are worth to be underlined.
In 2008, 1,75 million people around the world underwent dialysis. The 89% (1,55 million) were on hemodialysis and the remaining 11% (197.000) were on peritoneal dialysis. It is interesting to notice the difference of therapy applied in the two categories of nations. In fact, out of 197.000 patients around the world receiving the peritoneal dialysis treatment, the 59% was in developing countries and the 41% in developed ones. On the other side, out of the 1,55 million patients receiving the hemodialysis, only 38% was in developing countries, while the remaining 62% was in developed ones (Karopadi et al., 2013).

The authors create a range of ratios for the costs of hemodialysis and peritoneal dialysis in the studied countries. Considering the rate “cost hemodialysis (HD) compared to cost of peritoneal dialysis (PD)”, they categorize the countries in three groups according to the results:

- In 22 countries (17 developed and 5 developing) the cost of HD compared to the cost of PD is between 1,25 and 2,35. The highest ratio has been recorded in Hong Kong, which is exactly 2,35.
- In 15 countries (2 developed and 13 developing) the cost of HD compared to the cost of PD is between 0,90 and 1,25. There are four countries (Argentina, Colombia, Germany, and Vietnam) that have a ratio equal to 1,00 that means that the cost for hemodialysis and peritoneal dialysis are the same.
- In 9 countries (1 developed and 8 developing) the cost of HD compared to the cost of PD is between 0,22 and 0,90. The lowest ration has been recorded in Egypt, which is exactly 0,22.

The conclusion is that developed countries can guarantee the peritoneal dialysis with lower expenses in comparison to the hemodialysis (Karopadi et al., 2013). Anyway, there are several exceptions in many countries.

In India, the costs are very different based on where the therapies are done, either at government hospitals (150 rupees) or corporate hospitals (up to 2.000 rupees). The yearly average cost is 40.000 rupees, equivalent to $3.000. Compared to the average annual cost of $60.000 in the US and UK, the therapy is very cheap, but anyway more than 90% of Indians could not afford it (Khanna, 2009). In Pakistan the average cost for a patient for an annual treatment of dialysis is between $4.000 and $4.668 (Shekhani and Lanewala, 2021).

In France, the average yearly cost for a continuous ambulatory peritoneal dialysis (CAPD), which is the most expensive option, is €50.000 and for a hemodialysis is up to €81.5000. Anyway, there are cheaper option like proceeding with the dialysis at home. Only in year 2005, the total cost related to the dialysis procedures for the Health Insurance is estimated around 2,1 billion euros (Benain et al., 2007).

In the Canadian region of Manitoba, the average annual cost for peritoneal dialysis is around $38.500 and for hemodialysis varies from $39.000 for home therapy to $64.000 for in-center therapy (Beaudry et al, 2018).

In Tanzania, it has been calculated that the average cost for a hemodialysis session is $176. Considering three sessions per week (156 dialyses per year), the average annual cost for the hemodialysis is around $27.440 (Mushi et al., 2015).

In the United Kingdom, the average annual cost for continuous ambulatory peritoneal dialysis is £21.655 (corresponding to approximately $29.500) and for the hemodialysis is £35.023 (corresponding to approximately $47.700) (Baboolal et al., 2008).

Average cost for peritoneal dialysis and hemodialysis in Italy

Trying to quantify the direct and indirect costs of dialysis in Italy is a fundamental step towards the comprehension of the extremely high expenses that must be borne in these medical practices. Although, the exact costs may vary from one transplantation center to the other, having an average is a useful starting point.

Collecting data from 9 transplantation centers around Italy in a period that varies from three to four years, the average cost of a non-transplanted patients is €123.081. Out of this sum, €109.923 is only the direct dialysis cost. To them, the indirect costs (hospitalization costs, pharmacological therapies, other additional medical therapies) need to be added to have a full picture of the situation (Censis, 2013).

Santoro (2016) quantifies the average annual direct costs of dialysis in Italy: for the peritoneal dialysis the average cost is €29.000, while for the hemodialysis the cost raises up to €43.800. The author underlines that several indirect costs are left out and that, in order to understand deeply the expenses, they need to be calculated as well. The costs are not just related to physical items, but also the psychological situation of the patients and of their families.

Kidney Transplantation (KT) or Renal Transplantation (RT)

The kidneys are the most transplanted organ worldwide in year 2021 (Statista, 2021). The John Hopkins Medicine (2021) defines the kidney transplantation as a "surgery done to replace a diseased kidney with a healthy kidney from a donor". This specific operation can take place thanks to a donation from a living donor or from a deceased donor (Axelrod et al., 2018; Rudge et al., 2012; Shepherd et al., 2014; Nicolò and Rodriguez-Alvarez, 2012).

The kidney transplantation (KT) or renal transplantation (RT) is the optimal solution for end-stages kidney diseases and kidney failures (Mazzucchi et al. 2000; Garcia Garcia et al. 2012; Axelrod et al., 2018; Stel et al., 2012; Abu Jawdeh et al., 2014; Roth et al., 2004; Gentry et al., 2017; Kher and Kumar Jha, 2020; Genie et al., 2020).

In comparison to both hemodialysis and peritoneal dialysis, the replacement of the kidney is a better solution in term of percentage of graft reject and mortality rate both in the short term and in the long term. Abu Jawdeh et al. (2014) insist on the fact that the kidney transplantation, in comparison to the chronic dialysis, offers both a better quality of life and a higher rate of survival for the patient.

No longer than fifty years ago, the transplantation was still considered risky and experimental. Nowadays, thanks to the great efforts made by the medicine in the last decades, this practice has become common. Transplantations are always more frequent for all the people in all the countries. USA, China, Brazil, and India are the ones in which the highest number of interventions are done.

There are two main types of transplantation: deceased donor kidney transplantation (DDKT) and living donor kidney transplantation (LDKT). A transplantation from a living donor is the optimal option, ceteris paribus (Axelrod et al., 2018; Vinson et al., 2021).

Finding a compatible donor is always challenging due to the several specific conditions that the kidney needs to satisfy in order to work properly in the recipient body. Unfortunately, the search process requires a lot of time, and this fact negatively affects the health of the patient. The timing plays a pivotal role, and it is recommended to proceed with the intervention as soon as possible. For this reason, it often happens that a relative, a close friend or the partner of the patient offers their own organ for the transplantation.

It is crucial to underline that not all the organs are the same and even if the donor is part of the family of the recipient, it is not sure that the kidney can properly fit. If the transplantation is not possible, the patient is still supposed to undergo the dialysis process waiting for a compatible organ. Consequentially, the waiting time is not negative factor only by the health point of view, but it is also very expensive.

Many people are reluctant to offer their organs for the transplantation for several reason. One of the most relevant ones, is the fact that they are afraid that in future they may suffer the same problem, but they will not be able to find somebody prone to donate the organ to help them. Cozzi et al. (2016) define “unavoidable” the reduction of kidney functions after the donation of a kidney by a living donor.

Kidneys can be transplanted also by deceased donors (Axelrod et al., 2018; Gjertson and Decka, 2000; Vinson et al., 2021). In order to receive a compatible kidney, in many countries there is a waiting list in which people should be registered. What people need to do is to make clear their willingness to donate their own organs in case of death. After the death of a potential donor, the organs, if healthy and well-functioning, can be used to replace others that stopped to work how they were supposed to do. In this way, the donated kidneys may save the life of other two patients in the waiting list, although they are completely strangers to the deceased donor. The same donation process can be applied to the other organs such as liver, heart, lungs and even pancreas and intestine.

History of kidney transplantation

The first attempt of kidney transplantation has taken place in Ukraine in 1933. Unfortunately, it did not work, and the patient died after a couple of days. The kidney was harvested by a deceased donor. The first attempt of transplantation from a living donor took place in France in 1952, but unfortunately, once again, the operation failed, the kidney was rejected and the patient departed few days later (Hatzinger et al., 2016).

The first successful transplant took place in 1954. The donor and the recipient were two homozygotic twin brothers with the same blood type. The operation lasted more than 3 and a half hours and the kidney worked properly until the natural death of the patient, caused by a heart attack, 8 years later. Joseph Murray, the surgeon who operated the patient, was awarded, jointly with his colleague Donnal Thomas, with the Nobel Prize in Physiology and Medicine in year 1990 "for their discoveries concerning organ and cell transplantation in the treatment of human disease" (Hatzinger et al., 2016).

In year 1962 another milestone for modern science has been reached. In this year, the first successful transplantation between two non-related people took place (Hatzinger et al., 2016). This fact changed the perception of transplants enlarging the pool of possible donors for every patient. If only the relatives could have been able to donate, the possible options would have been extremely limited in several cases. This discovery opened for many possibilities making possible also the kidney exchange programs.

In 1987, in Japan, was performed the first successful kidney transplantation between a donor and a recipient with a different blood type. Nowadays, this procedure represents the 14% of the total transplantations in Japan, although it is not considered the optimal choice and, for this reason, is not very common in other countries (Axelrod et al., 2016).

Numbers of kidney transplantation in the world

Worldwide the number of transplantations is constantly increasing for several reasons: better knowledge of the procedure, enlargement of the target population, decreasing costs of the operations, higher awareness of the problems that leads to more frequent kidney check-up and the detection of diseases. Nowadays it is possible to intervene in advance, being able to detect the problem before it becomes unsolvable. The prevention is one of the best tools for the chronic kidney diseases.

The Scientific Registry of Transplant Recipients (2021) in the annual report of 2019 shows the increasing trend of this specific medical surgery. In fact, in year 2019 the highest number of transplantations has been reached: 24.273. This number should not surprise: it is the result of the increasing trend of the last decade.

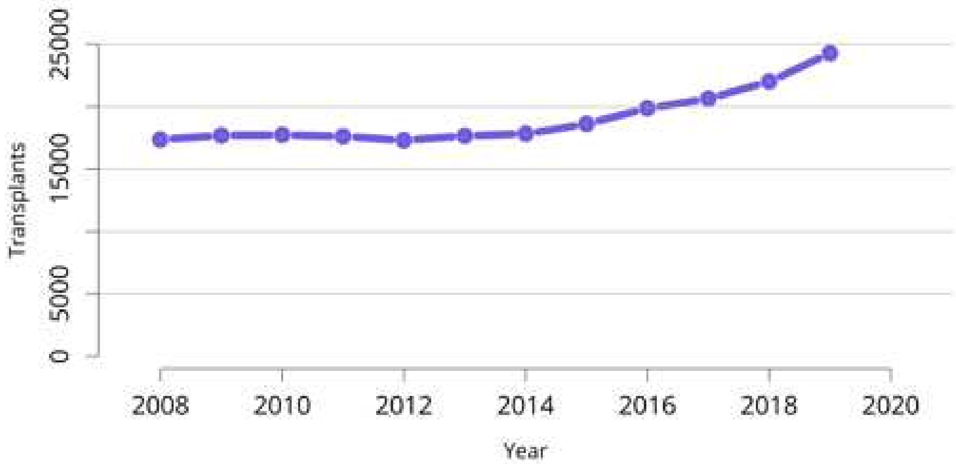

Figure 4: Annual Count of Kidney Transplantations Worldwide. Source: Scientific Registry of Transplant Recipients (2021).

In year 2020, the number was expected to decrease due to the Covid-19 pandemic that required a major effort by the medical staff in limiting the devastating effects of the virus. This fact has affected the number of transplantations performed in the whole world (not only the ones regarding the kidneys). The expectations have been confirmed by the Health Resources and Service Administration (2021). In their annual report, they show how all the types of transplants have decreased. In detail, the number of kidney transplantation is 22.817, which correspond to a reduction of almost 6% (there have been 1456 transplantations less). Obviously, the most urgent cases have been treated and the transplantation performed, but by a general point of view, the number has decreased.

Numbers of kidney transplantation in Italy

Italy, as in the rest of the world, has recorded an increasing trend of transplantation in the last decades due to an increased awareness of the kidney issues. As for the rest of the world, it is important to keep in mind that year 2020 has been heavily influenced by the catastrophic effects of the Covid-19 pandemic.

According to the Italian Health Ministry (2021), the kidney transplantations performed in 2018 have been 2124, while in 2019 have been 2137 (+0,6% increase rate). The data take into consideration both the transplantation from living donor and from deceased donor. In year 2020, due to the mentioned reasons, the number of transplantations has recorded a strong reduction: the number of transplantations in all the country is 1907 (CaricaVitale, 2021). This data shows a decrease rate of 10,8%, which is a further proof of how badly has impacted the Covid-19 also on aspects not directly related with the pandemic itself.

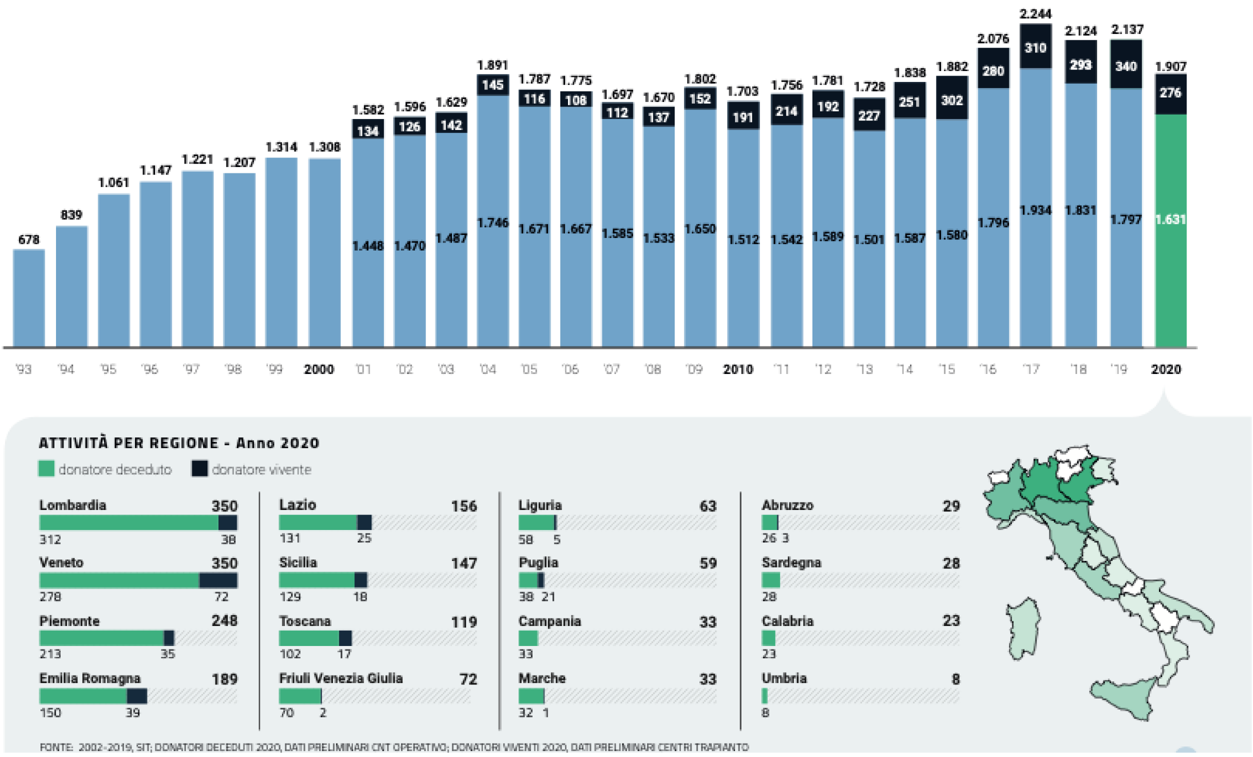

Figure 5: Kidney Transplantations in Italy.
Source: Centro Nazionale Trapianti (2021).

In the first registered year, which is 1993, only 678 kidney transplantations were performed. The increasing trend is strongly positive. The first kidney transplantation surgery with a living donor takes place in 2001. In this year, the total number of kidney transplantation is 1582: 134 from living donors and 1448 from deceased donors. The percentage of operations from living donors in year 2001 is around 8,5%, while in year 2019 is 15,9% (and in year 2020 is 14,5%). This change is fundamental to understand how important is becoming the transplantation from living donors.

In total, in 16 regions there have been a kidney transplantation in year 2020. Lombardia and Veneto are the regions in which have been performed the highest number of kidney transplantation. Jointly, the two mentioned regions have performed more than one-third of the total number of kidney transplantations. To be precise, Lombardia has the highest number of transplantations from deceased donors, while Veneto is the region with the highest number of transplantations from living donors. Four regions (Campania, Sardegna, Calabria, and Umbria) have performed kidney transplantations only from deceased donors and not from living ones (Centro Nazionale Trapianti, 2021).

Another positive aspect is the reduction of the time spent in the waiting list by the patient before obtaining a compatible kidney. The aim is to reduce the waiting time as much as possible to order to furnish the patient a compatible organ as soon as possible in order to guarantee to them a better life condition, but it has also an economical reason: dialysis is expensive and cutting this cost would be a considerable saving. In comparison to year 2002, in the year 2019 it has been recorded a marked reduction of the waiting time for a kidney transplant in Italy: in fact, the average waiting time for a patient was 32 months, while in 2019 it was 26, with an average reduction of 6 months (18,75% of reduction on the previous average waiting time) (CaricaVitale, 2021).

In the ranking of the best medical centers for the transplantations, the Health Ministry (2021) identifies Torino, in Piedmont, Bologna, in Emilia-Romagna, and Padua, in Veneto, as the best ones. In detail, Padua is considered one of the most one advanced kidney transplantation centers in Italy. In fact, the Padua hospital has performed the highest number of kidney transplantations in year 2019, followed by the ones in Torino, Verona, Bologna and Rome (Associazione Nazionale Trapianti di Rene, 2021).

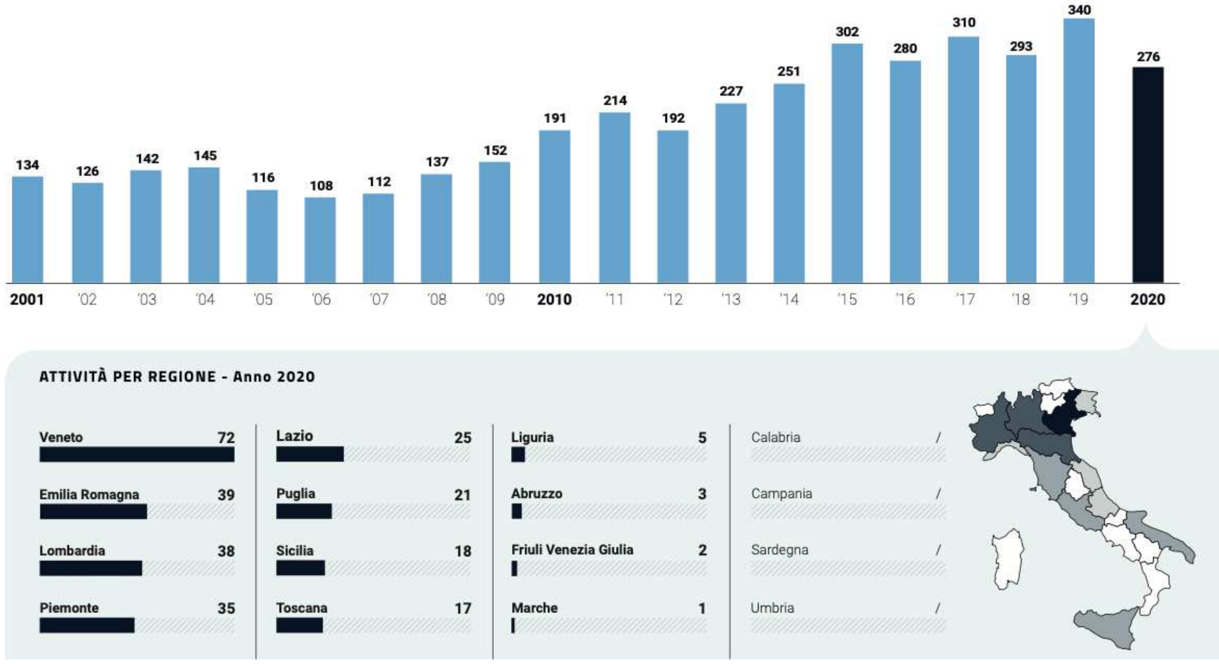

Figure 6: Kidney Transplantations from Living Donor in Italy.
Source: Centro Nazionale Trapianti (2021).

The number of kidney transplantations performed from living donor in Italy in year 2019 is 340 (Centro Nazionale Trapianti, 2021). In the following year, due to the well-known effects of the pandemic, the number decreased to 276, which is a reduction of 64 operation, almost the 19% less. Out of 20 Italian regions, in 12 of them there has been at least one kidney transplant from living donor. Veneto, the region in which Padua is located, has been the most active one in year 2019 with 72 transplants from living donors, followed by Emilia Romagna (39), Lombardia (38) and Piedmont (35).

The number of people needing a kidney transplantation is constantly increasing and, currently, 6732 patients are on the waiting lists for a kidney. Moreover, more than 2500 have been waiting for more than 3 years (Genie et al., 2020).

Kidney Exchange Programs

Transplantations from Living Donor

The transplantations can be performed either through a deceased donor kidney (DKK) or through a living donor kidney (LDK). In the last decades, thanks to the great improvements of the medicine, it has been possible to increase the number of kidney transplantation from living donors, which represent the optimal option (Axelrod et al., 2018; Vinson et al., 2021). Delmonico et al. (2004) underline how important has been the contribution of the living donor to the increase of successful transplantations. Worldwide, the number of performed transplantations thanks to the organ donation from living donors is more than 27.000, which result in around the 40% of the total patients (Cozzi et al., 2016; Rehse et al., 2019).

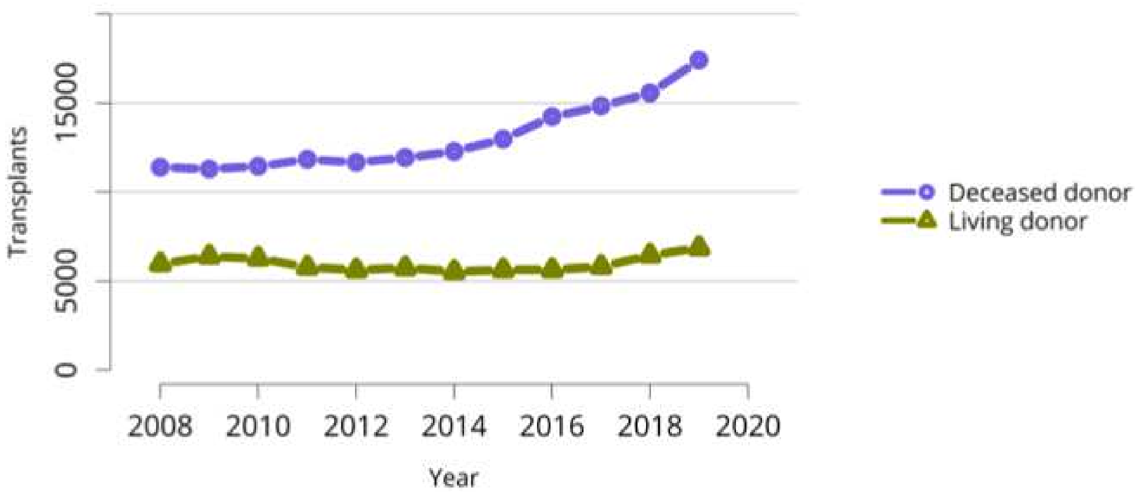

Figure 7: Annual Count of Kidney Transplantations from Living and Deceased Donors Worldwide.
Source: Scientific Registry of Transplant Recipients (2021).

Although the number of transplantations has increased drastically in the last years, there is much more to do. More transplantations are needed in order to reduce the waiting time and assure to the people a better life condition. Gjertson and Decka (2000) analyzed that between 1987 and 1998 most of the living donors were related to the recipient. Unfortunately, it is not always true that the organ of a spouse, of a friend or of a relative is compatible to the recipient. The medical literature defines “a patient and a donor compatible if they are both group and tissue type compatible” (Andersson and Kratz, 2020).

Non-related donors should be encouraged to donate their organ: up to the 15% of patients in the waiting list for a kidney from a deceased donor may be transplanted in this way, reducing the waiting time for the others (Gjertson and Decka, 2000). This situation is still valid nowadays with the need of promoting the organ donation.
It is essential to underline another category of willing donors. There are, in fact, donors that would like to donate their organs, but they are not compatible to the needing person. Some characteristics must be respected in order to furnish a working kidney to the recipient. First of all, the donor/recipient weight ratio should be as near as possible to the value 1 (this value would indicate that both the people weight the same). For instance, if the donor is a person with a weight of 50 kilograms will be more difficult for the kidney to be able to perform the required functions for a person of 120 kilograms. The problem would be the same also in the opposite condition since in both cases the dimensions of the kidney would be slightly different. There are other factors that may determine the incompatibility. The main ones are ABO blood type incompatibility and HLA incompatibility (Delmonico et al., 2004).
In detail, these two main incompatibilities regard the blood types and the tissue type or Human Leucocyte Antigen (HLA) sensitization (LUMC Transplantatie Centrum, 2021; Montgomery et al., 2005).
In fact, the living donors should be selected also based on their blood type, which has to be compatible with the recipients' one. If this does not happen, the risk of organ rejection is extremely high, and it definitely would not represent an optimal option for the transplantation. (John Hopkins Medicine, 2021). The transplantation performed with the presence of a blood type incompatibility is defined "ABO incompatibility" or "ABOi".
Dean (2005) underline how important is the blood type for the transfusion and for the transplants. The four main blood types are: A, B, O, and AB. This discover made by the Austrian scientist Karl Landsteiner earned him the Nobel Prize in Physiology and Medicine in year 1930. The genes that determine the blood type of a person are inherited by the parents.
Moreover, each of these four blood types can be either positive or negative resulting in a total of 8 possible blood groups. Usually, red blood cells present a protein called RhD, whose presence determines the positivity or negativity of the blood type. If this is present, the blood group is RhD positive. If it is absent, the blood group is RhD negative (National Health Service, 2021). Consequentially, the eight blood groups are:

- A RhD positive (A+)
- A RhD negative (A-)
- B RhD positive (B+)
- B RhD negative (B-)

- O RhD positive (O+)
- O RhD negative (O-)
- AB RhD positive (AB+)
- AB RhD negative (AB-)

ABO genotype in the offspring		ABO alleles inherited from the mother		
		A	B	O
ABO alleles inherited from the father	A	A	AB	A
	B	AB	B	B
	O	A	B	O

Figure 8: The ABO Blood Types.
Source: Dean (2005).

Worldwide, the most common blood group is the blood group O, with a percentage that varies for every population, while the less common on is AB (Dean, 2005). The National Health Service (2021) point out the fact that 85% of the UK population is RhD positive (the red blood cells present the RhD protein). These percentages are consistent with the general percentages worldwide.

The blood transplantations follow the same rules of the organ transplantations: in fact, not every blood type can donate or receive an organ from another blood type (LUMC Transplantatie Centrum, 2021). Every blood type can donate to (and consequentially receive from) the same blood type. Anyway, there are some exceptions to this general rule. In fact, the blood type AB is considered "universal recipient" since it can receive blood and organs from every blood type (A, B, AB, and O), while the blood type O is called "universal donor" since it can donate to every blood type (obviously including the type O itself).

RECIPIENT BLOOD TYPE	DONOR BLOOD TYPE			
	A	B	AB	O
A	✓	✗	✗	✓
B	✗	✓	✗	✓
AB	✓	✓	✓	✓
O	✗	✗	✗	✓

Figure 9: The ABO Donor/Recipient Scheme.
Source: LUMC Transplantatie Centrum, (2021).

Nowadays, thanks to the enormous medical progresses, it is possible to perform transplantation between people from different blood groups. In case of initial incompatibility, there is the option of undergoing an immunosuppressive treatment (Andersson and Kratz, 2020). These treatments aim at lowering the activity of the immune system and has the positive side effect of reducing the risk or organ rejection.

Moreover, it is fundamental to consider the tissue type of the donor as well. It is represented by the Human Leucocyte Antigen (HLA) antibodies, which are considered the most problematic factor for every organ transplantation (LUMC Transplantatie Centrum, 2021). In fact, they represent the main cause for rejection, that may happen even months or years after the transplantation. Basically, they are responsible for the proteins that regulate the immune system (Krishnan et al., 2012). Human Leucocyte Antigen are, consequentially, also a fundamental factor to keep under control for kidney transplantation (Furian et al., 2020). There are several types of HLA, and they have different role: Kosmoliaptis et al. (2014) identify six main types: HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DRB3/4/5, and HLA-DQ. If they differ from the donor to the recipient, there is a risk of rejection, which increase with the number of mismatches. Logically, it is better to find a donor without any mismatch. The authors also underline the fact that, in average, the rejection happens more than 12 months after the first operation. This fact will lead to the need of re-listing of the patient in the waiting list for repeat transplantation.

HLA incompatibly represent a severer risk of graft rejection in comparison to ABO incompatibility (Ko et al., 2017). Kidney exchange programs should consider this fact.

Costs of Transplantations

As mentioned before, the correct allocation of kidney should take into consideration several factors that determine the compatibility and assist in the improvement of the expected outcome for the transplantations. This concern is fundamental for the health of the patients, but also for the related economic costs.

It is essential to take into consideration the economic costs in order to be aware of all the conditions to choose properly. In fact, transplanting two incompatible people is much more expensive than transplanting compatibles ones. Axelrod et al. (2016) estimate an average overall for ABO incompatible couples of \$65.080, while for ABO compatible couples of \$32.039. This huge difference, which is almost half of the total, does not include the expenses for the acquisition of the kidney.

The authors identify a third category of recipients: the A2 incompatibles. In detail, the blood group A has two sub-groups: A1 and A2. A1 represents the majority, while A2 represent a minority. Moreover, since there are other subgroups in the AB blood type: the A1B and the A2B (Giriyan et al. 2017).

Axelord et al. (2016) analyze the cost of the categories including the pre-transplant costs (in which are included the dialysis costs), the transplant event costs, and the post-transplant costs (in which are included the costs for a graft failure). The graph shows the costs for the transplantation and the for the first three years after. In every aspect, the ABOi transplantations result to be more expensive than the ABOc ones. In both cases, the average annual costs decrease year by year.

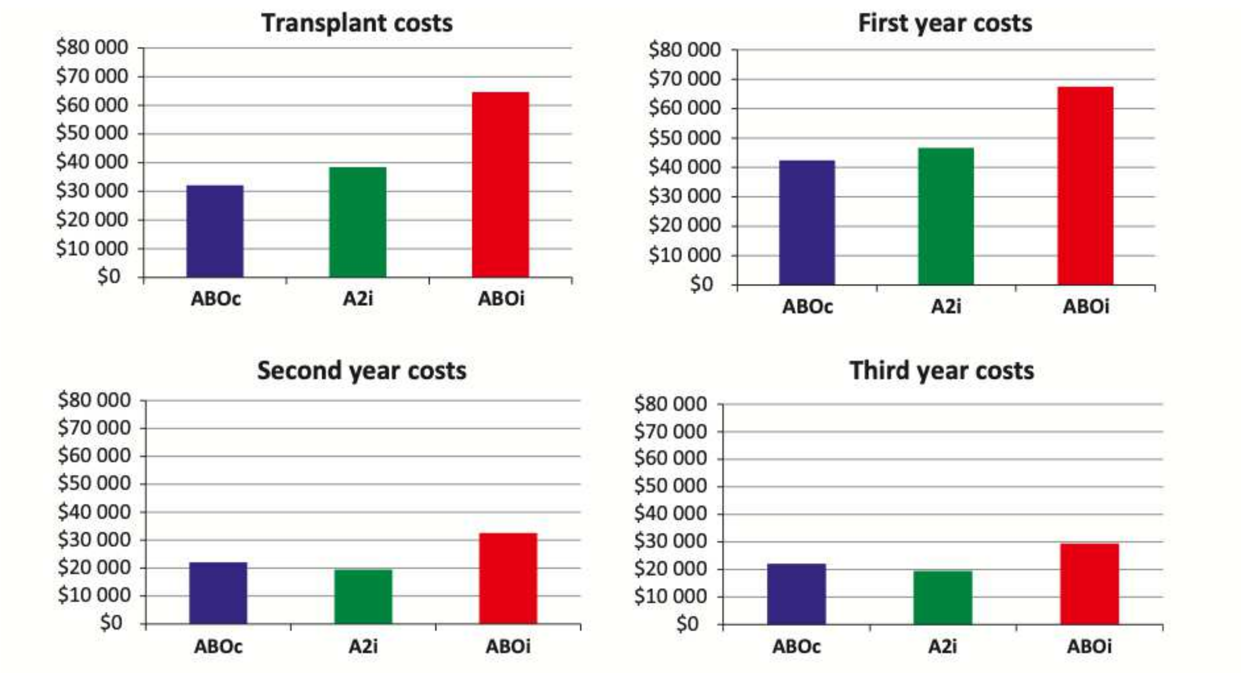

Figure 10: Average Transplantation Costs for ABOc and ABOi.
Source: Axelord et al. (2016).

The desensitization protocol

It has already been stated that the transplantation from living donor, ceteris paribus, represent the possible solution for a kidney transplant (Axelrod et al., 2018; Vinson et al., 2021). Unfortunately, the availability of compatible organs cannot be guaranteed, and the risk of shortage is concrete. The shortage of organs from deceased donors is another problem to take into consideration. For this reason, there have been several initiatives with the aim of enlarging the pool of possible donors (Saidi and Hejazii Kenari, 2014).

The transplantation between incompatible people is not impossible anymore, but logically it is still not the best option. In the last decades, the transplantation between people that were considered “incompatible” have become possible thanks to specific processes. Through the “desensitization protocols”, it is possible to transplant between HLA incompatible people (Marfo et al., 2011). Marfo et al. (2011) show how the results for this specific kind of transplantations are satisfactory: in fact, the patient and the graft survival rate were, respectively, 95% and 86%. These data are based on 21 different studies between year 2000 and year 2010 with a sample of 725 patients. Through the desensitization protocols, the antibodies responsible for the HLA antigens incompatibility are removed and the production of the new ones is inhibited, enabling the transplantation. Some of these protocols also need the use of a practice called “plasmapheresis” (PP) (“apheresis” is the Greek word for “withdrawal”). This procedure is used to separate the plasma from the blood cells, which then return to the body (Reimann and Mason, 2000).

Other desensitization procedures are immunoadsorption (IA), intravenous immunoglobulins (IVIg), and rituximab (Abu Jawdeh et al., 2014):

- Schwenger and Morath (2010) underline the fact that immunoadsorption (IA) is becoming a very common practice for kidney transplantation, both for ABO incompatible and HLA incompatible patients. In comparison to plasmapheresis, this method allows a more effective clearance of circulating immunoglobins.
- Glotz et al. (2002) retain that the intravenous immunoglobulins (IVIg) protocol is an efficient strategy to enable the transplantation between HLA incompatible people. Although the transplant has been performed in the first few weeks after the treatment, only 1 patient out of 13 has presented the organ rejection. Although the sample is not large, the number are in line with the other desensitization procedures.
- Barnett et al. (2013) state that, nowadays, rituximab is widespread in the ABO blood group incompatible organ transplantation. This medicine, that is supposed to be taken in multiple doses, can also be used for HLA antibody incompatibility and the evidence has shown that it is a useful tool in the prevention of rejection.

Marfo et al. (2011) state that, in average, the cost for a transplantion that needs a desensitization protocol is around 21.000$ higher than a compatible transplant (that does not need any desensitization treatment). Moreover, if there is the need of plasmapheresis to complete the protocol, the average cost would rise of around $10.000.

It is important to remember that without these operations, the patients would have stayed for an indefinite time in dialysis and the cost to bear may be even much higher. The dialysis costs are difficult to identify because there are different types of dialysis and the costs for them can be estimated on a yearly base, but it is not possible to know how many years this medical treatment will be needed.

The Living Kidney Donor Profile Index (LKDPI)

LKD is the acronym for Living Kidney Donation, which represent an increasing percentage of the total transplantation activity (Claisse et al., 2020). The alternative is using a Deceased Donor Kidney (DDK) (Rehse et al., 2019). Ceteris paribus, a kidney from a living donor is preferable in comparison to a kidney from a deceased donor (Axelrod et al., 2018; Vinson et al., 2021). In reality, finding two kidneys that have exact the same characteristics is extremely unlikely. The questions that follow are: when is it better one kidney in comparison to another one? Would it be better to choose a kidney from a living donor although it presents some mismatches? Eventually, which and how many mismatches would be accepted to proceed with the transplant operation? Those question marks are difficult to answer without a "unit of measurement" for the expected quality of the transplant. The need of a common way to try to predict the outcome became a priority in the last years.

Massie et al. (2016) propose an index that assists in the clinical decision-making process between kidney with a different expected quality for the transplant. The Living Kidney Donor Profile Index (LKDPI) is the ideated tool to be able to sort out the doubts regarding the kidney that better fits for a transplantation, choosing the better fitting kidney from living donors. It is a useful to predict the risk of total graft failure. Jackson and Segev (2021) insist on the importance of the measurement of the Living Kidney Donor Profile Index as a tool that allows the enlargement of the pool of people participating to the kidney exchange programs. This fact would happen as a consequence of the better understanding, sustained by concrete numbers, that the people would have of the exchange programs.

The metrics used to determine the LKDPI are donor age, sex, estimated glomerular filtration rate (eGFR), systolic blood pressure, Body Mass Index (BMI), race, history of cigarette use, recipient sex, biological relationship between donor and recipient, ABO compatibility between donor and recipient, donor/recipient weight ratio, and donor/recipient HLA-B and HLA-DR mismatches (Shantier et al., 2020).

$$\log(h(t)\text{-}\log(h_0(t)) + \beta_1 KDPI * (1 - I[LDKT]) + \beta_2 I[LDKT] + \sum_{i=1}^{n} \beta_{i+2} L_i + \sum_{j=1}^{m} \beta_{j+n+2} C_j$$

Figure 11: Calculation of the Living Kidney Donor Profile Index. Source: Massie et al. (2016).

The range of the LKDPI measurement varies from -100 to 100 (Chipman et al., 2021). The higher it is, the more likely it will be to find a kidney that better fits the recipient's characteristics. On the contrary, the lower it is, the more unlikely it will be to find a kidney that gives a better expected outcome for the recipient and, consequentially, it will be less recommended to join the exchange programs.

Massie et al. (2016) underline that if the value of the LKDPI is less than 0, the kidney from the "originally designated" donor would have a better expected outcome than any other potential kidney donor. On the other side, if the index score is 100, it means that any kidney coming from deceased donors would have a preferred outcome in comparison to the one coming from the "original" donor.

The Living Kidney Donor Profile Index has played, and is still playing, a pivotal role in the enlargement of the pool the potential donors. This happens because the classification and the comparison allow to understand if there is room for improvement for transplantations that are still possible due to not marked incompatibility, but that do not represent the optimal available option overall. Without a fixed measurement, this comparison would not be possible, and the people would prefer the option of being transplanted with the original donor, although there would be better solutions.

LKDPI is not the only measurement to take into consideration when choosing among kidneys to transplant. For example, Chipman et al. (2021) in their research, evidence that the size (often indicated as the ration between the recipient's and the donor's body mass index) is a factor that determine the optimal choice, although the authors themselves reserve to have doubts about the long-term outcomes.

Kidney Paired Donation (KPD) and Kidney Exchange Programs (KEP)

Most of the kidney transplantations are from deceased donors, although the number of operations performed with living donors is increasing (Roth et al., 2004). This fact is very important because, as we mentioned before, the transplantation from living donor is considered a better option for the recipient, ceteris paribus (Axelrod et al., 2018; Vinson et al., 2021). The desensitization protocols are for sure a useful tool, but they cannot be considered the best option and an alternative needed to be found (Marfo et al., 2011). However, the aim of the great majority of the exchange programs is to find a compatible partner for the non-transplantable couples in order to maximize the number of possible transplantations after the program (Biró et al., 2009).

To encourage the living donor transplantation without the need of bearing the cost of desensitization and eventually of the plasmapheresis or of other practices, several organ-exchange programs have been proposed and developed trying to find the best application. In the first attempt of an exchange program, there are two couples of donors and potential recipients, which result incompatible. The swap of recipients in the couples may conduct to two possible transplantations instead of no one (Nicolò and Rodriguez-Alvarez, 2012). This practice is the so-called "Kidney Paired Donation (KPD)", and it currently represents around the 12% of all the transplantation from living donor in the United States (Wall et al., 2017).

Even a basic exchange program may give an alternative. In fact, if donor A is incompatible for donating to patient A and the donor B is incompatible for donating to patient B, there could be an exchange in which donor A gives the kidney to the patient B and the donor B gives the kidney to the patient A (Roth et al. 2004). Therefore, the blood incompatibility can be overcome through this conventional pair donation with the result of having an improved situation for both the recipients (Montgomery et al., 2005). Incompatible couples that can become compatible after the overcoming of the blood group barrier are also referred to as "half-compatible" (Andersson and Kratz, 2020). Nowadays, they represent an important resource for the transplantation chains.

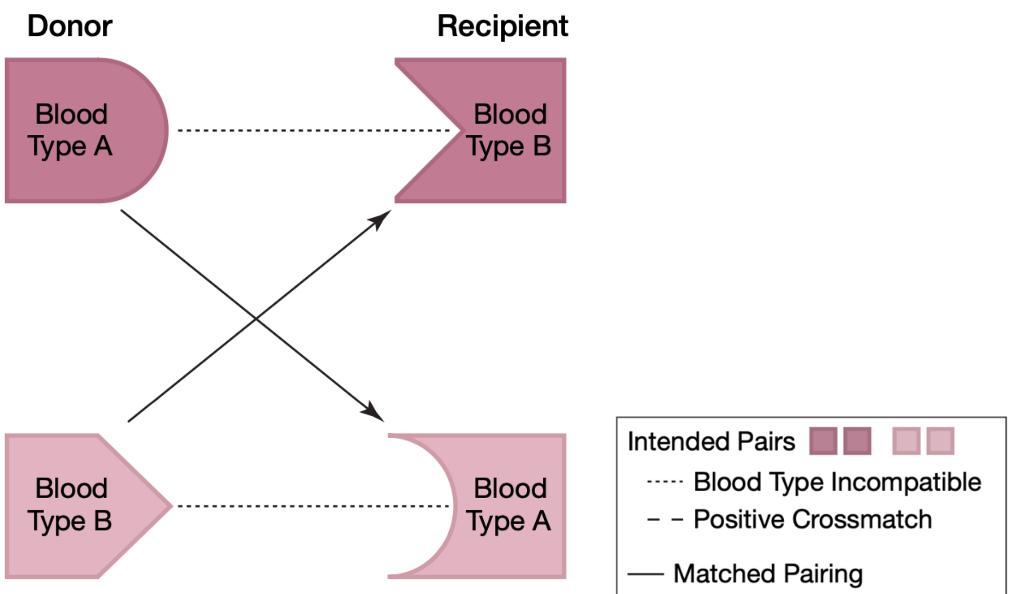

Figure 12: Conventional Kidney Paired Donation.
Source: Montgomery et al. (2005).

This fact has several positive consequences. Since the pairs were incompatible, the patients would have needed to wait for two kidneys from deceased donors to proceed with the transplantations. The waiting time for a kidney transplantation from deceased donor is around 2 or 3 years (UK: National Health Service, 2021; Italy: CaricaVitale, 2021). In 2011, in the United States there were more than 90.000 people waiting for a kidney transplantation (Marfo et al. 2011). As a consequence, the costs to bear would have been much higher since they would have needed medical assistance and dialysis during this time. Thanks to these kidney exchange programs there have been two positive effects: the patients have taken benefit by the health point of view and the medical costs have been drastically reduced. It is essential to enlarge the pool of people taking part to them.

In kidney paired donation, there is no risk of withdrawal from one of the donors since the transplantations take place (almost) simultaneously.

This linear exchange allows the exchange from already formed couples with other couples, but the situation is more complex. There have been other models that tried to develop this concept into more sophisticated exchange programs: for instance, it is possible to imagine three couple of incompatible donors. If donor A cannot donate to recipient A, donor B cannot donate recipient B, and donor C cannot donate to recipient C, all the three patients would not be able to undergo a successful transplant. It may be possible to perform desensitization protocols in order to enable the transplantations, but they are expensive procedures (Marfo et al., 2011). If we imagine a chain in which donor A gives the kidney to recipient B, donor B gives the kidney to recipient C, and donor C gives the kidney to recipient A, all the three patients would have been successfully transplanted with a compatible kidney. Once again, it is important to remind that this is reflected also in the saved costs of the therapies that the patients would have needed without the prompt transplants.

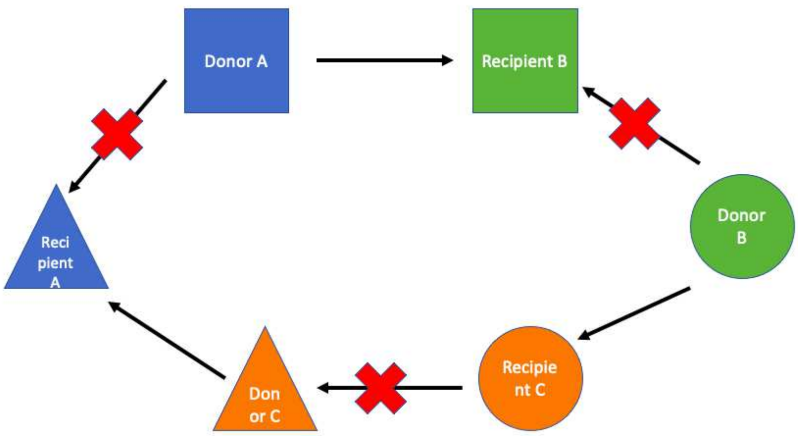

Figure 13: Three incompatible couples in a kidney exchange program.

In this way, there have been savings for the time that all the three patients would have need to be in dialysis. Furthermore, they did not clog the waiting lists for the other patients, allowing them to receive a compatible organ earlier meaning that also for them the time spent in dialysis is reduced.

Considering the number of people in the waiting list of every country, it is possible to broad this concept even more. It is possible to imagine chains of organ exchange in which people are able to find the best fit. If there are hundred incompatible couples, it is almost impossible that nobody of the recipient fits with at least one of the donors. Just this concept should be an incentive to develop this program, but the figure of the "Samaritan" is still not very popular and in some countries is illegal. The so-called "Samaritan" is a person who is willing to donate the kidney to any unknown patient, just for the purpose of doing a good action without a personal return (Kranenburg et al., 2007).

In the case of the previously formed couple, the donor is willing to donate the kidney to their relative, partner or friend and the desire of helping another random person is not so strong to convince them pursuing this choice. Their expectation is to donate the organ in order to improve the health condition of the beloved person. The kidney exchange programs have the aim to treat the couple of donor and recipient together: if the donor of a couple donates a kidney, then the recipient of the same couple is supposed to receive one. The only, but fundamental, difference is that the exchanged kidney is supposed to not be the same, as seen in the previously explained examples. In fact, the goal is to furnish a better fitting kidney to all the participants to this kind of programs.

In a sample of hundred couples, it is unlikely to be able to create a continuous chain in which the donor A donates to the recipient B, the donor B donates to the recipient C and so on. This chain would have extremely high costs due to the waiting time and the organization of all the procedures, that would not be an optimal solution. It is easier to think about creating small group of couples in which the organ exchange can take place: for instance, there may be a chain including 15 couples, others including maybe just three or four of them, and also incompatible couple that do not comply with the standards remaining unfortunately isolated.

In general, the bigger is the pool (the number of couples participating to this kind of programs), the easier and the more likely it will be to find a suitable match for all the participants. A positive aspect worth to be underline is that always more couple are entering the kidney exchange programs (Chipman et al., 2021). This fact would have positive effects also on the people waiting for the organ transplantation due to a reduced waiting time in average and, therefore, less time spent in dialysis (Wall et al. 2017). For this reason, it is fundamental to incentive the participation.

New projects with innovative ideas for the exchanges are continuously taken into consideration, aiming at improving the already existing ones and creating efficient chains for the optimal allocation of the available organs (Wall et al., 2017).

Countries with Kidney Exchange Programs

This procedure is already common and well-developed just in a few countries, while in many others it is still expanding (Furian et al., 2019). One of the first national kidney exchange program in the world has started in South Korea and it is considered a successful example still nowadays (Park et al., 1999). It started back in the 1991 and it is considered the first country with a kidney exchange program (Fortin, 2013; Kher and Jha, 2020).

Some of the programs are not only on a national scale but they try to involve several countries in order to enlarge the donor sample. The Scandinavian countries are an example of international collaboration for kidney exchange programs, with the first transplantation that took place in 2019 thanks to the exchange happened between patients from Denmark and Sweden (Skov et al., 2020).

Furian et al. (2019) underline how this kind of programs are widespread in the United Kingdom and in the Netherlands, while most of the other European countries (Spain, France, Italy, the Czech Republic, Austria, Belgium, Switzerland, Poland, and the Scandinavian countries) are just moving the first steps towards an organized kidney exchange program.

The kidney exchange programs in the United States are another good example from which many countries can take inspiration (Gentry et al., 2017). The UNOS, which is an acronym for United Network for Organ Sharing, is a no-profit organization with the aim of best allocating the available kidneys for the people in a needing situation. The kidney exchange programs exist since the year 2000 (Fortin, 2013).

Kranenburg et al. (2004) illustrate the first attempts of similar programs in Europe. They mention the first attempts in Switzerland and Romania. The aim of the article is to promote a kidney exchange program in the Netherlands. They advance the important issue about introducing a new program. This fact may interfere with the already existing distribution procedures. The idea behind the proposal is not to eliminate the previous ones, but to find the right balance between them. In fact, an essential point is the role of the deceased donors: their organs can be used to start the new hybrid programs.

In Australia, the kidney exchange programs are characterized by many administrative stages, which indirectly discourage this procedure. The situation is similar in Canada, where the political representants have caused a legislative uncertainty about the programs that negatively influences the potentially good results (Toews et al., 2017). It is important to overcome these problems and to encourage as much as possible the participation to the programs: in this way, the hospitals and the national medical system would take tremendous economic benefits from a successful implementation of the exchanges.

Other countries with kidney exchange programs are France, India, Portugal and the already mentioned Netherlands and Sweden (Andersson and Kratz, 2020). The authors list some differences among the various programs, which are designed and developed following the national rules of every country.

Biró et al. (2017) collect the information from experts coming from 23 different European countries analyzing the development of the of the Kidney Exchange Programs in Europe. The countries are classified into four main categories (with the addition of countries with no available data) according to the state of development of their programs: large and advanced programs; new and smaller programs; programs in preparation and ad-hoc exchanges; countries with no kidney exchange activity; and no data available for the country.

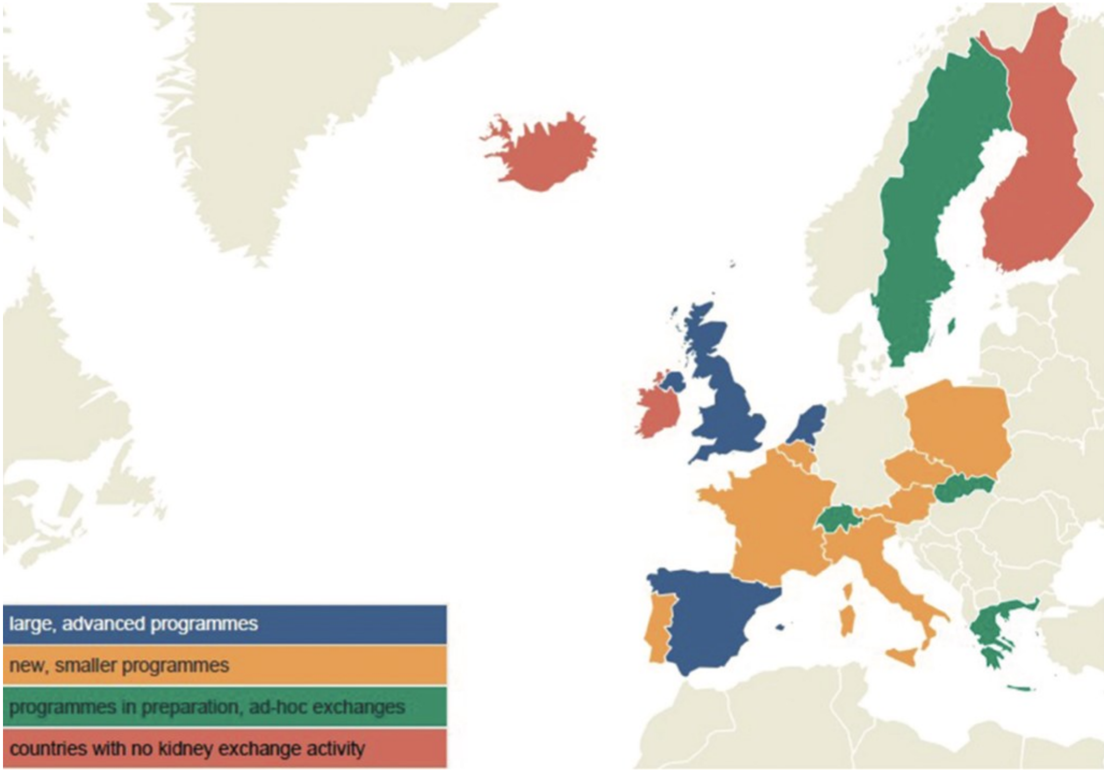

Figure 14: Development of the Kidney Exchange Programs in Europe. Source: Briò et al. (2017).

The authors underline, how efficiently the Netherlands are working on them. In fact, the Dutch country has the highest number of living kidney donations per million population in Europe, followed by United Kingdom and Spain.

Furthermore, there are some exceptions in the world, but also in Europe, of countries in which any kind of kidney exchange programs is not allowed by law. For instance, Finland does not allow it. (Biró et al., 2017).

Referring to Italy, the authors list the country in the category of countries with new and smaller programs. As can be seen in the figure 14, most of the European countries are part of this category (Biró et al., 2017).

In fact, in Italy there are kidney exchange programs, but unfortunately, they are not developed and have been defined as an “underutilized resource” (Segoloni et al., 2004). The authors underline how crucial it is to fully exploit this underrated option in Italy. Salvioli et al. (2016) insist on the need to enlarge this procedure in order to shorten the waiting time for the patients. In Padua, the programs do exist and some transplantations in the last years have been performed thanks to the exchanged organs.

Kidney exchange program with deceased donors

Finding the right kidney for every incompatible couple is a hard task even for a well-structured exchange program. Their aim is to give a more suitable kidney to all the recipients. If the program has the same number of donors and recipients, finding the best match is possible, but it is not always feasible. A good solution would be enlarging the pool of donors from which the organs can be selected and that makes possible the realization of the chain. This organ is defined as the “Chain-Initiating Kidney” (CIK) (Wall et al., 2017). Taking the organs of deceased donors, it is possible to increase the number of available kidneys without altering the number of needing recipient in the incompatible couples. The incompatible donors would donate their organ to the people on the waiting list, i.e. the people that would have been supposed to receive the kidney from the deceased donors that have started the exchange chain. This fact allows to have a greater number of “couples”, improving the likelihood of finding an optimal option for the patients.

Wall et al. (2017) underline an important fact: the family of the potential deceased donor (or the donors themselves before the death) must agree with the donations of the organs. Moreover, they can direct the organs to any related person. This is a fundamental right that does not allow a blind program but must inform and have the consent of every part involved. If this condition is satisfied, it is possible to donate the kidney, or actually the kidneys, to strangers in the waiting lists. Furthermore, it is important to remember, that also the recipient can decide on their own to refuse a kidney. This fact, although it may seem illogical, may depend on the fact that the recipient hopes to obtain a kidney from a living donor, which is a more desirable option, ceteris paribus. Anyway, this refuse may have consequences (for instance a penalization in order to discourage this choice) in the position of the recipient in the waiting list, but every country applies a different policy to these situations.

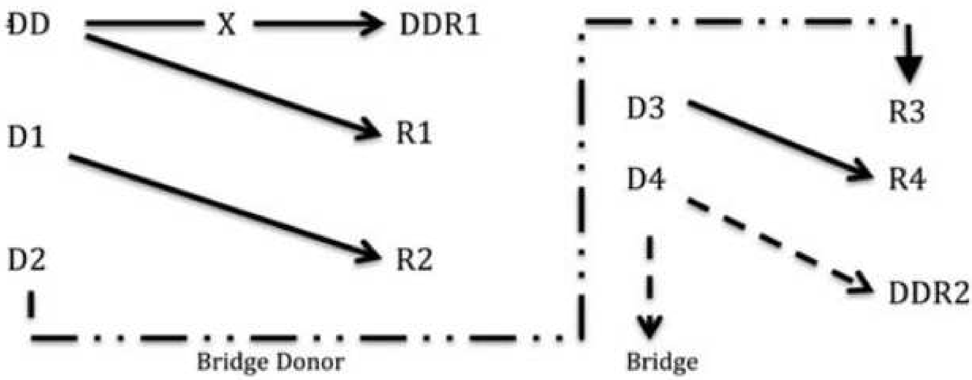

Figure 15: Deceased Donor Initiated Chain.
Source: Wall et al. (2017).

If the chain-initiating kidney comes from a deceased donor, there are several concerns that arise. They may regard both the ethical point of view and the logistic one. Furian et al. (2019) identify and classify them:

- The parameters used to select the chain-initiating kidney recipient from the waiting list of people needing a transplantation.
- The amount of risk features of the chain-initiating kidney donor(s).
- The number of kidneys coming from deceased donors that can be give the start to the kidney chain.
- The chain-ending kidney (CEK) allocation strategies.
- The quality comparison between the living donor’s kidney, even incompatible, and the deceased donor’s kidney.
- The risk of withdrawal of one or more donors due to the non-simultaneity of the transplantations, with the concrete possibility of undermining the whole credibility of the project. For this reason, at the beginning, the exchange programs envisaged the simultaneous transplantation for the participant to avoid such a risk inside the chain members (Wall et al., 2017).
- The Cold Ischemia Time (CIT) on chains in large geographical areas. The National Cancer Institute (2021) defines the cold ischemia time as “the time between the chilling of a tissue, organ, or body part after its blood supply has been reduced or cut off and the time it is warmed by having its blood supply restored”. Moreover, it is specified that it

can happen while the organ is in the body of the person of after the removal finalized to the transplantation. Salahudeen et al. (2004) highlight the higher risk of delayed graft function and graft loss related to a prolonged cold ischemia time, insisting on the importance of having an efficient and prompt regional distribution of the organs in order to improve the long-term success of the transplantation. The importance of this factor is stressed also by Chipman et al. (2021).

Nevertheless, the option of including the organs coming from deceased donors to initiate, or potentially even to continue, the chain for kidney exchange has to be taken into consideration and analyzed further. This theme has been debated, and currently is still nowadays, with most of the authors encouraging this option.

Furian et al. (2020) analyze the existing exchange programs in Italy, focusing on the potentiality that the inclusion of kidney from deceased donors would have. The authors stress the importance of this initiative also for the positive consequences that this fact would have on the waiting list of donors waiting for a kidney coming from deceased donors. As mentioned before, the average waiting time for a deceased donor kidney in Italy is around 26 months (CaricaVitale, 2021). This in a crucial factor with a lot of room for improvement that has to be shortened to guarantee better results.

Voucher for Future Kidney Transplantations

Another possible solution for kidney transplantations is giving a sort of "voucher for future kidney transplantation". Veale et al. (2017) underline how the hurdles for a successful transplantation are not only the blood group and the human leukocyte antigens incompatibility. Indeed, they stress the relevance of the so-defined "chronological incompatibility". This method aims at overcoming it and will create a hybrid between an altruistic donation and a transfer of a kidney to a relative, partner or friend.

Kher and Jha (2020) take as example the age limit that a donor may have. The authors take into consideration the case of a grandfather, potentially willing to donate a kidney to his grandson or granddaughter. If the grandchild needs the kidney in 10/20 years, it is very likely that the potential donor will have reached the age in which it is no more recommended to donate organs. This case represents a waste of a potential donor. Then, it can be useful to find a solution to avoid that it happens.

If the grandfather donates the kidney to a person who needs it at the moment without any personal return, it would be an altruistic or "Samaritan" donation (Kranenburg et al., 2007). If the donor receives a so-called “voucher”, the situation is different. If a person related to the donor will need a kidney in the future, they will have a priority in comparison to the other patients (Vaele et al., 2017). This is a way to compensate the already-happened donation and to encourage the donation in order to reduce the time spent in dialysis by the patients who do not have a compatible donor at the moment. The future recipient will be the ender recipient of an exchange chain because their donor has already donated the kidney several years in advance. The UCLA Living Donor Committee and the National Kidney Registry Medical Board in the United States approve this kind of donation but insert several limits. For instance, they impose the exact identification of the potential future recipient of the organ donation (and not any relative of the donor). On one side, the choice is specific, and it may be a disincentive for the potential donors, but on the other side, leaving the choice open for any time in the future for any related person may cause many problems.

The limits to the “voucher for kidney transplantation” solution are several, both under the logistic and the ethical points of view, but many authors are studying this option trying to understand how to successfully implement it in the kidney exchange models that are used nowadays (Vaele et al., 2017; Kher and Jha, 2020). For sure, this is a further option that cannot be ignored in order to reduce the cases of “chronological incompatibility” of patients with an available donor.

Compatible couples in kidney exchange programs

As mentioned before, there are some couples that are considered “compatible” after some medical interventions that allow the donation. One example is the possibility to overcome the blood incompatibility (Montgomery et al., 2005). These kind of couples are defined “half-compatible couples” (Andersson and Kratz, 2020). For sure, they would benefit from joining the kidney exchange programs.

There is another category to take into consideration: the compatible couples. Some of them result compatible without the need of any medical intervention that correct some sort of incompatibilities. Nevertheless, they may take benefits from joining the kidney exchange programs. In fact, the LKDPI of the donor may have a high value anyway due to other characteristics. If a so-defined “compatible couple” it is possible that donor donates their kidney to another recipient and the recipient receives a kidney from another donor. There is a gain if both the transplantations have a better expected outcome or one of the registers an improvement and the other one remains the same. The participation of compatible couples enhances the likelihood of finding better matches for all the involved couples (Chipman et al., 2021; Fortin et al., 2021; Weng et al., 2017; Kher and Jha, 2020).

The participation of compatible couples to kidney exchange programs should be strongly encouraged because they would represent an important enlargement to the pool of patients and donors from which the organs can be taken, favoring, and increasing the number of kidney transplantations from living donor. This practice is commonly known as “compatible pair participation” (Weng et al., 2017). Some of them, simply join the programs just for altruistic reasons (Chipman et al., 2021).

Anyway, there are some features to keep in mind while developing the exchange models. For instance, Fortin (2013) stresses the importance of finding a balanced mechanism that does not penalize the O blood type people. As mentioned before, the O blood type donors are the so-called “universal donors” because they can donate to any blood type, but the O blood type recipient can receive only from another O blood type person. The author underlines that this fact should not represent a disincentive to participate. There are many other to consider, both from the logistical and from the ethical point of view.

Weng et al. (2017) in their article analyze the effects for 11 compatible couples in joining the kidney exchange programs. They have different reasons to do it: mismatch of age, body or kidney size differences, or simply altruistic reasons. The average living kidney donor profile index before the program was of 27,6. The new matched couples have a significant improvement under the LKDPI point of view, scoring an average value of 9,4. Once again, LKDPI is a reliable predictor for the expected outcome, but it is not the only factor to keep into consideration for the transplantations.

The authors stress again the importance of the O blood group. In fact, they encourage couple in which the donor is O blood type, and the recipient has a different one (A, B, or AB) because through their participation, there will be an easier match for all the people taking part to the exchange program (Weng et al., 2017).

Moreover, it is important to avoid any form of coercion for these couples that must be completely free to take the decision by themselves, without feeling forced by external judgment. The couples should be fully aware the situation and a constant dialogue with nurses, nephrologists and psychologist is recommended. The medical staff is also in charge for the evaluation of the couples (Weng et al., 2017).

Chipman et al. (2021) analyze 154 compatible donor and recipient couples that joined kidney exchange programs. Once again, the result shows that the average LKDPI after the programs is better than before. In fact, the original couple would have had a LKDPI of 21, while after the matches, the LKDPI was in average 7. There are other advantages that need to be highlighted, like the fact that the recipient received, in average, a kidney that better also fits the parameters of their body mass. Another essential positive side is the lower rate of mortality or graft failure for the recipients. Furthermore, the authors underline how the participation of the compatible couples allows the transplantation of couples that would have had difficulties in finding a suitable partner for the kidney exchange.

Moreover, it is important to remember that the LKDPI is not the only factor to evaluate before a transplantation of before the choice of joining or not a kidney exchange programs. In fact, as mentioned before, some half-compatible couples decide to try the re-allocation of the kidneys with the aim of obtaining a more suitable organ by the size or by the age points of view, although the LKDPI score may be worse (Chipman et al., 2021).

Data and Model Analysis

Data analysis

Thanks to the collaboration of Kidney and Pancreas Transplant Unit of the School of Medicine of the University of Padua, we have been able to have the data referring to the period going from January 2010 until December 2019. This time frame of exactly 10 years allows a proper investigation of some fundamental aspects of the kidney transplantation.

The Associazione Nazionale Trapianti di Reni (2021) has identified Padova as the main kidney transplantation center in Italy, both by a general point of view and by the living donor perspective. 340 transplantations from living donors have been performed in 2019. In the whole region Veneto, the number of kidney transplantations from living donor was 72, and most of them, exactly 55, have been performed in Padua. The others were performed in Verona, Treviso or Vicenza. Padua is the only authorised hospital in Veneto to perform pediatric kidney transplantations (CRT Veneto, 2021).

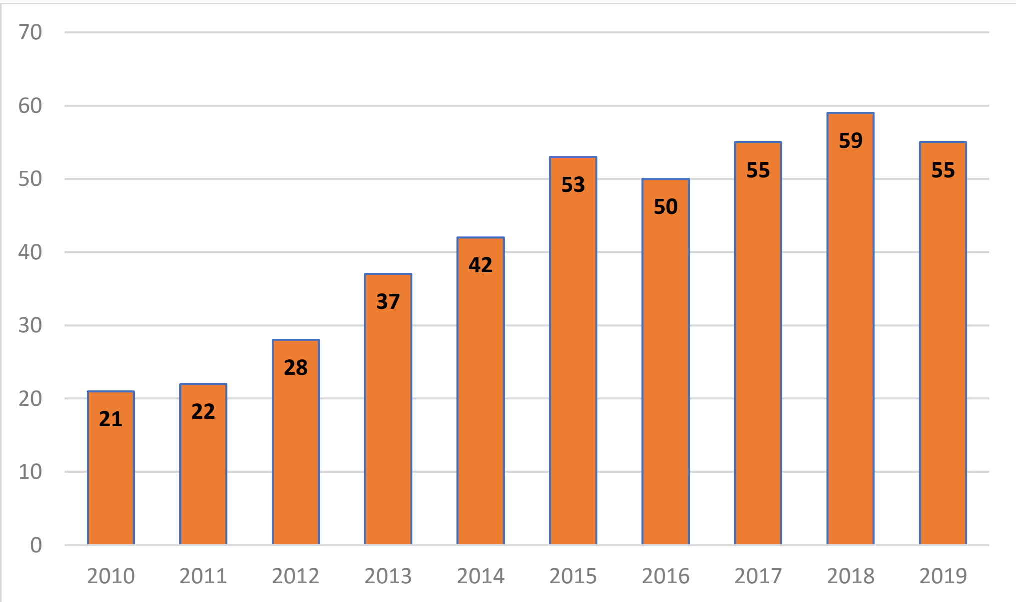

Figure 16: Number of Kidney Transplantations from Living Donors in Padova. Source: Azienda Ospedaliera di Padova (2021).

First of all, we can underline the number of kidney transplantations from living donors, that has been 422 from year 2010 to year 2019. Out of these number, we can classify 406 of these transplantations as successful ones. Out of the other 16, unfortunately there have been 7 demises and 9 organ rejections. The success rate of the transplantations is still very high: more than

96%. The average worldwide is different, and it depends on several factors, such as the amount time spent in dialysis before underwent the transplant operation and the number of incompatibility factors between the donor and the recipient. Anyway, the 96% is a remarkable result.

In average, as in the rest of the world, like for example in Japan (Yagisawa et al., 2018), the number of kidney transplantation has increased. In every one of the last 5 years, in Padua more than 50 kidney transplantations from living donors have been performed, resulting in a total of 272 for the time horizon from year 2015 to year 2019.

Out of 422 only 5 transplants took place from unknown people through crossover programs for incompatible couples. It represents around the 1% of the total and it cannot be regarded as a satisfactory data. For all the others, there was at least a direct relationship between the donor and the recipient. This fact does not mean that all the people were related: in fact, there were many couples represented by husband and wife (that are legally, but not biologically related), adopted child and foster parent or simply friends.

Nevertheless, the majority of transplantations has taken place between non biologically related people: in fact, 228 of the kidney operations involved non-biologically related people, while the ones between biologically related people have been 194. This fact should be an encouragement for potential donors because it concretely demonstrates how impactful can be the donation of a non-related, and consequentially also from an unknown person. Moreover, this is also a point in favor of the application of the kidney exchange programs as a concrete solution for the shortage of available kidneys.

What is essential to analyze is the number of people that have undergone a desensitization protocol in order to have a clearer idea about the cost that it implies and the room for improvement of the occurred transplantations. Out of 422 patients, 105 have been desensitized, which represent almost one quarter of the whole sample. There have been two main types of desensitization: for the blood incompatibility and for the Human Leukocyte Antigens. The other 317 recipients were compatible with the donor. Out of the 105 desensitized patients taken into consideration, we can divide them according to the protocols they have undergone in order to allow the transplantation process:

- 84 of them underwent only the ABO desensitization protocols.
- 15 of them underwent only the HLA desensitization protocols.
- 6 of them underwent both ABO and HLA desensitization protocols.

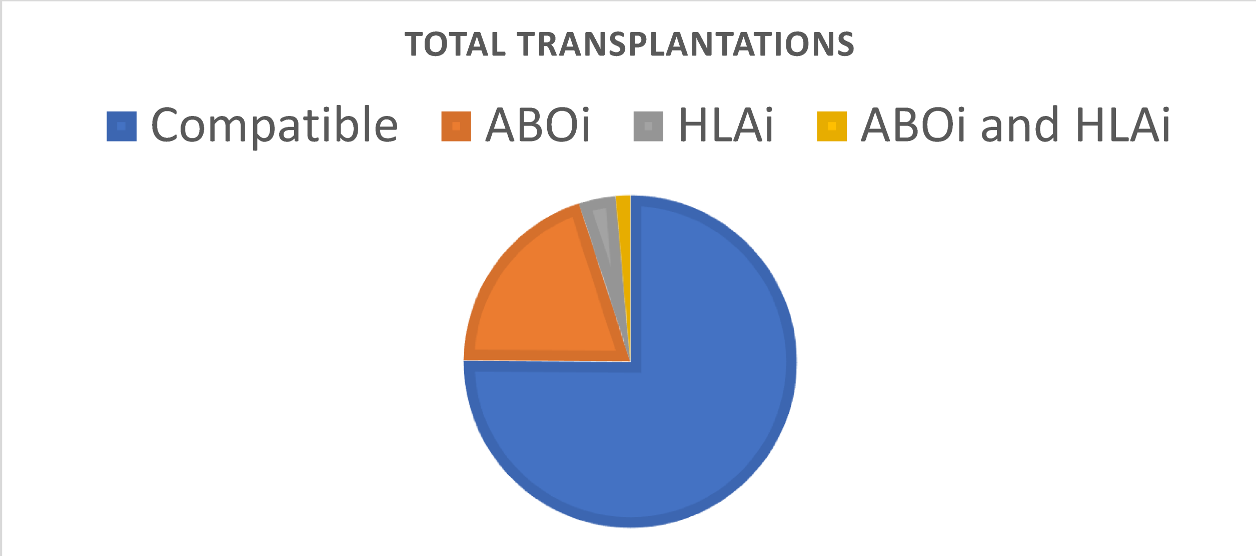

Figure 17: Total Transplantations according to the Compatibility.
Source: Azienda Ospedaliera di Padova (2021).

It is possible to affirm that with an efficient exchange program, most probably there would have been a more efficient allocation of the kidney. This fact is true especially among the 105 people that have undergone a kidney transplantation with blood group incompatibility, HLA incompatibility or both. Taking into consideration all the 422 transplanted patients, the average LKDPI is higher than 29,2.

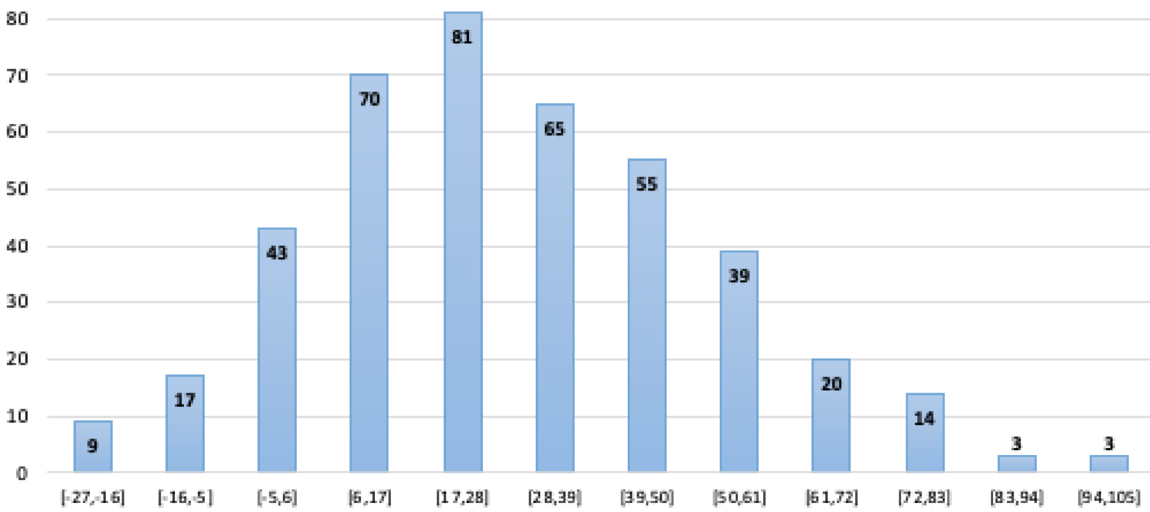

Figure 18: LKDPI Distribution.

The distribution of the scores evidences the high concentration in the middle values. The lowest LKDPI values is -27, while the highest one is 104. The median is 26. The categories on the right are more subject to potential improvement in joining kidney exchange programs with the concrete hope of finding a better match.

The average score 29 is a reasonable value, but it may be improved. Moreover, it is very likely that also the couples that have been initially defined “compatible” would have taken benefits from joining some exchange programs.
There are several limits to this reasoning. In fact, it is essential to remind the pivotal role that the time plays in such situations. In this case, the transplantations happen in a time horizon of ten years. If the compatible kidney (or better said: a kidney that better fits to the recipient) is not an available in the moment of the need, it does not make sense to wait longer than a specific time horizon. The simultaneous presence of an available donor and a needing patient is fundamental to allow a successful transfer with the right timing.
Another factor that must be analyzed in order to better have the point of view about the transplantations is the dialysis and the time spent doing it. Most of the time, the dialysis is a treatment done in addition to the transplantation, often used to treat the patient while waiting for a compatible kidney. Out of the 422 operated patients, the majority of them (213 to be precise) underwent a period of hemodialysis, other 84 were subject to peritoneal dialysis, and the remaining 125 patients did not do any dialysis protocol.
If a person is transplanted without any dialysis, it is said that it is the case of a “pre-emptive transplantation”. The average LKDPI is 31, which is a value that offers room for improvement in the transplantation, also if compared to the average of the whole sample, although the difference is minimal. This fact may depend on the hasty decision of proceeding with the transplantation related to several circumstances and uncertainties that are unavoidable in the real-life situations. Furthermore, the other patients that spent time in the dialysis, may have better values due to the reduced incompatibilities, which is a consequence of the treatment of the HLA mismatches.
In the case of the patients transplanted in Padua, the percentage of people that undergo a pre-emptive transplantation is very high, almost the 30% of the total. Averagely, the percentage is only around 17% (Jain et al., 2019). This difference may hinge on the fact that our sample counts only the patient that have been transplanted with a kidney coming from a living donor. For patients on the waiting lists for a kidney from deceased donors, it is more likely to need a dialysis treatment since the waiting time is averagely longer and the time worsens the condition of the unhealthy kidneys.
Patients that underwent hemodialysis present an average LKDPI of 28, which is a better value in comparison to the group that has proceeded with the pre-emptive transplantation. The average time spent in dialysis is around 23 months (22,7 to be precise).
Patients that underwent peritoneal dialysis present an average LKDPI of 29, which is a slighter worse value in comparison to patients that underwent hemodialysis but is better than patients

that proceed with the pre-emptive transplantation. The average time spent in dialysis is 21 months (21,2 to be precise), which is slightly lower than the time spent in dialysis by the group of patients that underwent the hemodialysis treatment.
Regarding the LKDPI, we can conclude that there is not a significant difference between the three categories of patients according to the dialysis that they underwent (peritoneal dialysis, hemodialysis, or no dialysis at all).

Introduction to the models and counterfactual exercises

The aim of the kidney exchange programs models, as has been pointed out by Freedman et al. (2020), is to find an efficient allocation of the scarce resources, which are the kidneys in this case. There is a central market maker that allocates the living donor kidney according to specific criteria, adjusting the algorithms to ad-hoc needs useful to balance the models to better meet the ethical principles. The desired solution is to develop a proposal for a cross-over program that includes the compatible and the half-compatible couples, whose task is to determine in advance the expected outcome for a pool of participants in a kidney exchange program. This exercise is very difficult, and it requires several attempts in order to adjust the characteristics to make them fit for both small and large pools.
To have an idea of how a model may be structured, it is possible to run a counterfactual exercise. A counterfactual exercise is an exercise made afterwards that has the aim of understanding how the things could have gone before. This tool is extremely useful in order to have a perspective of how the transplantations could have been organized in order to give a more efficient kidney to the recipients.
The counterfactual exercises regard the kidney transplantations that took place in the hospital of Padua between year 2010 and year 2019. This kind of exercise has been run several times in order to furnish a broader view about the concrete options. The principal features of the analyzed models are the waiting time, the required LKDPI improvement threshold and the frequency of the rounds for finding new compatibilities.

Limits

Unfortunately, the limits to the models, and in general to the counterfactual exercises are several. First of all, the models have been elaborated at a later stage, knowing all the patients

that would have joined in the future time periods. This fact allowed a precise analysis of the processes, but only afterwards. Logically, this fact is impossible in the reality because there is no way to foresee how many patients will join the programs and their features.
Several models try to furnish a better kidney allocation, but the results are comparable only with the afterwards data, knowing exactly what would have happened from the first day until the last one. It is clear that, with a complete view about the results, it is easier to choose which model performs in the best way. Once again, in the real situation, the model must be selected in advance and this fact make more difficult to predict which one performs the best retrospectively.

Analysis of the proposal for the kidney exchange program

To analyze the potential benefits of the participation of compatible and "half-compatibles" pairs to a kidney exchange program, it has been conducted a counterfactual analysis based on the data collected at the Kidney and Pancreas Transplant Unit of the School of Medicine of the University of Padua.
A KEP that includes the participation of compatible pairs has been designed and it has been tested using the data collected at the Padua unit in the last decade (from January 2010 to December 2019). Through a counterfactual exercise, it has been possible to determine the effectiveness of the program.
The designed KEP program involves incompatible pairs, half-compatible pairs and (fully) compatible pairs. Incompatible pairs do not have any viable alternatives, so in case they do not participate to an exchange, the recipient can only receive an organ from the deceased donor list, that usually takes a lot of time. Half-compatible pairs can be transplanted after desensitization, and compatible pairs can be directly transplanted. Therefore, a KEP that includes the participation of half-compatible and compatible pairs should guarantee to the recipients of those categories an outcome that is at least as "good" as the outcome that they could get by receiving the organ of their intended donor.
The main features of the designed program are the following:

1. Matches are run every 90 days at fixed dates.
2. Each compatible or "half-compatible" pair remains in the pool at most 180 days; after this span the donor donates the organ to her intended recipient. If the next round occurs after the deadline (180 days), the pair immediately leaves the pool after the second match run in which it was involved.

3. A compatible or “half-compatible” pair participates in an exchange if there is a gain for the recipient. The following criteria have been used to determine what is a “gain” for a recipient of a compatible pair:
    I. For the recipient of a half-compatible pair, “avoiding” the desensitization procedure, without considering the LKDPI of the new match.
    II. For the recipient of a compatible pair, a reduction of at least 20 points of the LKDPI in comparison to the original match.

Every KEP uses an algorithm to find the compatible matches. The algorithm works through a few objectives that are lexicographically ordered to identify which cycles to perform. The following objectives have been set:

1. the maximization of the transplants, meaning that between two cycles that intersect (and therefore cannot be performed at the same time) the algorithm chooses the cycle in which more incompatible pairs are transplanted.
2. the minimization of the HLA-desensitization procedures, meaning that between two cycles that intersect and involve the same number of incompatible pairs, the algorithm chooses the cycle in which more HLA-incompatible pairs can be transplanted avoiding desensitization, therefore the cycle in which more HLA-desensitized pairs are involved.
3. the minimization of ABO desensitization processes, meaning that between two cycles that intersect and involve the same number of incompatible and HLA-desensitized pairs, the algorithm chooses the cycle in which more ABO-incompatible pairs can be transplanted avoiding desensitization, therefore the cycle in which more ABO-desensitized pairs are involved.
4. the maximization of the exchanges, meaning that between two cycles that are equal in terms of the previous features, it selects the longest one (involving more pairs), and, eventually, in case of ties it randomly selects one cycle.

The reason why it is important to estimate by means of a counterfactual exercise using real data is because the potential benefits coming from the participation of compatible pairs to a KPE program should be balanced with their potential costs. The most relevant costs are represented by the additional waiting time that a compatible pair should bear when participating in the program. It is important to remind that most of the recipients who undergo a transplantation are in dialysis and the delay of the organ transplant represents a medical and psychological cost for the recipient, whose health conditions may worsen while waiting for the transplant.

The counterfactual analysis of the potential benefits of introducing a KPE program that includes compatible and half-compatible pairs has been performed collecting the data about all the living donor transplants performed in Padua from January 2010 to December 2019 and the data of the incompatible pairs that could not be transplanted. During this span at Padua were performed 422 living donor kidney transplants and the data of 417 transplants were collected for this purpose. Moreover, 27 incompatible pairs that could not be transplanted, have been included. The analyzed pool is then composed by 444 couples needing a kidney transplantation, specifically:

- 311 ABO and HLA compatible couples.
- 90 ABO incompatible couples.
- 16 HLA incompatible couples.
- 27 non-transplantable couples.

The distribution of LKDPI values among the pairs that were transplanted varies from the score -27 to the score 104, while the median is included in the category 17 to 28.

The pairs have been inserted in the pool according to the real chronological order and every pair enters the pool the day in which it has been transplanted or in case of an incompatible pair the day in which its incompatibility has been registered. In this way, it is possible to have a reliable simulation of the chronological order.

Results

In this counterfactual exercise, 105 couples out of 444 take actively part to the exchange program. The main results of the simulation, according to the lexicographic order of the objectives stated above, are the following:

- Out of the 27 non-transplantable couples, 11 find a compatible organ and can be transplanted.
- Out of the 16 HLA incompatible couples, 6 avoid desensitization.
- Out of the 90 ABO incompatible couples, 34 avoid desensitization
- Out of the 311 ABO compatible couples, 54 find a kidney with an LKDPI score improvement of at least 20 points.

In our pool, more than one-third of the half-compatible pairs (40 out 106, the 37,7%) could avoid desensitization and 11 out 27 (40,7%) of non-transplantable pairs could be transplanted. The overall percentage of the exchanges is 23,6%, which means that around 1 pair out of four could find an exchange that improves the recipient's expected outcome with respect to the outside option.

It is straightforward to not that the minimum improvement threshold equal to 20-points reduction (for fully compatible pairs) reduces the number of exchanges compared to a less demanding one like 10-points LKDPI improvement threshold.

ABOc	54/311	17%
ABOi	34/90	38%
HLAi	6/16	38%
NoTx	11/27	41%
Average LKDPI improv	-29,44	

Figure 19: The Results of the proposed KEP.

Not every couple has a better LKDPI score, but it is compensated by other factors. First of all, it is essential to highlight that 82 couples have a better LKDPI score, while 23 have a worse one in comparison to the original matches but avoid desensitization.

Out of the 82 couples which have a better LKDPI score, not every couple has an improvement of 20 points, but the advantages are other. In detail:

- 55 simply have a better LKDPI score. For this category, all the couples have a LKDPI improvement of at least 20 points.
- 4 are non-transplantable couples: three of them overcome the ABO incompatibility and the other one the HLA incompatibility.
- 1 couple overcomes both the ABO and the HLA incompatibilities (the LKDPI improvement is more than 20 points).
- 10 couples find a match that overcomes the ABO incompatibility, but their LKDPI improvement is lower than 20 points.
- 12 couples find a match that overcomes the ABO incompatibility and their LKDPI improvement is higher than 20 points.

The remaining 23 couples have registered a worsening in their LKDPI score. However, it is crucial to underline that all the couples obtain an advantage of avoiding desensitization procedures. In detail:

- 7 are non-transplantable couples: one of them solves the ABO incompatibility and the other six overcome the HLA incompatibility.
- 11 overcome the ABO incompatibility
- 5 overcome the HLA incompatibility.

Overall, considering the 105 couples, 50 couples overcome the ABO and the HLA incompatibilities (counting the 11 non-transplantable couples that find a suitable match), while 55 register an improvement of at least 20 LKDPI. Out of this 55 couples, 54 are the one that were already fully compatible before joining the program. 33 couples overcome the ABO incompatibility, 5 couples overcome the HLA incompatibility and one couple overcome both ABO and HLA incompatibilities.

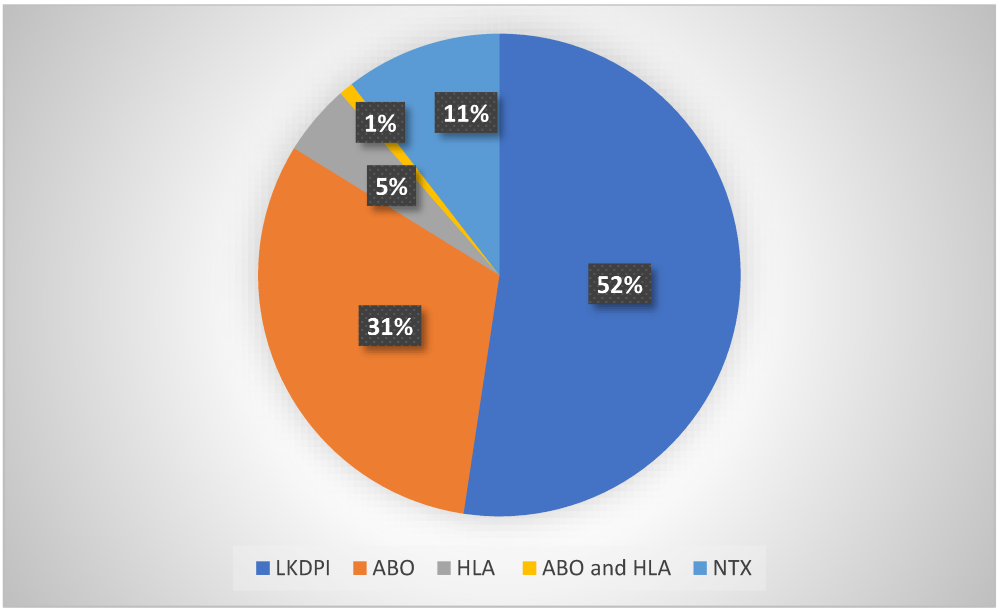

Figure 20: Improvement for the 105 Exchanged Couples.

Considering an average cost of desensitization between €17.000 and €33.000[1], the saving just for the 40 couples that avoided either the ABO or the HLA desensitization processes can be estimated between €680.000 and €1.320.000. To these savings should be added the benefits deriving from a better expected outcome for the other 54 compatible couples that improved the LKDPI score. On the other side, the remaining 323 couples that joined the program without

[1] Private communication with the nephrologist Umberto Maggiore, who is collecting data for a not-yet published research

finding a match, bear an extra cost due to the postponed transplantations and to the dialysis procedures required in waited time.

As mentioned at the beginning of this chapter, the benefits of the program, in term of an improvement in the expected quality of the transplant, should be compared with the cost of an increase in the waiting time, and the associated psychological and physical cost, especially for those patients who are in dialysis. Equitable considerations in particular suggest that the postponement of the transplant is a net cost for those recipients who participated in the program without finding a better match. Clearly, the non-transplantable pairs do not suffer any additional cost, because they would be forced to wait for a compatible match in the waiting list for deceased donor kidneys.

In the simulation there are 323 compatible or half compatible pairs that did not find a better match with an average waiting time of 136 days. Moreover, there are still 16 non-transplantable couples that do not find a match at all.

Discussion

The previous analysis suggests some guidelines to improve the design of a kidney exchange program with the participation of compatible pairs. The waiting time of the 323 couples who did not exchange their donors is ex-post inefficient that, with the benefit of hindsight, should be avoided. In fact, these couples need more dialysis treatments and conclude by being transplanted with the original donor.

It is reasonable to discuss on the factors that determine the LKDPI and understand which one is more likely to lead to an improvement of the expected outcome. These factors are mainly combined into three categories: characteristics of the donor, characteristic of the recipient and the mismatches (HLA and ABO). The characteristics, such as the age and the BMI, of the donors and of the recipients cannot be changed. However, the BMI ratio between donor and recipient can be subject to improvement after new matches.

If a couple is compatible, they do not have any mismatch. Thus, if it has a high LKDPI, it is reasonable to think that a factor, such as the age of the donor, negatively affects the result. The age cannot be modified. The exchange, ceteris paribus, with another compatible couples would determine a higher score for one recipient that recipient a younger kidney but would be balanced by the worsening of the other one that receives an older kidney.

A half-compatible or incompatible couple presents mismatches between donor and recipient. Clearly, these mismatches are more damaging for the expected outcome than an aged kidney.

The exchange between the two couples may induce an improvement for both: the incompatible recipient will overcome the incompatibility, while the compatible one will have a younger donor, that may improve the LKDPI score.
The focus should be on the characteristics that improve the likelihood of obtaining a better match. Applying this reasoning to the pool, we notice that the original donors of the compatible couples are, in average, older than the donors of the half-compatible couples: 56,1 years vs 50,2 years. It is consistent with the assumption: on one side, to half-compatibles couples is better an older kidney than a desensitization process; on the other side, the benefit for compatible couples is a better LKDPI score (due to a younger donor).

Categories of LKDPI

Massie et al. (2016) in their research classifies the patients undergoing kidney transplantations into four categories, according to their LKDPI value. The four categories are:

- LKDPI lower than 0.
- LKDPI between 0 and 20.
- LKDPI between 20 and 40.
- LKDPI higher than 40.

In their article, they show the relationship between two variables: LKDPI values and graft loss.

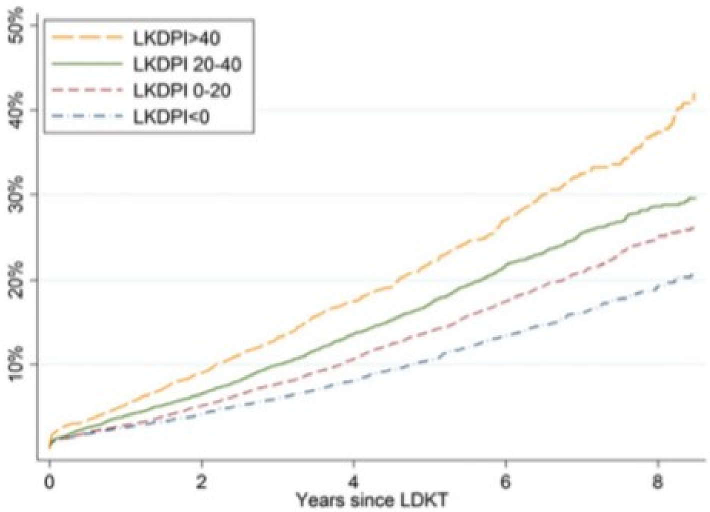

Figure 21: Graft Loss by LKDPI Category.
Source: Massie et al. (2016).

The authors show how a high LKDPI score tends to increase the risk of graft loss. This difference is lower at the beginning, but the discrepancy increases year by year. In 8 years, the risk of graft loss is almost the double for the category of "LKDPI > 40" in comparison to the category "LKDPI < 0".

Rehse et al. (2019) analyze the efficiency of the transplantations, measuring the estimated glomerular filtration rate (eGFR), which measures the efficiency of the filtration capabilities of the kidneys. They take into consideration both deceased and living donors and analyze two categories: "LKDPI between 0 and 20" and "LKDPI between 20 and 40".

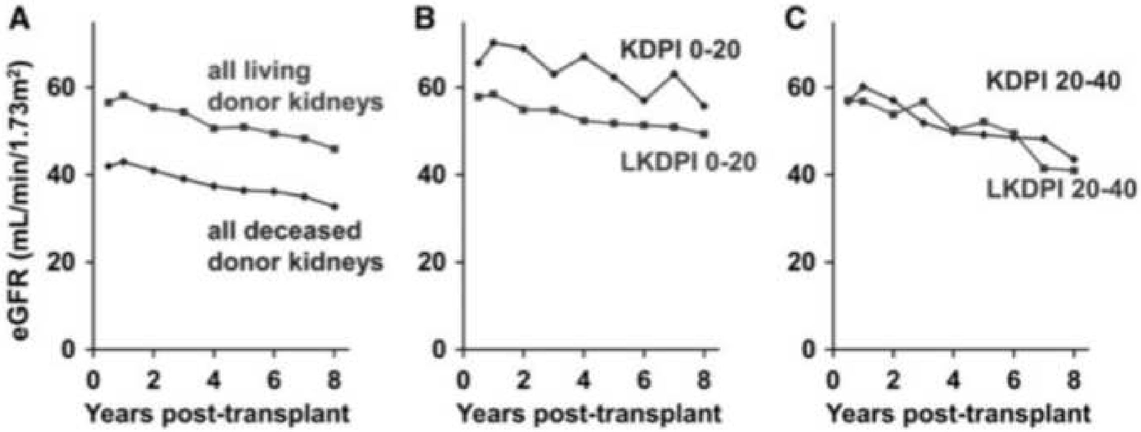

Figure 22: Estimated Glomerular Filtration Rate (eGFR) by Category. Source: Rehse et al. (2019).

The higher is the percentage of transplanted couples that reaches the eGFR threshold, the better it is because it is a consequence of a working kidney and of a successful transplantation. Even in this case, the category with a lower LKDPI score shows a better outcome than the one with higher LKDPI score.

In our case study, we do not have concrete results about the outcome, because most of the features need to be observed several years after the actual transplantation. However, it can be useful to try to predict the outcomes. As value, it is reasonable to take the same used by Massie et al. (2016) and by Rehse et al. (2019). Thus, the 417 couples (the total number without considering the incompatible ones) are divided into the same four categories, according to their LKDPI score: "LKDPI lower than 0", "LKDPI between 0 and 20", "LKDPI between 20 and 40", and "LKDPI higher than 40".

In the category "LKDPI lower than 0", there are 74 couples. In the category "LKDPI between 0 and 20", there are 133 couples. In the category "LKDPI between 20 and 40", there are 110 couples. In the category "LKDPI higher than 40", there are 100 couples.

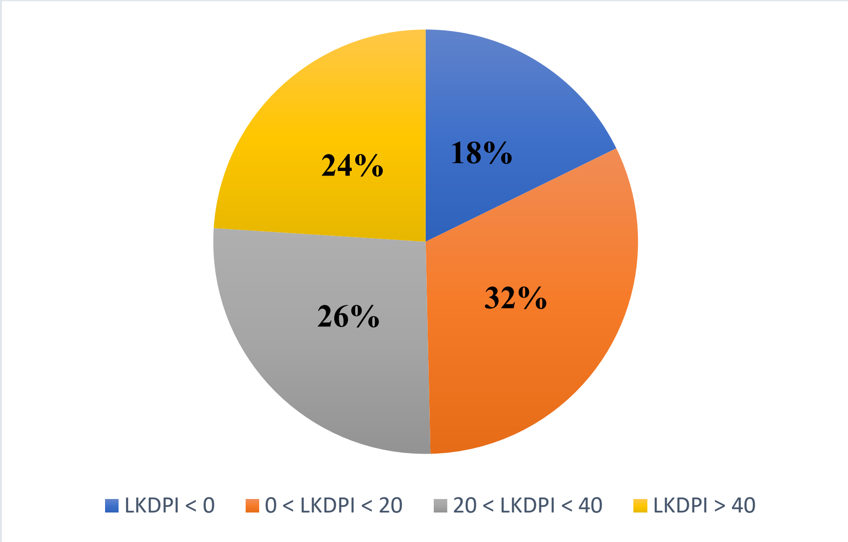

Figure 23: LKDPI Categories in the Pool.

In the first category, out of 74, 24 find a better match (32,4%) with an average waiting time of 80 days. All of them have an increase LKDPI of at least 20 points and two of them improve the ABO incompatibility. The average waiting time is 80 days.

In the second category, out of 133, 30 find a better match (22,6%) with an average waiting time of 79 days. Out of 30 couples, 28 have an LKDPI improvement of at least 20 points and only two couples have a worsening LKDPI result, but it is balanced by either an HLA or an ABO incompatibility improvement. The average waiting time is 79 days.

In the third category, out of 110, 19 find a better match (17,3%) with an average waiting time of 62 days. Out of 19 couples, 11 have an LKDPI improvement of at least 20 points, 7 overcome the ABO incompatibility and one overcomes the HLA incompatibility. The average waiting time is 62 days.

In the fourth category, out of 100, 21 find a better match (21,0%) with an average waiting time of 57 days. Out of 21 couples, just 3 have just an LKDPI improvement of at least 20 points, while 15 overcome the ABO incompatibility and 3 overcome the HLA incompatibility. The average waiting time is 57 days.

It is interesting to notice that the average waiting time decreases with the increase of the LKDPI score. This fact is reasonable: the factors are inversely proportional because for couples with a high LKDPI it is easier (and then it is likely to happen in a shorter time) to find a better match, while for couple with a low LKDPI the potential improvements are more difficult to be found (and then they require more time).

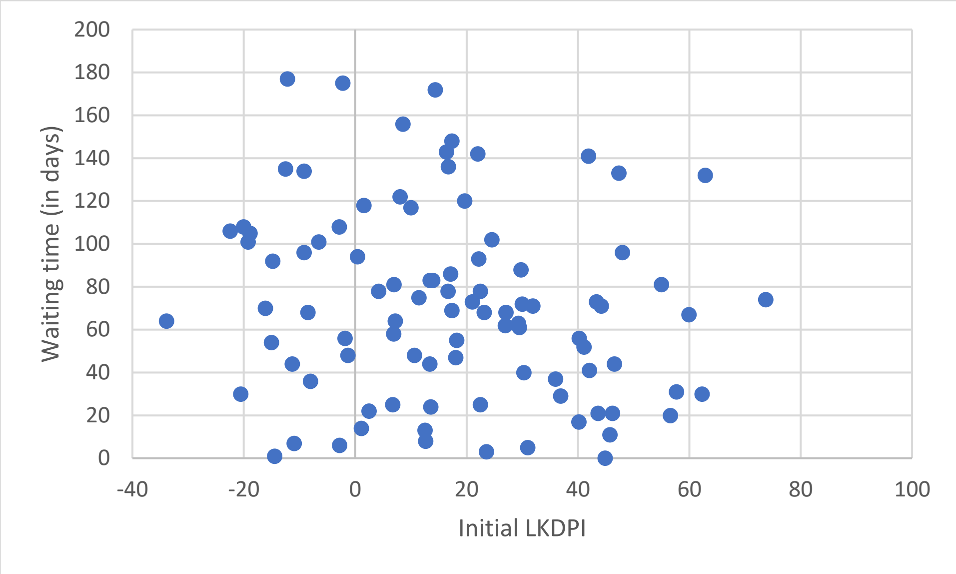

Figure 24: Waiting Time by LKDPI Score.

Different LKDPI improvement thresholds

The same model has been run different times with the same objectives: maximization of the transplantation, minimization of the HLA desensitization processes and minimization of the ABO desensitization process. The only difference is the LKDPI improvement required: in the first case it has been set to 0, while in the second one to 10 points. Frequency of the matches, the pool and the other characteristics did not change.

- Without any LKDPI threshold, the results are the followings: out of the 27 non-transplantable couples, 12 (44%) find a possible transplantation match. Out of the 16 HLA incompatible couples, 9 (56%) avoid the desensitization. Out of the 90 ABO incompatible couples, 48 (53%) avoid the desensitization. Out of the 311 ABO compatible couples, 183 (59%) find a kidney with an LKDPI score improvement.
- With a 10-points LKDPI improvement threshold, the results are the followings: out of the 27 non-transplantable couples, 12 (44%) find a possible transplantation match. Out of the 16 HLA incompatible couples, 8 (50%) avoid the desensitization. Out of the 90 ABO incompatible couples, 43 (48%) avoid the desensitization. Out of the 311 ABO compatible couples, 117 (38%) find a kidney with an LKDPI score improvement of at least 10 points.

With the progressive reduction of the LKDPI improvement threshold, the percentage of the exchanges increases. The overall increase is not sufficient to justify the lowering of the threshold. In fact, the main category that benefits from it is the one of the compatible couples, but their improvement is minimal. The other categories show a higher percentage of matches that either allow the transplantation or avoid desensitization, but it is not as considerable as the other. In reality, it is reasonable to believe that most of the compatible couples would prefer the immediate transplantation with the original partner instead of entering the program and obtaining a minimal LKDPI improvement.

Alternative Proposals

There are other models analyzed through with the same counterfactual exercise. A simplified version of the same model has been studied. The initial requirements were the maximization of the exchanges and the improvement of the LKDPI score, without any objective for the transplantations of incompatible couples and the minimization of the desensitization processes. The pool was the same (444 couples), the frequency was the same and the maximum waiting time was 180 days. Another relevant restriction was the maximum of three pairs involved in the same exchange chain.

The result was an increase of the number of the exchanged couples, but most of them benefitted only from an LKDPI improvement. In fact, the percentage of non-compatible and of the half-compatible exchanged couples decrease.

Previously, another model, less sophisticated, has been applied to a pool of 316 selected couples from the data collected by Kidney and Pancreas Transplant Unit of the School of Medicine of the University of Padua. The only required factor was the improvement of the LKDPI, without favoring the half-compatible and the non-compatible couples. The matching stages are run every 90 days and the couples stay inside the program for a maximum of 360 days. This model has been tested with four LKDPI improvement thresholds:

- Setting the LKDPI threshold at 10 points, the number of matches combined is 121 with an average waiting time of 133 days.
- Setting the LKDPI threshold at 20 points, the number of matches combined is 70 with an average waiting time of 136 days.
- Setting the LKDPI threshold at 30 points, the number of matches combined is 33 with an average waiting time of 141.
- Setting the LKDPI threshold at 40 points, the number of matches combined is 16 with an average waiting time of 126.

LKDPI THRESHOLD	10	20	30	40
PERFORMED TRANSPLANTATIONS	121	70	33	16
% OF TRANSPLANTED COUPLES	38%	22%	10%	5%
AVERAGE WAITING TIME (IN DAYS)	133	136	141	126

Figure 25: Results of the Alternative Proposals.

The choice of not including a prioritization for half-compatible and non-compatible couples is limiting because the focus should be on those couples, since they are in a more complicated situation which relates to higher costs, due to dialysis protocols and desensitization processes needed. The exclusion of objectives finalized at their transplantations is constrictive and is the main reason why this kind of programs are not employed.

Proposal for a new model

Developing a new model for finding matches requires some conditions that need to be respected. In comparison to analyzed model, we can take some points, while other may be different. However, the final goal of the model is to understand the probability of every couples to join or not the program.

For instance, the division of the categories according to the model of Massie et al. (2016) and Rehse et al. (2019) can be kept. We can consider the four categories: "LKDPI lower than 0", "LKDPI between 0 and 20", "LKDPI between 20 and 40", and "LKDPI higher than 40". These categories have created in order to understand their probability for joining the kidney exchange programs. It is reasonable to suppose that:

- The couples belonging to the category "LKDPI lower than 0" will not join the program because the chances to obtain a better kidney is very limited and the risk of waiting more time without a compensation is high. Thus, their probability to join the exchange program is 0.
- The couples belonging to the category "LKDPI between 0 and 20" will join the program with a probability between 0 and 0,5. The choice depends on several factors and on their willingness to wait.

- The couples belonging to the category “LKDPI between 20 and 40” will join the program with a probability between 0,5 and 1. The choice depends on several factors and on their willingness to wait.
- The couples belonging to the category “LKDPI higher than 40” will join for sure the program because it is very likely to find a better match from an exchange program. Moreover, whit such a high LKDPI score, it is likely that there are also ABO or HLA mismatches that can be improved. Thus, their probability to join the exchange program is 1.

This categorization and its percentages assist in the prediction of the number of compatible couples that join the program. The estimation cannot be accurate because the willingness to wait varies for every couple and cannot be foreseen. Genie at al. (2020) shows how the willingness to wait varies according to several personal characteristics of the involved people, such as age and duration of the dialysis.

All the non-compatible couples will take part to the kidney exchange program because of the lack of a viable alternative. All the half-compatible couples (ABO and/or HLA incompatible) will also join the program, with the expectation of avoiding the desensitization processes. It is reasonable to allow them to stay inside the program for a longer time because the expected advantage compensate the risk of waiting more time.

First, the most critical category is formed by the incompatible couples. They should have a fast track in case of a possible match that allows the transplantation. Any exchange chain that includes one (or more) non-transplantable couple should have the priority on the others. Thus, the overall number of the kidney transplantations should be maximized.

Another factor to be included is the minimization through the exchanges of the ABO and HLA desensitization processes. It takes priority over the LKDPI improvement. This choice is important for two main reasons:

- ABO and HLA mismatches are worsening factors for the expected outcome of the kidney transplantations both for the graft loss and for the survival rate and then is recommendable to limit them.
- ABO and HLA desensitization processes are expensive and require time. In Italy, the additional costs related to the desensitization varies from €17.000 to €33.000 depending on the required procedures and on the degree of sensitivity of the patient.

Matches that avoid the HLA desensitization procedures are preferred to the ones that avoid ABO desensitization procedures.

The inclusion of a LKDPI improvement threshold is a reasonable requirement, but it is subordinated to the desensitization processes. If the donor and the recipient of a couples do not have a mismatch, but they decide to join the program anyway, it is required that they improve at least the LKDPI score. A reasonable threshold is 10 points.

Furthermore, for compatible couples, it is more likely that couples, in which the donor is old and/or in which the BMI donor/recipient ratio is not balanced, find a more suitable kidney that ameliorates the LKDPI score.

Conclusion

The increasing number of kidney diseases and the shortage of kidneys for transplantations are critical points for the public health in the world and in Italy as well. Dialysis procedures are helpful treatments, but they do not represent the optimal choice in the long term, neither for the costs nor for the health of the patients. The waiting list for an organ from a deceased donor require a lot of time and cannot be predicted. Anyway, the transplantation from living donor is the best choice, ceteris paribus.

There are incompatibilities among the people that hinder the transplantations and others that can be overcome only through extremely expensive. Thanks to the kidney exchange programs, it is possible to find the best matches for the couples, but it is important which objectives need to be prioritized.

Through the counterfactual exercise conducted on the pool of transplanted couples and incompatible couples in Padua, it has been possible to verify the efficiency of a proposal for an exchange program. The three categories of couples (compatible, half-compatible and incompatible) have different urgencies and the likelihood of participating to a kidney exchange program is not the same.

The priority should be given to the incompatible couples, who do not have a viable alternative for the transplantation but are forced to wait for a deceased donor with a compatible kidney. They should be the first target of the exchange programs.

The half-compatible couples can be transplanted after desensitization, which is an expensive treatment, and does not guarantee the same expected outcome of a compatible kidney. Therefore, half-compatible couples should be favored in finding a match that avoids desensitization. The objective of avoiding the HLA desensitization is prepended to the objective of avoiding the ABO desensitization due to the higher graft reject.

The compatible couples are the ones with less incentive to participate to such programs because they may undergo transplantation, but there are factors that suggests that they may benefit from finding another match. For instance, a younger organ or a more balanced BMI ratio between donor and recipient are factors that improve the expected outcome. The threshold of the LKDPI improvement should balance the expected benefits and the risk of participating without finding a better match, that is the worst option.

The Living Donor Kidney Profile Index (LKDPI) is a measurement that assist in the prediction of the outcome of a transplantation. It is useful to classify the compatible couples and understand their likelihood to take part to a kidney exchange program. A low value of the

LKDPI means a lower probability of finding a better match. Consequentially, a high value implies a high probability of finding a better match.

For this reason, it is useful to create four categories for the compatible couples, according to their LKDPI score. To each category there is a probability associated, which represent the likelihood of participating or not to a kidney exchange program. It is downward according to the LKDPI of the couple. The participation of all the compatible couples is not an optimal choice because a large part will not find a better match and will have to bear the extra costs of the dialysis with all the psychological and physical costs related. The inclusion of the categories is finalized to limit this time waste.

The results of the counterfactual exercise confirmed that the participation of the compatible couples is fundamental because it enlarges the number of couples participating. With a larger pool, it is easier to find a compatible match for the incompatible couples, that can finally undergo the transplantation, and for the half-compatible couples, that can avoid the desensitization processes. Thus, the participation of the compatible couples is fundamental for the right functioning of the kidney exchange programs.

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