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Review

REVIEW OF THE HISTORY OF LIVING DONOR SOLID ORGAN TRANSPLANTS

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Summary

In the history of transplantation, living donors were among the first to be used successfully, with the living donor kidney transplantation being the first successful transplant ever performed on human beings. On December 23, 1954, Joseph Murray and colleagues marked a milestone with the first successful living donor kidney transplantation. The transplant was performed between monozygotic twins; Richard Herrick, affected by renal failure, received a kidney from his twin brother, Ronald, at the Peter Bent Brigham Hospital, Boston, Massachusetts. The graft survival was 8 years. Subsequently, this route was taken for many other solid organs such as, sequentially, the pancreas, liver, intestines, lung, and uterus. For many organs, living donation makes it possible to avoid the shortage of cadaveric donor organs with excellent results for the recipient, often superior to cases of cadaveric donation, whilst maintaining the utmost safety for recipients. The objective of this review is to retrace, organ by organ, all the stages that have marked the recent history of living donor solid organ transplantation, which have allowed us surgeons to achieve the extraordinary results we are able to guarantee our patients today.

Key words: living donor, solid organ transplantation, historical timeline

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INTRODUCTION

The history of solid organ transplantation is characterized by a succession of multiple alternating successes and failures over the last century, up until the great results reported in the past two decades with the advent of minimally invasive surgery techniques.

Since the earliest attempts at organ transplantation, living donors have always been the first real source of organs. In fact, long before the brain-dead cadaveric donor (DBD), the living donor used to be the first and only available source of organs for transplantation on human beings.

Historically, the first organ transplants to be performed were kidney transplants. In the early period of organ transplant surgery, these were burdened with a high failure rate due in part to the lack of essential knowledge about the histocompatibility of tissues between donor and recipient and the absence of immunosuppressive therapies.

Some great pioneers, such as the French surgeon Alexis Carrel, developed techniques that were innovative for their time, making it possible to achieve

the results we see today. Carrel first laid the foundation for the surgical technique of vascular anastomosis, still used in solid organ transplantation today. For his development of these techniques, he was deservedly awarded the Nobel Prize in Medicine in 1912, only one of two surgeons ever to be so honored in history.

But the really big milestones came about 30 to 40 years later, with Yu Yu Voronoy performing the first human-to-human kidney transplant in 1933, followed by the first living-donor kidney transplant in 1954 performed at the Peter Bent Brigham Hospital in Boston, Massachusetts, officially marking the beginning of the history of living-donor solid organ transplantation.

A timeline with all the milestones that mark the history of living donor transplantation, can be traced in Figure 1. The objective of this review is to retrace, organ by organ, all the stages that have marked the recent history of living donor solid organ transplantation, which have allowed us surgeons to achieve the extraordinary results that we are able to guarantee our patients today.

Kidney

Historically, living donor kidney transplantation (LDKT) was the first transplant to be performed successfully on human beings. Initially, experimental procedures were carried out on animals or using animal donor organs. In 1902, the first successful animal (dog to dog) kidney transplantation was performed by the Austrian surgeon Emerich Ullmann [1]. In 1906, the first two renal transplants in humans were performed by Jaboulay and colleagues using a pig donor for one and a goat donor for the other. In 1910, the first xenotransplantation attempt in humans was performed instead. In the case of xenotransplantation, several donor species have been tried: goats, dogs, lambs and monkeys, but always without success. After these initial steps, the Russian surgeon Yurii Voronoy performed the first human-to-human transplantation from a deceased donor, in 1939. The kidney graft never worked and the recipient died two days after the operation. In 1953, in Paris, Jean Hamburger and colleagues performed the first temporally successful human kidney transplantation. The mother of a 16-year-old patient donated her kidney to her son. Then, on December 23, 1954, Joseph Murray marked a milestone with the first long-term successful kidney transplantation: Richard Herrick, a patient with renal failure, received a kidney from his healthy monozygotic twin brother, Ronald, at the Peter Bent Brigham Hospital in Boston, Massachusetts. The graft survival was 8 years [2]. The Nobel Prize in Medicine was awarded to Murray for his efforts in kidney transplantation, in 1990 [3]. On January 24, 1959, the same surgical team performed the first successfully living donor kidney transplant between two dizygotic twins [4]. According to many authors, due to the breaking down of

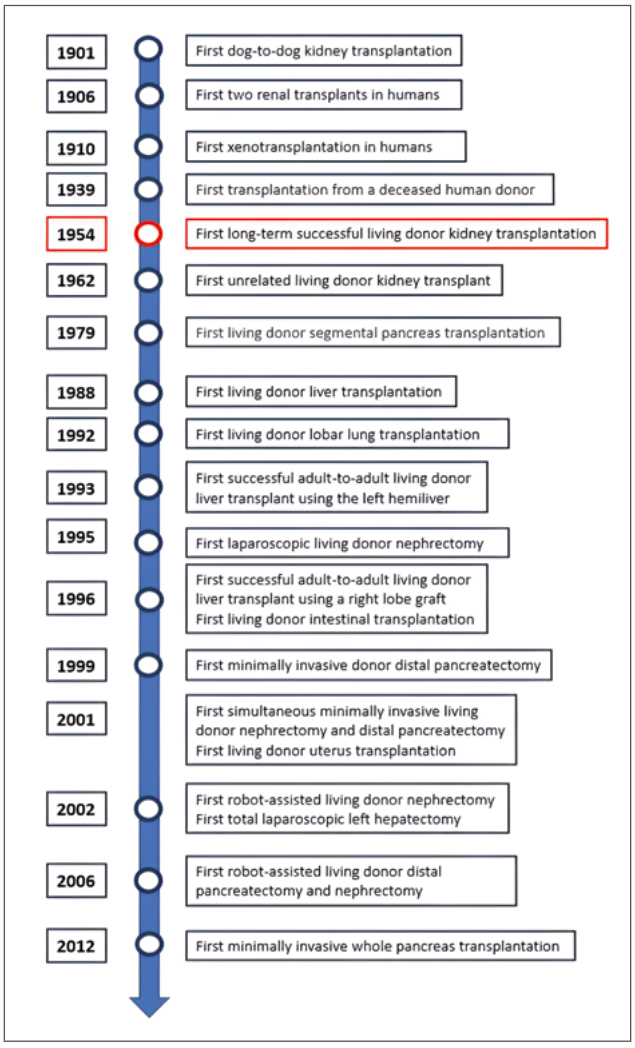

Figure 1. Timeline.

such a genetic barrier, this was the most important case in the history of transplantation. Another similar case was reported by Jean Hamburger and colleagues a few months later in Paris. The two recipients survived 20 and 26 years, respectively, after receiving total-body irradiation as immunosuppression. After this long-term follow-up, the two patients died of cancer. Using irradiation in the period between 1959 and 1962, Hamburger and his group [5] and a second team in Paris headed by Kuss [6] performed four additional long-surviving living donor kideny transplants, but in these case with more distant donors: one case with a non-twin sibling, one case with a cousin as a donor, and in the two Kuss cases donor and recipient were non-relatives. Although they initially seemed very encouraging, these early successes were fortunate exceptions. On April 5, 1962, the introduction of the first immunosuppressive therapy, azathioprine [7], permitted Murray and colleagues to perform an unrelated living

donor kidney transplant that functioned for 17 months [8]. Another major contribution was made by Starzl and colleagues, who in 1963 combined azathioprine with prednisone [9]. Rejection was prevented by the combination of azathioprine and prednisone, reducing the immune barrier without the need for general immunodeficiency. The use of this drug combination became known over the next year, and about 50 new kidney transplant programs were established in the United States. The introduction of cyclosporine in 1978 by Calne and colleagues [10] and its combination with prednisone experimented by Starzl [11] was followed by a proliferation of liver, cardiac, pancreas, lung, and intestinal transplant programs — as well as an increased use of cadaveric kidneys. The consequence, by the late 1980s, was a shortage of all cadaveric organs and a drift back to live donors. Thanks to the consolidation of surgical techniques, in 1995, minimally invasive surgery also took its first steps in the world of transplant surgery. In Baltimore, the first laparoscopic living donor nephrectomy was performed by Ratner and colleagues [12]. Many centers adopted hand-assisted techniques because these are perceived to be faster and safer than the pure laparoscopic technique [13]. In 2002, Horgan and colleagues [14] described the first robot-assisted living donor nephrectomy performed in Chicago, United States. After many years, the superiority of robotic assisted *versus* the pure laparoscopic technique is still under debate [15].

Pancreas

The pancreas was the first extrarenal organ from an LD to be used successfully. The world's first living donor segmental pancreas transplantation (LDSPT) was performed at the University of Minnesota on June 20, 1979, in the same institution as the first clinical pancreas transplant from a deceased donor performed on December 16, 1966 [16]. In the "cyclosporine era" the technical complication rate was higher for LDSPT compared to transplants from cadaver donors. However, the immunological advantages offered by living-related donors ensured better long-term results. LDSPT offered a number of advantages: a preemptive transplantation for simultaneous pancreas-kidney (SPK) recipients avoided the morbidity and mortality risk of dialysis, decreased the rate of rejection given the historically high risk of early rejection and graft loss, and avoided a second operation on the pancreas after the kidney. Because of the potential risks for the donor and the technical challenges in the recipient operation, this procedure has not become very popular since then.

The first minimally invasive donor distal pancreatectomy was performed in the same institute in 1999. A hand-assisted laparoscopic donor distal pancreatectomy was performed in an attempt to decrease the morbidity associated with donor open distal pancreatectomy [17]. The same group described the first simultaneous minimally invasive nephrectomy and distal pancreatectomy from a living donor in 2001 [18].

Just as the advent of robotic surgery enabled increasingly better outcomes for kidney donors, reducing and minimizing intra- and post-operative risks, achieving better cosmetic outcomes, reducing pain, and reducing postoperative hospital stay, so too did robotic surgery emerge as an excellent surgical procedure for LDSPT. The first robotic-assisted distal pancreatectomy and nephrectomy for a LD pancreas–kidney transplantation was performed in 2006 at the University of Illinois in Chicago and proved a promising technique. The application of minimally invasive techniques has allowed an increased acceptance of the procedure among potential donors and may increase the number of donors for this life-saving transplantation. More recently, the first whole pancreas transplantation performed laparoscopically with the assistance of the da Vinci SiHD surgical system was reported by Boggi and colleagues in 2012 [19] at the University of Pisa in Italy.

Short-term and long-term outcomes of LDSPT recipients have been well documented and, for 3 decades, have been comparable to or better than the outcomes of deceased donor (DD) transplants [20]. However, over the last decade, with improvements in brain-dead donor management, organ preservation, surgical techniques, and especially immunosuppression, DD pancreas transplant outcomes have significantly improved [21]. In a recent series by Kirchner and colleagues [22], no donor mortality was reported; moreover, the risk of donor major perioperative complications requiring reoperation was 10%, new onset of diabete mellitus (DM) requiring oral hypoglycemic management was diagnosed in 7 (15%) donors and insulin-dependent DM in 5 (11%).

Liver

The idea of using living donor liver grafts for orthotopic liver transplantation was conceived at the end of the 1960s, but 20 years passed before this idea was implemented in clinical practice. The increase in interest in living donor liver transplantation (LDLT) in the late 1980s was a response to the increased demand for organs at a time when liver transplantation was becoming increasingly successful. The demand for organs has remained high, especially in countries without deceased donor organs.

On December 8, 1988, Raia and colleagues made the first attempt at a living donor transplant in Brazil on a 4-year-old girl suffering from biliary atresia [23]. The donor of the liver graft composed of segments II and III survived, but the recipient died on the sixth postoperative day during hemodialysis. The same authors made a second attempt on July 21, 1989, on a recipient suffering from hepatic fibrosis and Caroli's disease. The donor had a regular

postoperative course, while the recipient's course was characterized by slow functional recovery of the graft with persistence of jaundice until the twenty-fourth postoperative day; the subsequent outcome of this recipient was not reported [23].

That same month, Strong et al. in Australia performed the first successful adult-to-pediatric living donor transplant, using a graft composed of segments II and III (left lobe) [24]. After this first great success, Broelsch et al. refined the surgical technique carrying out the first adult-to-child LDLT program and made LDLT a valuable lifesaving procedure for pediatric patients [25]. Boillot in Lyon and Otte in Belgium performed the second and third pediatric LDLTs in July 1992 and July 1993, respectively. The first series of adult-to-child LDLT was then reported both in the United States [26] and in Europe [27].

Adult-pediatric LDLT has developed rapidly in Asia, where deceased donor liver donation is virtually absent [28]. In 1990, in Japan, Nagasue and colleagues performed the first Asian LDLT in 1989 [29]; the recipient died 285 days after transplantation due to rejection and subsequent multiorgan failure. Subsequently, in June 1990 Ozawa and colleagues performed the first successful LDLT, and in 1992 they reported the first 20 series [30]. After experiencing four cases of hepatic artery thrombosis, they became proponents of the microvascular surgical technique for hepatic artery reconstruction, which revolutionized the practice of LDLT and led to exceptional outcomes [31].

Following the successes achieved with pediatric patients, LDLT was extended to adult patients. In 1991, Haberal and colleagues performed the first attempt at adult-to-adult LDLT using the left hemiliver, but the outcome was unsatisfactory [32]. In 1993, a second attempt was performed with success by Makuuchi and colleagues [33] at the the Shinshu University. The donor was a son donating to his mother, affected by primary biliary cirrhosis. The recipient survived for 17 years after the operation until she passed away at 70 years of age. Instead, in 1996, the first successful adult-to-adult right lobe LDLT was performed in Hong Kong, at Queen Mary Hospital [34]. In this first case, the middle hepatic vein was included in the right liver graft, leading to the onset of the problem of small-for-size syndrome. The same group reported their first series shortly after [35]. Further advances in LDLT techniques were then reported in other Asian centers. We can mention the report by Miyagawa and colleagues in Japan, who in 1998 showed how to add the caudate lobe to the left lobe graft [36], and the case of the use of dual grafts from two different donors transplanted into one recipient reported by Lee and colleagues in Korea in 2001 [37]. In Table I, donor outcomes in right lobe living donor donation are reported.

Living donor hepatectomy has traditionally required extensive laparotomies, resulting in donor cosmetic damage and also postoperative pain, and slow resumption of daily activities. This may lead to a compromise in quality of life after the donation. In 2002, Cherqui and colleagues [38] successfully performed the world's first total laparoscopic left hepatectomy for LDLT. After this initial success, Soubrane and colleagues demonstrated the feasibility of laparoscopic donor hepatectomy of the left lateral sector from an adult donor for pediatric LDLT [39]. A kind of "hybrid" technique [40] was described by Koffron using the laparoscopic approach to mobilize ligamentous attachments of the liver and a conventional open technique to resect the hepatic parenchyma through an upper midline incision. This hand-assisted technique is applicable to various major hepatic resection procedures, including right lobe living donor hepatectomy.

In 2011, in partnership with Ugo Boggi from the University of Pisa, Italy, the first European, and the second worldwide, ever performed living donor right lobe procurement for liver transplantation was performed at the ISMETT center in Palermo [41].

Since 2013, the improvement in surgical techniques of the total laparoscopic donor hepatectomy of the left lateral section for pediatric liver transplantation [42] has subsequently enabled the development of techniques for laparoscopic right lobe donor hepatectomies. The first important series was reported by Suh and colleagues [43], who in 2017 published the results of their laparoscopic right lobe living donor hepatectomy. Though the operating times and rates of biliary complications were higher, the length of stay and complication rates were similar to donors undergoing open surgery, allowing the further application of this minimally invasive technique. In these series, the right lobe was extracted through a Pfannenstiel incision, which is much more cosmetically desirable and causes less postoperative pain.

Robotic surgery is also playing an increasingly important role in living donor liver procurement. A recent series by Broering et al. reported 35 consecutive cases of robotic right lobe procurement using a robotic technique, with significantly decreased blood loss and a shorter hospital stay compared to the open procedure [44].

To date, more than 10,000 LDLT have been performed worldwide. Some technical and ethical controversies identified in past years have been resolved. Undoubtedly, LDLT saves lives but at the expense of a living person. Therefore, whether it represents a turning point or a "dark chapter" in the history of liver transplantation is still a matter of debate. Nonetheless, the knowledge and practice of LDLT has made recent advances possible in all related specialties, including hepatobiliary surgery and deceased donor liver transplants.

It is hoped that, with the reduction of donor morbidity, with objective publications and with the open discussion of results, a consensus can be reached in the near future.

Table I. Donor outcome after right lobe living donation.

Author	Year	Country	No. of donors	Morbidity No. (%)	
Ito et al. [105]	2003	Japan	200	69 (34.5)	0
Gruttadauria et al. [106]	2008	Italy	75	23 (30.6)	0
Baker et al. [107]	2009	USA	66	14 (21.2)	0
Adcock et al. [108]	2010	Canada	202	57 (28)	0
Azoulay et al. [109]	2011	France	91	51 (56.0)	0
Kim et al. [110]	2012	Korea	500	139 (27.8)	0
Salah et al. [111]	2012	Egypt	100	38 (38)	1 (1)
Kim et al. [112]	2013	Korea	300	48 (16)	0
Facciuto et al. [113]	2013	USA	137	45 (33)	1 (0.7)
Hong et al. [114]	2019	Korea	1116		3 (0.1)

Lung

As with other organs, the shortage of brain-dead donors has always prompted surgeons to seek the possibility of living-donor lobar lung transplantations (LDLLT). The first case of LDLLT was reported in the literature from the Starnes group at Stanford University, in 1992 [45]. In the first case, a mother's right upper lobe was transplanted to her 12-year-old daughter affected by bronchopulmonary dysplasia. The operation was a success and the patient survived. The second attempt involved a 3-year-old patient. The patient was affected by Eisenmenger's syndrome. He received a right single-lobe transplantation form his mother using the donor's middle lobe. Unfortunately, the patient died of primary graft dysfunction. This unsuccessful experience suggested a change of strategy, and the same group proposed a new technique, harvesting the lower lung lobes of two healthy living donors for a bilateral LDLLT [46,47]. In that case, the LDLLT procedure consisted of the use of the right and left lower lobes from two different donors, transplanted to the same recipient after bilateral pneumonectomy. Due to the small volume of the two transplanted lobes, surgeons have always been inclined to perform this procedure only on pediatric recipients, almost exclusively to cystic fibrosis patients [47].

Through the consolidation of this technique, LDLLT application was extended to other indications, including infectious, obstructive, vascular and restrictive diseases [48–50]. Even if LDLLT was initially developed in the US, the changes in the allocation system caused its gradual decrease in use. In recent years, most of the reports were received from Japan, where the waiting time for a cadaver lunge exceeds 800 days [51]. Besides the Japanese experience, England [52], Brazil [53], and China [54] have reported their small number of results. After many years of practice, Date and colleagues demonstrated that bilateral LDLLT provides equal or better survival than conventional cadaveric lung transplantation [55]. Currently, the group led Date, at Kyoto University, is continuing to pioneer this procedure with excellent results in a difficult group of patients.

Intestine

Intestinal transplantation (IT) has become a curative treatment for patients with irreversible intestinal failure and life-threatening total parenteral nutrition (TPN) complications (such as hepatic failure, absence of vascular insertion and recurrent catheter infections). As reported by the International Intestinal Transplant Registry [56], until 2015, 82 programs permitted 2887 IT in 2699 recipients. At the last update, patient survival rates at 1, 5 and 10 years were 76, 56 and 43%, respectively. Grafts that included a colon segment had better function. An important improvement in graft survival was made possible by the use of induction immune-suppression therapy, the inclusion of a liver component, and maintenance therapy with rapamycin. Outcomes of IT have modestly improved over the past decade even if the volumes have recently declined.

Especially at the beginning of the experience with IT, the vast majority of IT was from cadaver donors; only a few hospitals used living-related donors with varied techniques and results. In 1988, Grant and colleagues performed the first worldwide case of successful cadaveric transplantation of a combined small bowel/liver graft in London, Canada [57]. In the same year, Deltz et al. reported the first successful case of living donor intestinal transplantation (LDIT) [58]. In this case, a woman donated a 60 cm segmental graft to her 42-year-old half-sister suffering from short gut syndrome. From the same group, a second case was also performed, in which a 5-year-old recipient received a graft from her mother, but this graft was lost due to rejection after 12 days. The second case of successful allogeneic clinical LDIT was performed in Leeds, United Kingdom, in 1995 [59]. This case in many ways typifies the 'last resort' status of bowel transplantation in the clinical setting. The patient was a 28-year-old woman who had undergone total colectomy for Gardner's variant

of familial adenomatous polyposis but subsequently developed a desmoid tumor of the mesentery involving the superior mesenteric vessels, causing intestinal obstruction at multiple sites. After resection of the tumor, the patient was left with a duodenostomy. The patient's mother donated a 1.8m length of distal ileum on a pedicle of distal superior mesenteric artery and vein. These supply vessels were anastomosed to the recipient's aorta and inferior vena cava. The recipient survived for 18 months before dying of pneumonia.

The first LDIT standardized surgical technique was reported by Gruessner et al. in 1997 [60]. This group, at the University of Minnesota, first performed a LDIT in a 16-year-old paraplegic patient with life-threatening TPN complications. The donor was his father, who was subjected to the resection of 200 cm of the ileum preserving the vascular pedicle composed of the ileocolic vessels. This graft vascular pedicle was anastomosed to the recipient's infrarenal aorta and cava; an end-to-end anastomosis between the recipient's jejunum and the donor's ileum permitted to restore bowel continuity. The postoperative courses were uneventful for both donor and recipient. The maintenance immunosuppression was with tacrolimus, mycophenolate mofetil, and prednisone. After one year, in both the donor and recipient, the dosage of urine methylmalonic acid demonstrated good vitamin B12 absorption. The recipient was discharged on postoperative day 21, completely off TPN; he gained 20 kg, and had no evidence of infection, rejection, or graft-versus-host disease.

After 25 years, Gruessner has recently published the results of the long-term use of this standardized technique [61]. In a systematic review, he documented 85 cases of LDIT worldwide performed in 20 different transplant centers in 12 different countries. In about 70 transplants, the standardized technique was used. There was no difference in outcome between LD vs DD intestinal transplants. Long-term studies have shown that > 10 years of graft function is not uncommon. Since the introduction of the standardized surgical technique, LD intestinal transplantation has evolved from an experimental to an established and standardized procedure.

As has been the case with other organs, recently, Wu and colleagues [62] reported the first 5 cases of robotic-assisted LDIT. In this scenario, as for other organs, the minimally invasive donor procedure was associated with less post-operative pain, a shorter hospital length of stay, and a faster recovery of bowel function compared to open surgery.

Uterus

Uterus transplantation (UT) is still considered a highly experimental clinical procedure, although it has proved successful in many settings. The first worldwide UT attempt performed from LD was reported in 2001 by Fageeh et al. in Saudi Arabia [63]. The second human UT attempt took place more than ten years later in Turkey by Ozkan et al. [64], and in this case it was performed using a uterus from a DD. No births were demonstrated from these single cases of LD and DD transplantations. The first world successful living-donor uterus transplantation (LDUT) resulting in a healthy pregnancy was performed in 2012 in Sweden, reported by Brännström et al. at Sahlgrenska University Hospital [65]. This was made possible after more than ten years of basic research, including comprehensive animal and clinical studies [66]. A few years later, in 2019, Brännström and colleagues showed the results of 15 procedures which had been performed in Sweden, resulting in 10 children being born from women with transplanted uteri. Lastly, in 2018 in India, Puntambekar and colleagues [67] reported the first case of laparoscopic-assisted uterus retrieval for LDUT. They demonstrated how laparoscopic-assisted uterus retrieval offers all the advantages of a minimally invasive surgical technique, with a reduction in the morbidity for the donor. Moreover, the first case of a live birth after a robotic-assisted laparoscopy in LDUT was reported in 2020, again by Brännström et al. [68], with a uterus aged 64 years at delivery, thereby providing proof-of-concept for the use of minimally invasive surgery in this new type of transplantation. Further developments in robotic UT surgery are needed to progress to complete robotic surgery in a live donor and in the recipient.

Conclusions

Living donors, in the history of transplant surgery, have always been an indispensable source of organs to make up for the lack of cadaveric donor organs. For ethical and moral reasons, donor safety has always remained at the center of the donation process in order to minimize risk as much as possible. In the future, the use of artificial intelligence and robotic systems, in both surgical procedures and preoperative diagnostics, will certainly allow further minimization of the risks faced by donors, with a net benefit in terms of morbidity and mortality in the host as well. Even now, compared with the early days of living donation, immense strides have been made.

It is also important to mention the advent of genetic engineering, which in the perhaps not-too-distant future may make it possible to obtain engineered organs without the need for living donors.

Conflict of interest statement

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Ethical consideration

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