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Title: Can living donor liver transplant in the United States reach its potential?

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Abbreviations:

Living donor liver transplant (LDLT)

Deceased donor liver transplant (DDLT)

Non-directed living liver donation (ND-LLD)

Model for End Stage Liver Disease (MELD)

United Network for Organ Sharing (UNOS)

Non-simultaneous extended altruistic donation (NEAD)

Minimally invasive donor hepatectomy (MIDH)

Laparoscopy-assisted right hepatectomy (LARH)

Purely laparoscopic donor hepatectomy (PLDH)

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Abstract

Living donor liver transplantation (LDLT) is a vital tool to address the growing organ shortage in the United States caused by increasing numbers of patients diagnosed with end-stage liver disease. LDLT still only makes up a very small proportion of all liver transplants performed each year, but there are

many innovations taking place in the field that may increase its acceptance amongst both transplant programs and patients. These innovations include ways to improve access to LDLT, such as through non-directed donation, paired exchange, transplant chains, transplant of ABO-incompatible donors, and transplant in high MELD patients. Surgical innovations, such as laparoscopic donor hepatectomy, robotic hepatectomy and portal flow modulation, are also increasingly being implemented. Policy changes, including decreasing the financial burden associated with LDLT, may make it a more feasible option for a wider range of patients. Lastly, center-level behavior, such as ensuring surgical expertise and providing culturally competent education, will help towards LDLT expansion. While it is challenging to know which of these innovations will take hold, we are already seeing LDLT numbers improve within the last two years.

Despite increasing numbers of liver transplants performed each year, there remains a growing gap between organ supply and demand due to the rise of chronic liver disease in the United States (US)[1]. Expansion of living donor liver transplant (LDLT) is vital to close this gap, and while there has been substantial technical progress since its inception, it still comprises only ~5% of all liver transplants each year[2] (**Figure 1**). LDLT offers many benefits over deceased donor liver transplant (DDLT) including lower risk of pre-transplant and overall mortality, shorter waiting times, better outcomes, and increased access for those disadvantaged under the MELD allocation system or for those who otherwise may not have paths to deceased organs[3]. Despite LDLT's multiple benefits, it has been slow to be adopted in the US, perhaps because of lack of the necessary surgical expertise in many programs, reluctance to embrace it among transplant teams, and the difficulty of conveying its benefits to potential donors and recipients in an allocation system that prioritizes disease severity.

There are many new innovations taking place in the field that have the potential to increase LDLT. These include non-directed living liver donation (ND-LLD), paired exchange, use of ABO-incompatible organs, use of LDLT in high MELD patients, new surgical techniques, and public policy and center behavior-related changes. It is challenging to predict whether any of these innovations will allow LDLT to grow, but increased knowledge among all health care providers is necessary to promote the maximal expansion of this lifesaving procedure.

The past and present state of LDLT

The first successful LDLT in the US was performed in 1989 at the University of Chicago and involved the donation of a left lateral segment graft from a mother to her 21-month-old daughter with biliary atresia[4]. While early LDLT involved only the transplantation of left lateral segments, early allograft dysfunction (EAD) prompted the need to transplant larger grafts, such as right liver lobes[5,6]. Since that time, hundreds of adult-to-adult LDLTs have been performed each year in the US[1] with most currently being right lobe donations[7].

While in the early days of LDLT, there were some recipient and donor complications, highly publicized donor deaths, and reports demonstrating inferior outcomes[8], it has become clear that with increased center experience, LDLT has post-transplant outcomes similar to DDLT[9]. Centers outside of the US lead the way in LDLT given the relative lack of deceased organs. Asan Medical Center, in South Korea, has conducted over 5,000 LDLTs since 1989, and with its significant expertise, this center has reported excellent surgical outcomes for both donors and recipients with low morbidity and mortality rates[10]. In the US, the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL), a

NIH-funded, multi-center study investigating the recipient and donor outcomes in LDLT in the US, paved the way for LDLT research. In the original A2ALL study, 90-day and 1-year survival for LDLT were both >80%[11], and after following patients prospectively, 10-year survival for LDLT was significantly higher than DDLT[9,12]. The survival benefit of LDLT has also been demonstrated across all MELD scores[13]. A recently published meta-analysis found LDLT to be associated with reduced risk of mortality of 17%, 15%, and 13% at 1-, 3-, and 5-years post-transplant with similar graft survival, lower MELD at transplant, shorter waiting time, and lower risk of rejection compared to DDLT[14].

Though many studies on LDLT outcomes focus on post-transplant outcomes, including donor safety, recipient complications, graft survival, and rejection, it is clear from studies examining survival that the true benefit of LDLT is derived from reduced waitlist mortality[12,14]. Compared to DDLT, patients undergoing LDLT do not have to wait as long on the waiting list and are more likely to be transplanted when they are less sick. LDLT has additional benefits in that it is an elective surgery where anatomic variants can be planned out and programs can screen ideal donors[14]. Centers that have been successful in LDLT have advocated for LDLT for most patients regardless of disease etiology or MELD score[3].

Most transplant programs, however, base their decisions regarding the use of LDLT on the perceived availability of deceased donor organs. With the new UNOS allocation policy based on acuity circles, it is thought that there will be a reduction in the geographic variation in MELD scores at the time of transplant. Though data thus far is scarce and possibly impacted by the COVID-19 pandemic[15], preliminary Organ Procurement Transplantation Network (OPTN) data suggests that the new policy has led to increased access for high-MELD patients and decreased access in low-MELD patients, thereby necessitating an increased use of donation after circulatory death (DCD) organs[16]. Prior work has demonstrated superior outcomes for LDLT in low-MELD patients as compared to DCD transplant[17]. Thus, if these patterns continue, programs may look to broaden their LDLT programs to increase organ access.

Innovations in LDLT

It has become clear that as center experience has increased, the outcomes of living donation have improved, including safety and efficacy. Additionally, a focus on reduced waitlist mortality truly highlights LDLT's survival benefits. There are several innovations taking place that have the potential to increase the numbers and acceptance of LDLT. While it is difficult to know whether living liver donation will ever be utilized as often as it is in kidney transplantation (34% of all kidney transplants

performed each year)[2], it is imperative to continue to grow LDLT in order to try to address increasing organ shortages and to decrease waiting list mortality. **Figure 2** highlights all of the innovations to be discussed.

Non-Directed Living Liver Donation (ND-LLD)

First, LDLT numbers may improve by increasing access for those candidates without any identified matching donor through non-directed living liver donation (ND-LLD). ND-LLD, whereby an organ is transplanted from a donor who is unknown by the recipient, first started with kidney transplant[18]. It is a procedure that has been adopted by only a small percentage of centers performing LDLT in the US and makes up a very small percentage of all liver transplants each year. A recent study by The University of Toronto demonstrated that ND-LLD is safe for both donors and recipients with no donor deaths and one-year recipient survival above 90%. Despite its safety and efficacy, there are several unresolved issues with ND-LLD, including allocation principles. Currently, there is no data on the best practice for allocation of non-directed liver donor organs. Many have been left lateral segment grafts donated to children, but to date, there has been no standardized recommendation. There is also no standardized process for assessment of non-directed donors, though most centers pay particular attention to the psychosocial evaluation.

Additionally despite the protection of anonymity, many centers remain concerned about donor motivation, ethics, and risk assessment[18]. Non-directed donors do not necessarily have a clear incentive to donate, such as to help a family member, friend or loved one. The lack of a clear incentive elicits global fears surrounding historical organ trafficking and coercion of donors that targeted vulnerable populations[19]. To address these concerns, UNOS has developed specific guidelines for ND-LLD that deem ND-LLD to be an ethically justifiable form of organ donation provided programs use a strict informed consent process, appropriate donor evaluation, and equitable organ allocation[20].

Non-directed kidney and liver donation have been increasing significantly each year. In 2017, 4.4% of all living kidney transplants were non-directed, which increased to 6.3% by 2020. In liver, according to publicly available OPTN data, non-directed donors made up 3.2% of all living donor transplants in 2017 and increased to 11.8% by 2020, though this has mainly been concentrated at particular centers[2] **(Figure 3).** If this trend continues, the addition of ND-LLD can reasonably be expected to increase total LDLT numbers.

Paired exchanges and transplant chains

Paired exchange is a potential method to increase access and occurs when pairs of incompatible donors and their recipients exchange organs leading to two compatible transplant pairs. Incompatibility can occur with regard to ABO-blood type, hepatic mass, and anatomy and potential donors are often rejected for these exact reasons[21]. Though theoretically greater numbers of transplants could take place with paired exchange given recipients can be better matched with compatible donors, thus far, paired exchange has occurred in small numbers of select US transplant centers.

Because there could be unexpected findings at the time of operation, such as altered anatomy, and because there needs to be communication between donor and recipient operative teams, most of the paired exchanges that have taken place to date have been within the same center. Performing both procedures at the same center has also been standard given the liver is sensitive to prolonged cold ischemia time and thus may be adversely impacted by distant travel[21]. A potential concern with all types of paired exchange is that a donor could decide to back out of an exchange, thereby leaving a recipient without an organ[22], however this has been demonstrated to be very rare with kidney donation[23]. This scenario is sometimes avoided by performing the surgeries simultaneously, though this is not always possible. One can imagine a policy by which recipients whose donors drop out are prioritized for transplant with a deceased donor through UNOS, though no such policy yet exists.

For liver, there is currently no organization or central database that oversees exchanges. While such a system does exist for kidney paired exchange, there are additional considerations for liver including different mortality rates and post-operative complications, higher financial cost, and issues of organ transportation[24–27]. A centralized, standardized system would be beneficial to increase the number of exchanges and to start to overcome these additional challenges faced by liver paired exchange.[21]

One way to combine ND-LLD and paired exchange is by starting a transplant chain, known as a non-simultaneous extended altruistic donation (NEAD). NEAD is an extension of the paired exchange process that creates the greatest benefit for the greatest number of patients. The chains begin with a non-directed donor who donates to a recipient who has a willing, but incompatible, donor. Then, that incompatible donor will donate to a different compatible recipient who has an incompatible donor, and so on and so forth. While successful for many years in kidney transplantation[28], the first successful liver transplant chain in the US only took place last year[29]. NEAD and other types of paired exchanges can significantly increase the number of transplants without the requirement that they be done simultaneously[30].

ABO-incompatible LDLT

The safe use of ABO-incompatible (ABO-I) grafts may be an additional way to increase LDLT numbers. In fact, the transplant of the A2 phenotype of blood group A to blood group O patients has been successful[31], though special immunological protocols are not necessary for this type of transplant. The use of other ABO-I grafts, however, is typically avoided given the increased risk of antibody-mediated rejection[32], higher incidence of hepatic artery and biliary complications, and decreased graft survival. In certain areas of the world, where deceased donation is not an option, it has been necessary to develop protocols to utilize ABO-I grafts while simultaneously reducing the risk of poor outcomes. Currently, between 10-20% of Japan and Korea's LDLTs utilize ABO-I donors, by focusing on desensitization protocols[33]. In the US, however, this practice still remains very limited and is usually reserved for emergency situations. With the data that we do have, it seems that long-term survival of recipients of ABO-I grafts is similar to that of recipients with ABO-compatible grafts[34]. The institution of standardized protocols for desensitization in the US and the continued study of long-term outcomes may increase the use of ABO-I donors, though it is unclear how quickly this will occur.

LDLT for High MELD Patients

The use of LDLT for high MELD patients has historically been controversial given concern about success rate and potential risk to the donor if the transplant were to fail. More recent evidence, however, suggests that LDLT in high MELD patients can actually be quite successful[35]. A recently published study, for example, demonstrated that patients listed for LDLT with MELD>25 from 2008-2017 had lower death/delisting, higher rates of transplant, and superior 5-year overall survival compared to DDLT in an intention-to-treat analysis. This was true even in patients with hepatorenal syndrome[36]. The benefit of LDLT has also been shown in acute on chronic liver failure (ACLF). A retrospective study of 218 ACLF patients found post-transplant survival to be similar between ACLF grades and that in those who did not receive LDLT, survival was very poor at 5.9%[37]. The use of LDLT in high MELD patients in the US may not be necessary right now given allocation is based on degree of illness as determined by the MELD score. However, if the organ shortage continues to grow, median MELD at transplant rises, or if allocation changes, it is important to consider the possibility of LDLT in higher MELD patients.

New Surgical Techniques

An additional way to increase LDLT acceptance is by making the surgery safer and less morbid for both donor and recipient. One such surgical innovation is minimally invasive donor hepatectomy

(MIDH). Three minimally invasive techniques exist—laparoscopy-assisted right hepatectomy (LARH), purely laparoscopic donor hepatectomy (PLDH), and robotic donor hepatectomy[38]. With LARH, the right liver is mobilized using a laparoscopic approach, but the liver is actually resected by an open method. Compared to an open approach, LARH is associated with reduced blood loss, need for less pain control, and a lower post-operative complication rate, but does lead to a longer operative time[39]. PLDH is performed much less commonly given it requires greater expertise and is potentially more dangerous with exposure of multiple large vessels during the operation. In the small number of publications on PLDH, it has been associated with fairly similar outcomes compared to LARH[40,41]. There has been even less published experience with robotic donor hepatectomy, but in the cases that have been done, the results are similar to PLDH[42,43]. One recent study found that robotic surgery patients required less analgesia and had shorter length of stay with fewer complications[44]. Because all three techniques are technically challenging, surgical and center expertise is required. It is important to continue to study these techniques in LDLT given their introduction has been attributed as a major driving factor in the increase in living donor surgeries in kidney transplantation[45].

There is a newly utilized surgical technique that has been performed known as living donor hepatectomy and partial liver segment II-IV liver transplantation with delayed total hepatectomy (LD-RAPID)[46]. This procedure uses a partial left lateral segment (II and III) and transplants this into a recipient who has undergone a left hepatectomy with the right liver intact. The left segment is then allowed to grow sufficiently at which point the recipient is taken back to the OR for right hepatectomy. This procedure has the potential to allow for increased numbers of left lobe grafts which is safer for the donor, but there still remains a lot to be learned regarding the technicalities of the procedure[47]. Currently, it has only been described for those with colorectal metastases or those with compensated hepatocellular carcinoma who do not otherwise have suitable donors[47,48].

Portal flow modulation (PFM) is an additional surgical tool that can make transplants safer by preventing EAD and can increase the potential donor pool by allowing for the transplant of smaller grafts. EAD is thought to possibly be secondary to excessive portal flow transmitted to the graft in the postperfusion setting. Thus, modulating this excessive portal flow via splenic artery ligation, creation of a portosystemic shunt, splenectomy, or pharmacologic manipulation remain options[49]. The use of these techniques, however, are controversial given they may increase operative times, transfusion requirements, and infection risk[50]. A recent retrospective review conducted in Japan found that PFM helped to prevent EAD with minimal surgical risks in ABO-I or older donors[51]. The fact that not all

recipients benefitted implies that the data behind PFM for all patients remains mixed and it is perhaps best utilized in particular patient populations.

Policy

There are several policy changes that have been proposed to try to increase the number of LDLTs performed in the US. First, the idea of "financial neutrality" for donors has been proposed as a policy change that would decrease the financial burden suffered by all living donors. What this entails would be payment for all medical and travel expenses, compensation for lost wages, and reimbursement of other expenses. The National Living Donor Assistance Center (NLDAC) recently implemented a program that covers lost wages, travel and lodging, and dependent care for LDLT donors. Though this is certainly a step in the right direction, the determination of need is still made based on the recipient's income, which may not always reflect donor's financial capability[52]. Expansion of programs like these to be inclusive of those with all levels of financial need, will likely be imperative going forward to improve access organs.[53]

Some have gone a step further to suggest that not only should financial disincentives be removed, but that financial incentives should be provided. Financial incentives are distinct from removal of disincentives in that incentives mean the donor would actually profit from the act of donation[54]. This approach could decrease the gap between organ supply and demand and lead to fewer deaths of patients on the transplant waiting list. Providing incentives can actually lead to healthcare cost savings. In the kidney literature, there was a cost-analysis study performed that demonstrated cost savings of up to $12 billion per year with a government-initiated compensation program[55]. The potential pitfall of this type of approach is that it could be coercive especially for poorer, more vulnerable populations. In fact, in countries, such as Iran or Pakistan, that have a financial incentive program for organ donation, over 70% of kidney donors were from socioeconomically disadvantaged donors[56,57]. Though this system has led to the absence of a renal transplant list in these countries, there are obviously concerns regarding the patient population that is mainly targeted by this approach.

With regard to health insurance, some have proposed that lifelong health insurance should be provided to all donors to cover all health care costs that may or may not be related to the donation[58,59]. Right now, with the Affordable Care Act, insurance companies cannot discriminate on the basis of prior medical conditions, including liver donation or transplant. However, as insurance legislation is subject to change, this is not always guaranteed to be the case. Living donation can also impact disability and life

insurance policies, so donors are advised to talk to their individual insurers before making the decision to donate.

Center Behavior

Nationwide changes are necessary to increase LDLT, but ultimately, some of the greatest challenges faced in LDLT expansion occur at the center-level. However, centers must develop different initiatives in order to expand LDLT. First, centers that do not currently have LDLT programs need to think creatively about how to logistically start them. It may be helpful to establish a standardized process and infrastructure by which experts at established national or international centers can assist in training both fellows and faculty members, provide mentorship to new living donor teams, and proctor early cases. To encourage the establishment of new programs and because center experience is a major driving factor in outcomes[11], risk adjustment of the outcomes for the initial cases in UNOS reporting could be considered to allow a center to grow.

For centers that already have an established LDLT program, it is important to think about ways to increase utilization. First, programs can help to increase awareness of living donation within both the medical and patient communities. Awareness of LDLT amongst community practitioners could increase referrals to transplant centers for patients who otherwise may not have been transplantable under the current MELD-based system. Increasing education within the patient community through pamphlets, advertisements, or social media, could lead to additional inquiries for both directed and non-directed donation. In living kidney transplantation, culturally competent educational material provided in multiple different languages has actually led to decreased disparities in access to transplantation[60]. As program sizes increase, it will be important to be able to openly discuss reluctance and hesitancy for both physicians and patients, and to be able to troubleshoot when problems arise.

Conclusions

LDLT can improve access to transplant and lead to superior outcomes for patients awaiting LT in the US. With waitlist mortality remaining stagnant and high, increased utilization of LDLT provides a pathway to closing the gap between organ supply and demand. There are several new innovations to increase LDLT numbers including ND-LLD, paired exchanges, use of ABO-incompatible grafts and transplant in high MELD patients. New surgical techniques offer exciting new possibilities to make surgery less burdensome for both recipients and donors. Additionally, public policy changes can help to address some of the current limitations of LDLT, many of which are financial. Lastly, transplant centers

can help to increase LDLT by ensuring surgical expertise and by providing culturally competent education to community practitioners, patients, and their families. While there is still much to learn and there are always ways to improve upon the process, LDLT is moving in the direction toward addressing the growing organ shortage in the United States.

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Figure 1: Changes in Living and Deceased Donor Transplant Over Time

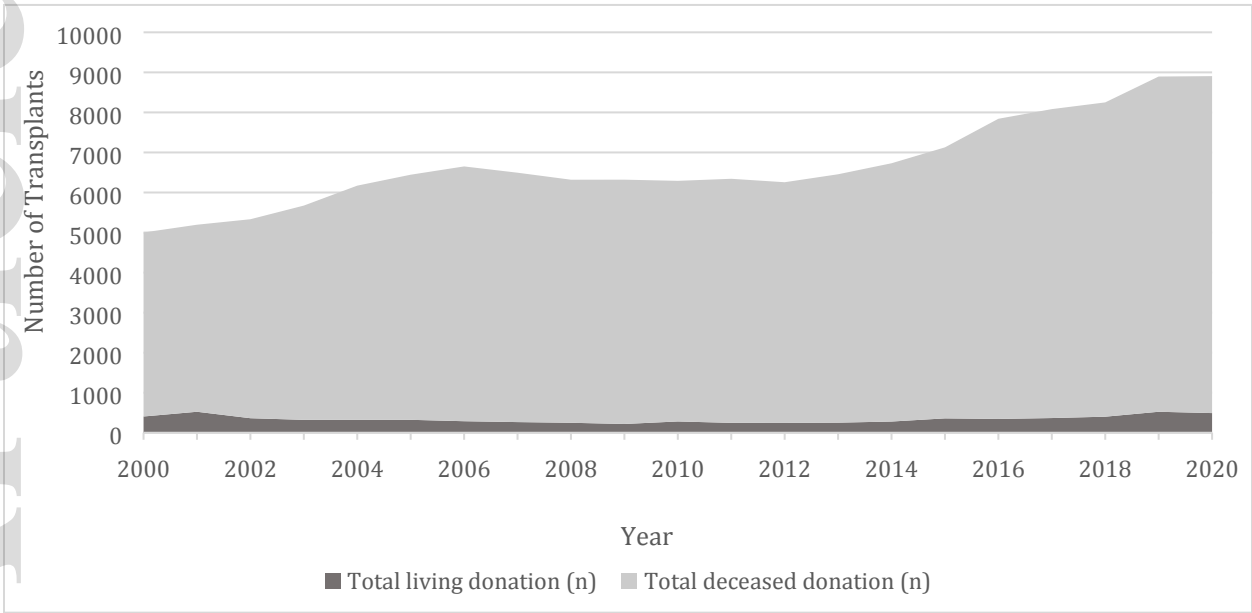
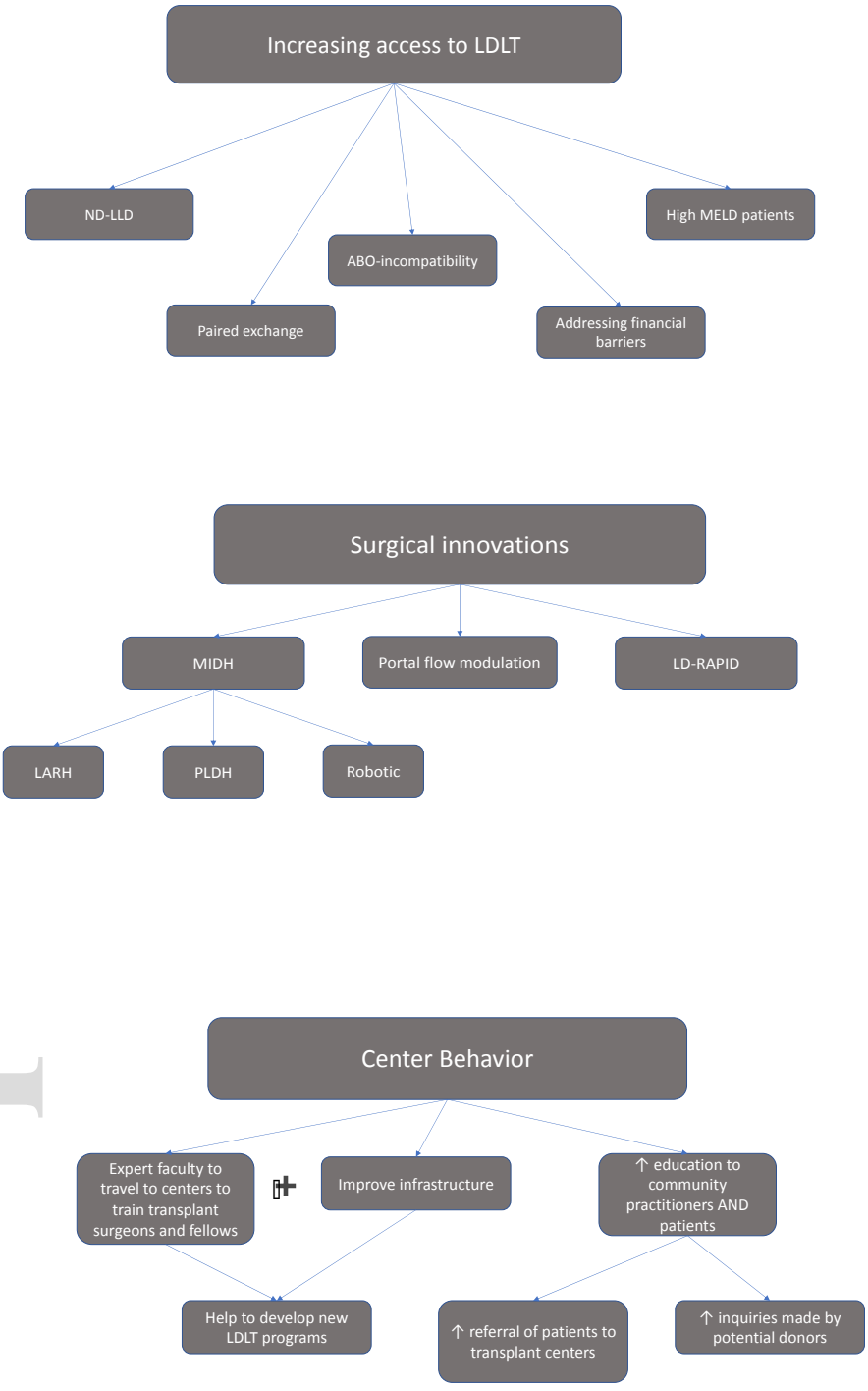


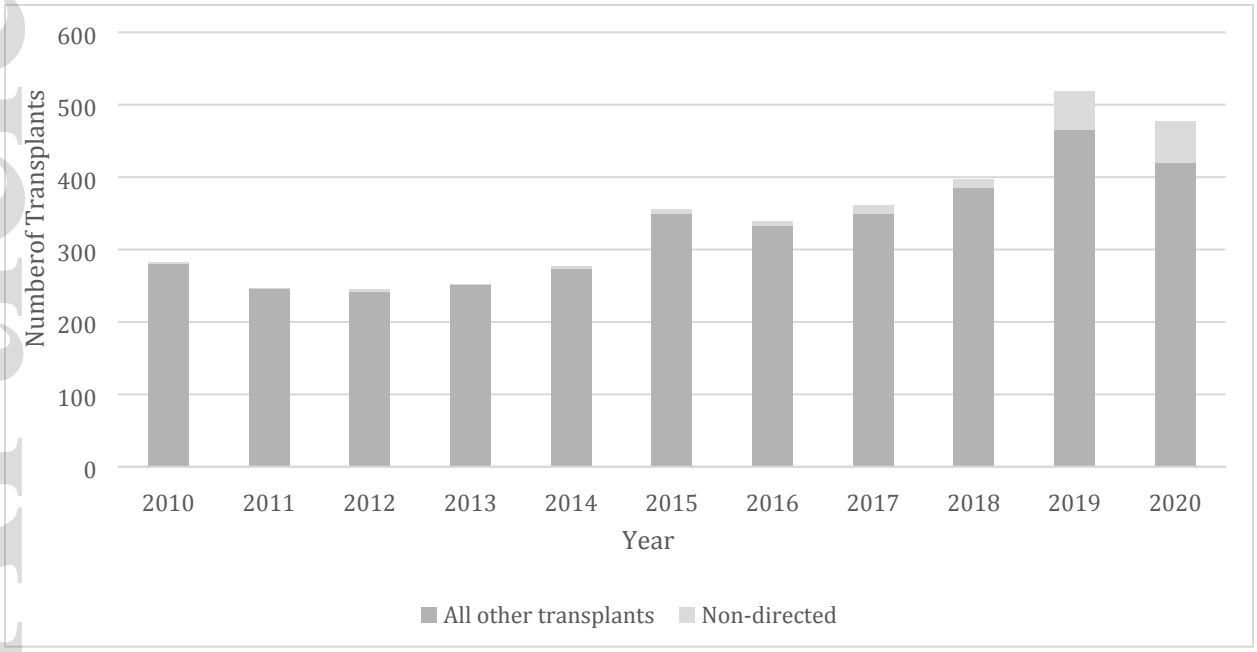
Figure 1 demonstrates changes in living and deceased donor liver transplants over time. While there was an 83% increase in deceased donation from 2000-2020, there was only a 20% increase in living donation.

Figure 2: Increasing access to LDLT and Innovations in Surgery



*ND-LLD: Non-directed living liver donation; MIDH: Minimally invasive donor hepatectomy; LARH: laparoscopy-assisted right hepatectomy; PLDH: purely laparoscopic donor hepatectomy

Figure 3: Changes in Non-Directed Living Liver Donation Over Time



Demonstrates total numbers of living donors from 2010-2020 with rising numbers of non-directed living liver donation.

*Data is obtained from OPTN National Data