The First 4-Way Liver Paired Exchange from an Interdisciplinary Collaboration between Healthcare Professionals and Design Economists

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Abbreviations:

In Main Text:

KPE: Kidney paired exchange

ABOi: ABO incompatible

ABOc: ABO compatible

ABOid: ABO identical

LPE: Liver paired exchange

LDLT: Living-donor liver transplantation

GRWR: Graft-to-recipient weight ratio

MELD: Model for End-Stage Liver Disease

Additionally, in Figures and Tables:

HCV: Hepatitis C virus

HBV: Hepatitis B virus

HCC: Hepatocellular carcinoma

NASH: Non-alcoholic steatohepatitis

PBC: Primary biliary cholangitis

HRS: Hepatorenal syndrome

LL: Left lobe

RL: Right lobe

Seg 2-3: Segments 2&3 of the Left Lobe

Abstract

We report initial results of a Liver Paired Exchange (LPE) program established at the Liver Transplant Institute at Inonu University through collaboration with design economists. Since June 2022, the program has been using a matching procedure that maximizes the number of living donor liver transplants (LDLTs) to the patients in the pool subject to the ethical framework and the logistical constraints of the program. In one 4-way and four 2-way exchanges, twelve LDLTs have been performed via LPE in 2022. The 4-way exchange, generated in the same match run with a 2-way exchange, is a first worldwide. This match run generated LDLTs for six patients, revealing the value of the capacity to carry out larger than 2-way exchanges. With only 2-way exchanges, only four of these patients would receive LDLT. The number of LDLTs from LPE can be increased by developing the capacity to perform larger than 2-way exchanges in either high-volume centers or multi-center programs.

1. INTRODUCTION

In kidney paired exchange (KPE), two or more patients with ABO-incompatible (ABOi) or HLA-incompatible living donors exchange their donors to receive a transplant from a biologically compatible donor. A KPE with $N \geq 2$ patient-donor pairs is called an N-way exchange. In order to mitigate kidney donor shortage for patients with end-stage renal disease, several regions and countries have adopted KPE programs since the early 1990s (1-6). While KPE was first proposed in 1986 by a healthcare professional (7), starting with the mid-2000s, the number of transplants from KPE increased significantly through interdisciplinary collaborations between healthcare professionals and design economists (2, 8). Two factors that contributed to this increase are the utilization of optimal matching algorithms (9) and the use of larger than 2-way exchanges (10, 11).

Following the increased role of KPE in transplantation, starting with the mid-2000s, similar liver paired exchange (LPE) programs have been established in a few Asian countries (12, 13). Most recently, in January 2023, a national pilot LPE program is established in the US (14). With the exception of two 3-way exchanges (15, 16), other LPEs reported in the literature are from 2-way exchanges. The LPE programs in high-volume Asian centers generate 1-1.5% of liver transplants from living donors (12, 17, 18).

In this study, we report the first results of an interdisciplinary collaboration between members of the Liver Transplant Institute at Inonu University (henceforth "the Institute") and two experts in design economics. Prior to adopting a computerized matching algorithm, the Institute performed 2-way LPEs in two occasions. The Institute started to identify potential LPEs through a computerized matching algorithm in June 2022. Within its first month, in one 4-way and two 2-way exchanges, the computerized system generated living donor liver transplantations (LDLTs) for 8 patients. To our knowledge, the 4-way exchange conducted in the Institute is a first worldwide. The 4-way exchange and one 2-way exchange are generated in the same match run in the first week of July 2022. Our main focus is the lessons from this more complex match run of the system.

2. MATERIAL AND METHODS

2.1 Background on LPE at the Institute: Earlier research shows that, even if LPEs are limited to 2-way exchanges, an organized LPE system can increase the number of LDLTs by more than 10% (19). Based on earlier research and field implementation of KPE systems worldwide, the increase in LDLTs can be expected to be considerably higher if 3-way or larger donor exchanges can be organized (10, 11). To assess its capacity to carry out up to 5-way exchange, the Institute carried out five simultaneous LDLTs in June 2019 (20). In September 2019, an agreement is reached between the Institute and the two design economists to set up an LPE system.

2.2 Directed Graphs: The matching algorithm used in the LPE system utilizes techniques from graph theory, optimization, and economic design (11, 21). A directed graph consists of a set of nodes and a set of directed edges that connect pairs of nodes (Figure 1). As new patients and their donors are included in the LPE pool, a new directed graph is constructed.

Here, a node represents each active patient in the pool. A directed edge from patient x to another patient y exists if patient x has a donor who can feasibly donate to patient y. The presence of directed edges from patient x to patient y and from patient y to patient x in Figure 1 means that both patients have a co-registered donor who can feasibly donate to the other patient. Therefore, a 2-way exchange is possible between patients x and y. LPE between three or more patients can be similarly determined in a directed graph. For example, in Figure 1, there are directed edges from patient x to patient w, patient w to patient z, and patient z to patient x. Therefore, there is a 3-way exchange between patients x, w, and z.

2.3 Operation of the LPE System and the Matching Algorithm: The following procedure (depicted in Figure 2) describes the operation of the system, and it reflects both the broader approach to LDLT at the Institute and the underlying ethical framework for LPE (further discussed in Section 4.1).

Step 1. When a patient-donor pair arrive for consideration for LPE, they are screened for whether they are biologically and psychologically eligible for LDLT and LPE. If they are, their data are entered into the LPE pool.

Step 2. For each donor in the system, the grafts feasible for LPE are determined as follows:

a. Left lobe (LL) or Segment 2-3 of LL (Seg 2-3) are feasible if there is no anatomical variation that would make them high-risk to transplant.

b. Right lobe (RL) is feasible if (i) there is no anatomical variation (except abnormal portal venous branching) that would make it high-risk to transplant, (ii) the estimated remnant liver volume is not smaller than 30% of the estimated liver size, and (iii) the lower risk LL or Seg 2-3 cannot be transplanted to the co-registered patient.

Step 3. All potential LDLTs between donors and patients in the pool are determined using the following criteria: A donor can feasibly donate a graft to a patient if (i) it is a feasible graft for LPE as defined in Step 2, (ii) the donor is ABOid or ABOc with the patient, and (iii) the graft-to-recipient weight ratio (GRWR) is at least 0.8% (and at most 4% for pediatric patients).

Step 4. Step 3 forms a feasible transplant directed graph. Using integer programming methodology earlier adopted for KPE in (11, 21) and new software using the GLPK optimizer on the MATLAB platform (22-24), a maximum-cardinality matching problem is solved, searching for a set of mutually exclusive exchanges (called a matching) that generate LDLT to maximum possible number of patients.

a. If a matching is found, the algorithm generates it as output. Step 4 is then repeated by adding a new constraint which deems this matching infeasible.

b. If no matching is generated, then the procedure terminates.

This procedure generates all feasible matchings and lists them in order of decreasing number of transplants. The maximum number of patients allowed in an exchange can be embedded into the procedure as a constraint. This upper limit is 5 for the Institute. However, so far, we did not encounter any exchange larger than 5-way.

3. RESULTS

A total of 2903 LDLTs were performed at the Institute from June 2005 to March 2023. In 2022, the 10 LDLTs from LPEs accounted for 3.7% of the 268 LDLTs performed at the Institute. Including the 4-way exchange, all operations for each LPE are performed simultaneously at the Institute. Except for one patient who joined the LPE pool for altruistic reasons with a compatible donor, all other patients had incompatible donors. As further elaborated in Section C of the Supplementary Materials, their reasons to join the LPE include ABOi, parenchymal problems such as small size graft or remnant liver, and incompatibility of arterial structures to anastomose. There has been no donor mortality or morbidity. With the exception of one recipient who died due to cardiac arrest, all other recipients are alive and well following their LPE operation (see Section D of the Supplementary Materials for details).

Prior to the June 2022 deployment of the LPE system's computerized matching procedure, the Institute carried out 2-way exchanges in two occasions. Starting with June 2022, data from consenting patients and their donors have been systematically collected in a database and all potential LPEs are identified through the procedure given in Section 2.3. In June 2022, the Institute carried out its third 2-way exchange.

3.1 Match Run in the First Week of July 2022: The true value of the interdisciplinary initiative became more visible shortly after the computerized matching process was adopted. Table 1 gives the list and characteristics of 12 patient-donor pairs in the LPE pool in the first week of July 2022. Figure 3a depicts the resulting directed graph, where dark blue edges correspond to ABOid and light blue edges correspond to ABOc transplants respectively.

The matching process revealed two possibilities: An isolated 5-way exchange (Figure 3f) or a 4-way exchange along with a 2-way exchange (Figure 3b). In order to ensure that the maximum number of patients benefit from LPE, the second option was selected by the transplantation team. Written informed consent was obtained from patients and donors, who were earlier informed about the risks and benefits of LPE.

The eight operations for the 4-way exchange were performed simultaneously on July 5, 2022. The four operations for the 2-way exchange were performed simultaneously on July 7, 2022. In each operating room, healthcare personnel included two surgeons, one surgery resident, two nurses, one anesthesiologist, two anesthesia technicians, and two assistants. In total, more than 80 healthcare personnel took part in the 4-way exchange. Following the general practice in the Institution, open surgery is performed for all donors and patients. Details of these LPEs are given in Table 1 and Figure 4.

As part of the 4-way exchange, patient R1, a 50-year-old man, received a RL from donor D2, a 42-year-old co-registered donor of patient R2 (66-year-old female), who in turn received a RL from donor D3, a 42-year-old female who was a co-registered donor of patient R3. Patient R3, a 62-year-old man, received a RL from donor D4, who is the 38-year-old father of pediatric patient R4. Patient R4, a 12-year-old boy, received a LL from donor D1, a 25-year-old co-registered donor of patient R1 (Figure 4a). All patients received ABOid transplants through the 4-way exchange.

The approval of all LPE operations in the first week of July 2022 is obtained from the Ministry of Health. This study protocol was approved by the Inonu University School of Medicine Ethics Committee (year 2023, number 4538).

3.2 The Role of the Capacity to Conduct 3-way or Larger Exchanges: If conducting a 4-way exchange is beyond the logistical capacity of an LPE program, then the maximum number of transplants obtained through the system can decrease. For example, for the LPE pool in Table 1, the maximum number of patients who can receive a transplant decreases to 5 if it is only possible to carry out 2-way or 3-way exchanges (Figure 3c). This number further decreases to 4 if it is only possible to carry out 2-way exchanges (Figure 3d). This observation shows that the Institute's capacity to carry out up to 5-way exchange has been instrumental in maximizing the number of patients who were able to receive a LDLT.

3.3 The Role of Optimal Matching Algorithms: The largest number of pairs who can participate in exchange is only one of the factors to maximize the number of LDLTs. Another factor is the optimal selection of exchanges. For example, suppose a donor exchange is carried out between patients R4 and R5 in Table 1. In this scenario, no other donor exchange remains available for other patients, and thus, only two patients receive

LDLT (Figure 3e). This observation highlights the importance of adopting an optimal matching algorithm in an LPE system even if only 2-way exchanges can be carried out.

4. DISCUSSION

4.1 Ethical Framework: The ethical framework of the Institute for its LPE program needs to be evaluated in relation to its guidelines and practices for LDLT. As further discussed in Section B of the Supplementary Materials, LDLT is limited to ABOid or ABOc donations at the Institute since 2013 (25). GRWR of at least 0.8% is desirable for LDLT, however, for patients with no tense ascites and MELD scores lower than 19, as low as 0.7% may be acceptable for direct donation from their co-registered donors. For donor safety, a minimum of 30% remnant volume is always maintained.

The primary ethical values which guide the Institute's LPE program are utilitarianism and the Pareto principle. Through its utilitarian goal the program strives to maximize the number of patients who can undergo successful LDLT. This is the reason the Institute developed the capacity to perform up to 5-way exchange. Also consistent with the utilitarian goal, preference is given to patients with relatively low MELD scores. Through the Pareto principle, neither a patient can receive a less favorable transplant, nor a donor can go through a higher-risk operation than the default option in the absence of LPE. For an incompatible pair who cannot go through a direct LDLT, this implies that patient and donor safety must be subject to the same standards followed in LDLT. The Institute's criteria for patient eligibility for LPE is more demanding in that, a GRWR of at least 0.8% is required. For a compatible pair whose default option is a direct LDLT, there are additional requirements. To assure that donor risk never increases compared to direct donation, a donor who can feasibly donate a LL or Seg 2-3 to her co-registered patient can never donate the higher-risk RL under LPE. A patient who can directly receive a transplant from her co-registered donor can never receive a less favorable transplant. Graft quality, volume, and anatomy after the donor exchange should all be at least as favorable as direct donation. Furthermore, a voluntary compatible pair is included in LPE only if there is no additional waiting time involved and their inclusion increases the number of patients who can receive LDLT.

With an increased number of patient and donor pairs enrolled in LPE, the matching process can also include a transplant priority. Currently LPE selections at the Institute are made by the transplantation team. MELD score can be used for transplant priority since adverse LDLT outcomes are known in patients with high MELD scores. Other considerations for patient priority may relate to complications that are not measured well by MELD, such as refractory ascites, esophageal variceal bleeding, incapacitating pruritus, hepatic encephalopathy, and hepatocellular carcinoma.

Concerns about coercion may be exacerbated by indirect transplants through LPE, because a reluctant or hesitant donor may no longer be able to invoke the incompatibility as a socially acceptable way to withdraw from consideration as a living donor (26). As such, donors in LPE need to undergo a thorough psychological evaluation.

One important consideration for LPE is a possible necessity to abort an operation. Moreover, the abort risk for at least one pair in LPE increases as the number of pairs in LPE increases. Prior to 2019, the rate of aborted liver hepatectomy was 3.8% at the Institute (27). After 2019, this rate reduced to 1% with experience. Nevertheless, aborting a donor hepatectomy is always a possibility at any stage of multiple donor operations when the unexpected is encountered. This possibility is explained to donors and patients in detail preoperatively. If this situation is encountered at an irreversible step of the operations for at least one donor or patient, the Institute policy is to continue with other LDLTs. If the situation is encountered at a reversible step for all operations but all donors and patients consented for other LDLTs to proceed in that contingency, in that case also the Institute policy is to continue with other LDLTs. So far, the Institute did not face this unfortunate situation in any LPE.

4.2 Operational Considerations: While the maximum-size matching is unique and provides compatible transplants to 6 patients for the patient-donor pool in Table 1, in general, there can be multiple maximum-size matchings. In choosing among them, the transplant team considers factors such as anatomical variations and MELD scores. While the transplant team makes an effort to select a maximal-size matching, these factors may also result in selecting a smaller-size matching. This is why all feasible matchings are generated by the matching process given in Section 2.3.

The experience at the Institute suggests that the logistical capacity to carry out 4-way exchanges in an LPE program can be important to utilize the full promise of LPE. This capacity may not be available in most single-institution LPE systems. For example, there has been a recent surge of interest in conducting LPEs in North America (26, 28-32), which houses many smaller-capacity centers. While Kim (33) argues that achieving the equity of transplant outcomes in cross-center LPE may be challenging, the number of LDLTs can be significantly increased with multi-institution LPE systems that can implement larger than 2-way exchanges. Indeed, with the participation of 15 transplant programs in the US, United Network for Organ Sharing (UNOS) launched the first national LPE pilot program in January 2023. We believe such collaborations are highly valuable; otherwise, LPE programs will be limited to relatively few high-volume LDLT centers worldwide. A larger pool of living liver donors and access to larger size donor exchanges means that patients can have increased access to LDLT, and transplant centers have the opportunity to grow their LDLT programs through collaboration.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

Table and Figure Legends

Table 1. Recipient and donor information in the BBS-LPE pool & donor exchanges conducted in early July 2022

Figure 1. Examples of a directed graph and 2-way & 3-way LPEs

Figure 2. The flowchart of the LPE matching procedure

Figure 3. Possible transplants & LPEs in the LPE pool in the first week of July 2022

Figure 4. The 4-way & 2-way LPEs conducted in the first week of July 2022

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Table 1. Recipient and donor information in the LPE pool & LPEs conducted in early July 2022

RECIPIENT								CO-REGISTERED DONOR							REASON FOR JOINING EXCHANGE POOL	LPE					
REC. ID	GENDER	AGE (yr)	ETIOLOGY	MELD/ PELD SCORE	ABO Type	WEIGHT (kg)	MIN./MAX. VOL NEEDED (ml)	PAIRED DONOR ID	GENDER	AGE (yr)	ABO Type	WEIGHT (kg)	ESTIMATED VOLUME* (ml)	LL REMNANT %		RECEIVED GRAFT	DONATION DIRECTION	TYPE	TRANSPLANT DATE	RECIPIENT OUTCOME	DONOR OUTCOME
R1	Male	50	HBV	17	A Rh(+)	101	810 (min)	**D1**	Male	25	A Rh(+)	76	RL: 730 LL: 390	35%	RL GRAFT VOLUME TOO SMALL	RL		4-way Exchange	Jul 5, 2022	Alive	No morbidity or mortality
R2	Female	66	Autoimmune cirrhosis	15	O Rh(+)	68	545 (min)	**D2**	Male	42	A Rh(+)	78	RL: 900 LL: 540 SEG 2-3: 340	38%	ABO INCOMPATIBLE	RL				Alive	No morbidity or mortality
R3	Male	62	NASH cirrhosis	16	O Rh(+)	97	780 (min)	**D3**	Female	42	O Rh(+)	61	RL: 600 LL: 360	38%	RL GRAFT VOLUME TOO SMALL	RL				Alive	No morbidity or mortality
R4	Male	12	Autoimmune cirrhosis	19	A Rh(+)	21	170 (min) 840 (max)**	**D4**	Male	38	O Rh(+)	74	RL: 970 LL: 460 SEG 2-3: 230	32%	MULTIPLE NARROW LL HEPATIC ARTERIES***	LL				Alive	No morbidity or mortality
R5	Male	50	Alcoholic cirrhosis	20	A Rh(+)	89	715 (min)	**D5**	Female	18	O Rh(+)	67	RL: 670 LL: 370 SEG 2-3: 220	36%	RL GRAFT VOLUME TOO SMALL	RL		2-way Exchange	Jul 7, 2022	Alive	No morbidity or mortality
R6	Male	48	PBC + HCC	18	O Rh(+)	80	640 (min)	**D6**	Male	19	A Rh(-)	76	RL: 720 LL: 450 SEG 2-3: 270	38%	ABO INCOMPATIBLE	RL				Died (bacterial sepsis related to multiorgan failure)	No morbidity or mortality
R7	Male	15	Cryptogenic cirrhosis	17	B Rh(+)	39	315 (min)	**D7**	Female	23	AB Rh(+)	50	RL: 700 LL: 320 SEG 2-3: 200	31%	ABO INCOMPATIBLE						
R8	Female	57	NASH cirrhosis	25	B Rh(+)	94	755 (min)	**D8**	Male	23	AB Rh(+)	72	RL: 630 LL: 380	38%	ABO INCOMPATIBLE						
R9	Male	47	NASH cirrhosis	17	O-	90	720 (min)	**D9**	Male	24	O Rh(+)	90	RL: 920 LL: 330 SEG 2-3: 230	25%	REMNANT LL VOLUME TOO SMALL						
R10	Male	65	NASH cirrhosis	16	O Rh(+)	76	610 (min)	**D10**	Male	24	B Rh(+)	73	RL: 780 LL: 470 SEG 2-3: 250	38%	ABO INCOMPATIBLE						
R11	Male	66	NASH cirrhosis + HCC	22	O Rh(+)	88	705 (min)	**D11**	Female	42	O Rh(+)	51	RL: 540 LL: 280 SEG 2-3: 150	34%	RL GRAFT VOLUME TOO SMALL						
R12	Male	69	Cryptogenic cirrhosis + HRS	24	B Rh(+)	70	560 (min)	**D12**	Male	39	AB Rh(+)	70	RL: 760 LL: 400 SEG 2-3: 230	34%	ABO INCOMPATIBLE						

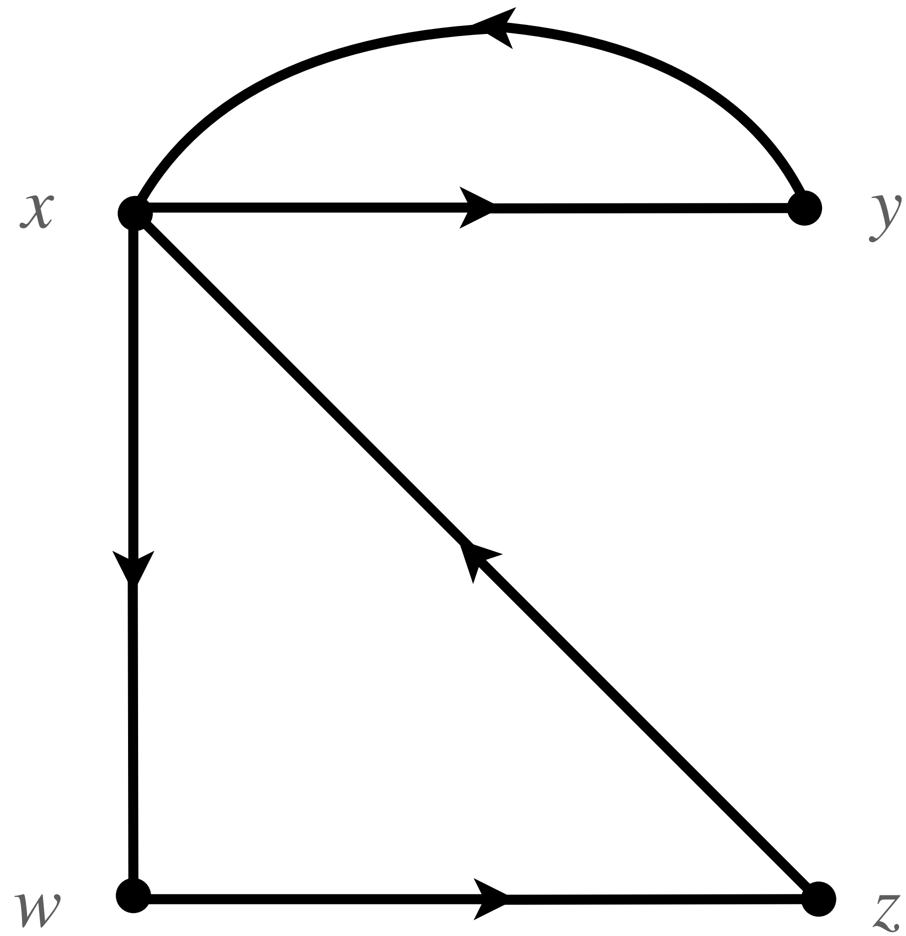
Notes: LPE: Liver Paired Exchange; HBV: Hepatitis B virus; NASH: Non-alcoholic steatohepatitis; PBC: Primary biliary cholangitis; HCC: Hepatocellular carcinoma; HRS: Hepatorenal syndrome; LL: Liver left lobe; RL: Liver right lobe; SEG 2-3: Liver segments 2&3.

* The donor graft volumes are estimates available when the exchange algorithm was executed.

** For pediatric recipient R4, maximum acceptable graft volume is also given.

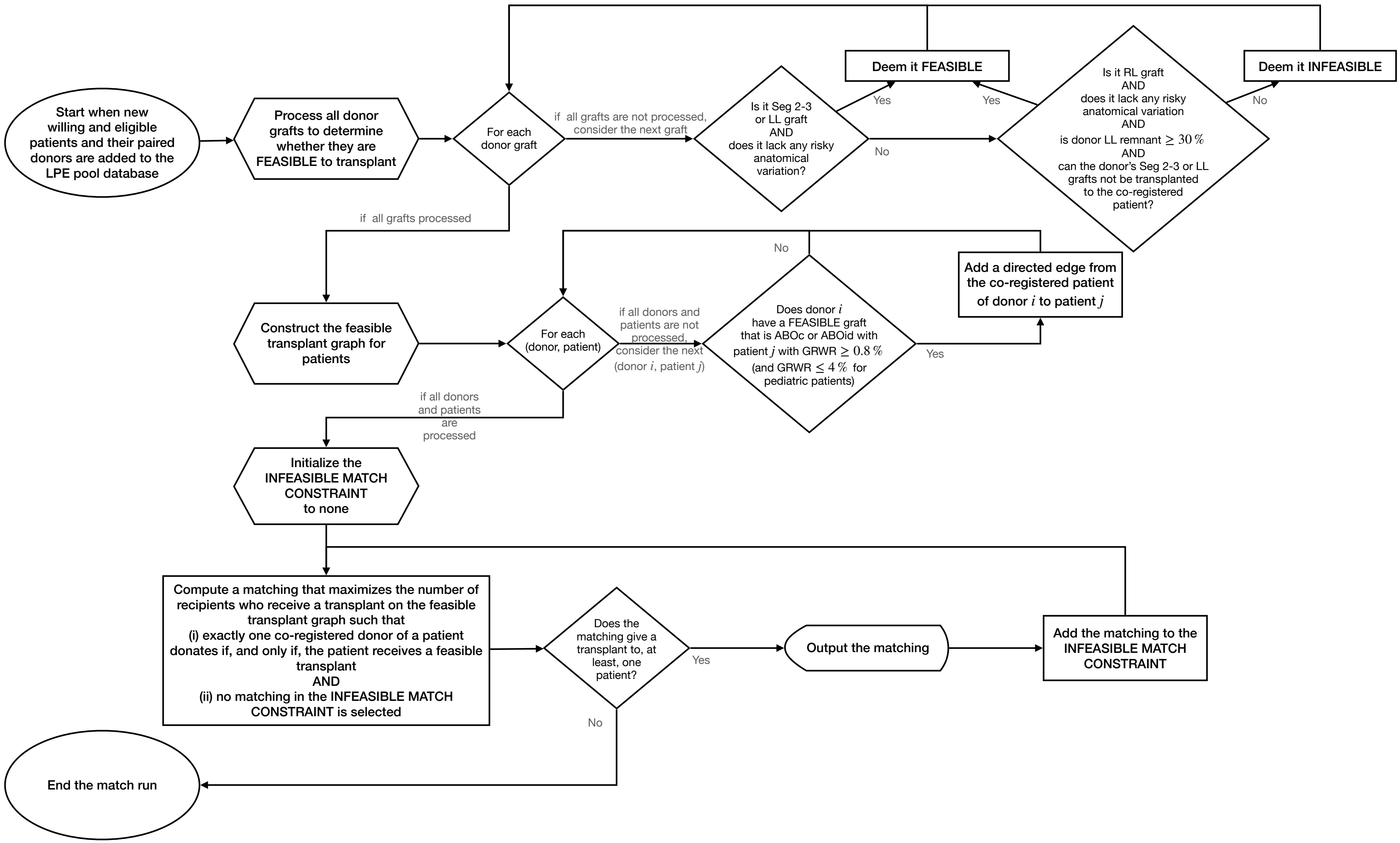
*** Although D4 is ABO-compatible with R4 and D4's SEG 2-3 and LL grafts are volume-compatible with R4, these grafts have multiple narrow hepatic arteries.

Figure 1. Examples of a directed graph and 2-way & 3-way LPEs



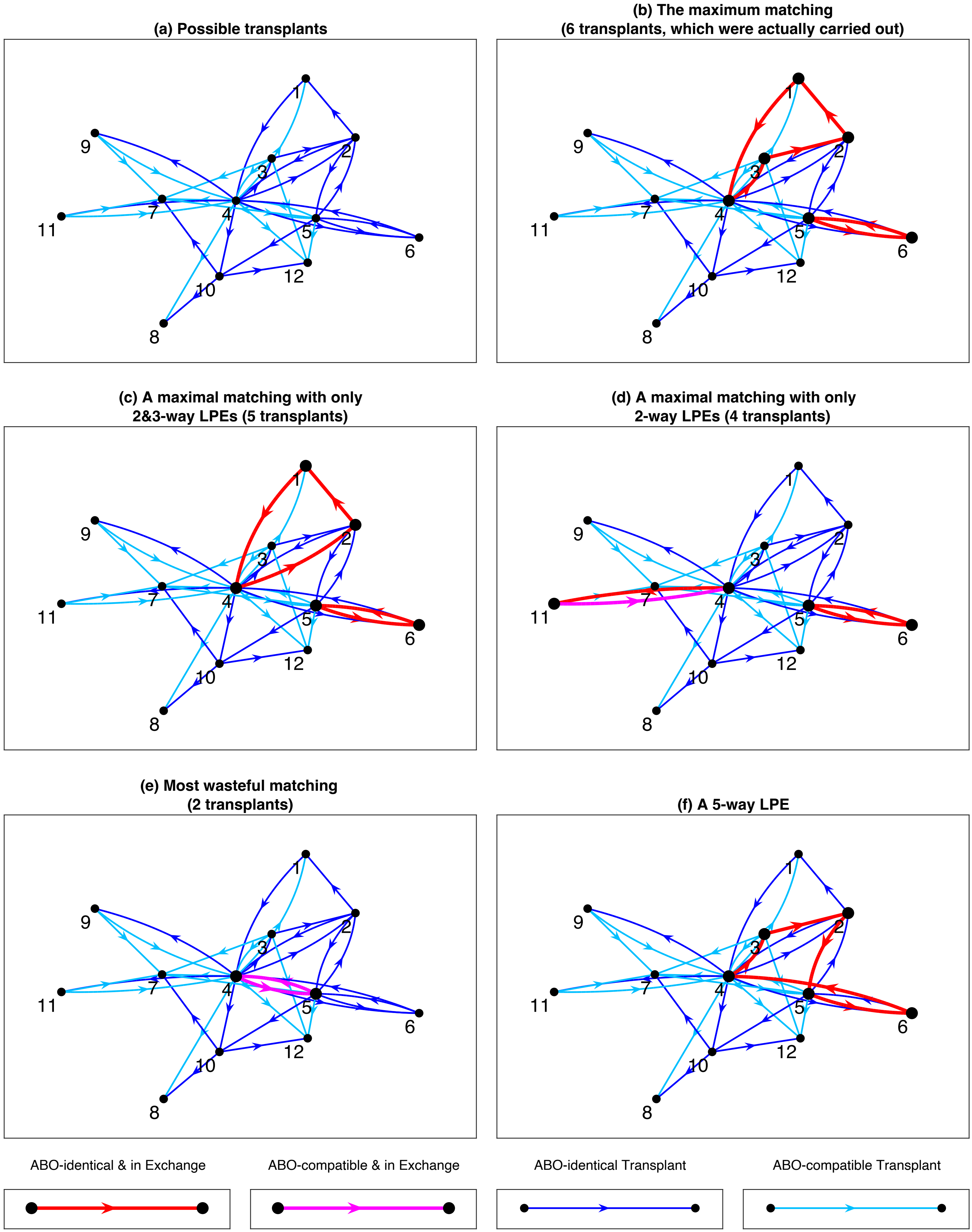
Note: Each of the nodes, w, x, y, z, refers to a patient. There is a directed edge from one patient to another if the paired donor of the first patient can compatibly donate a graft to the second patient. In this graph, there is a possible 2-way LPE between x and y, and a possible 3-way LPE between x, w, and z.
(LPE: Liver Paired Exchange)

Figure 2. The flowchart of the LPE matching procedure



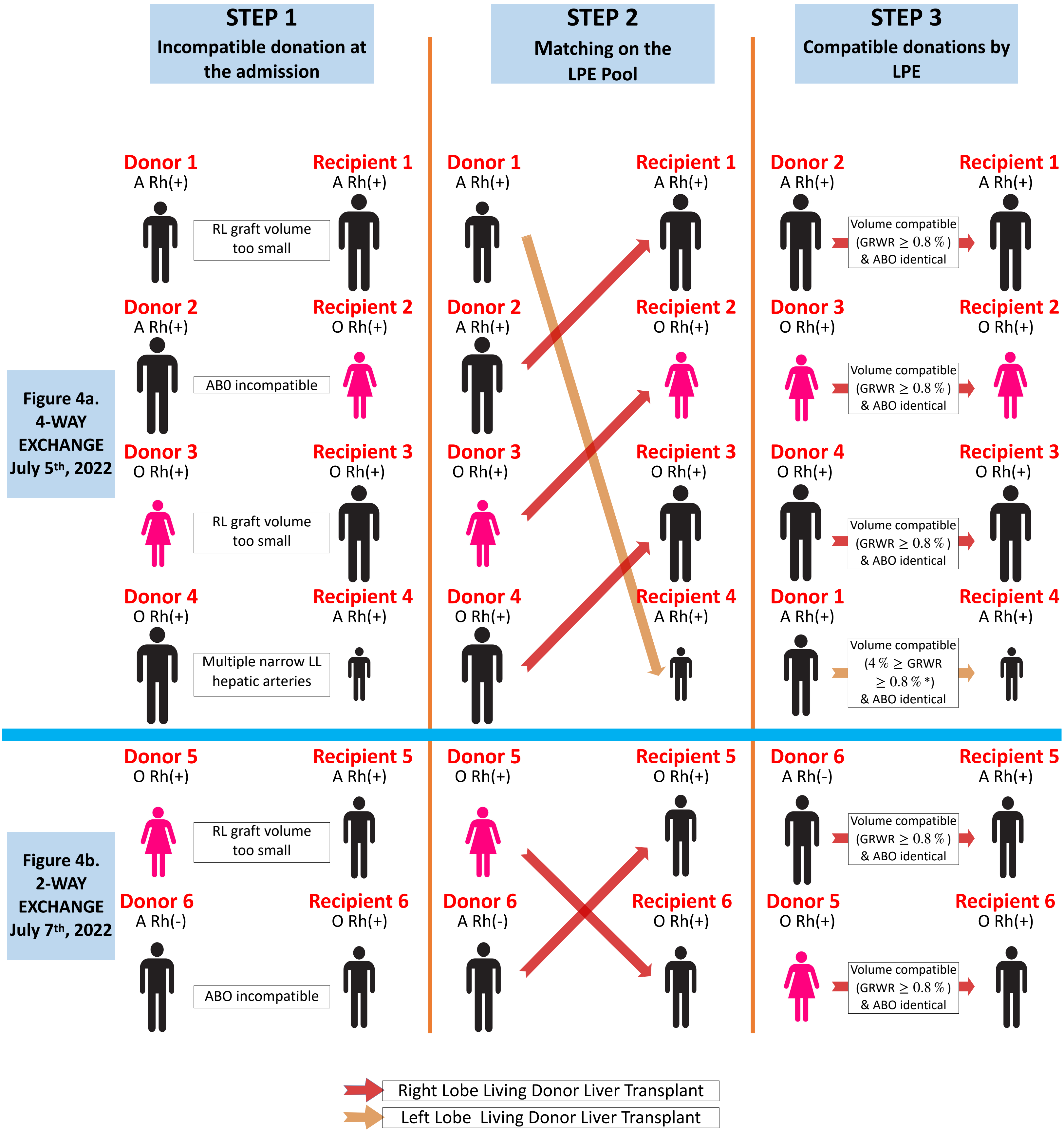
Note: LPE: Liver Paired Exchange; Seg 2-3: Liver Segments 2&3; LL: Liver Left Lobe; RL: Liver Right Lobe; ABOc: ABO-compatible; GRWR: Graft-To-Recipient-Weight Ratio

Figure 3. Possible transplants and LPEs in the LPE pool in early July 2022



Note: An arrow from one patient node to another means that the donor of the first patient can compatibly donate to the second patient.(LPE: Liver Paired Exchange)

Figure 4. The 4-way & 2-way LPEs conducted in early July 2022



Note: LPE: Liver Paired Exchange; RL: Liver Right Lobe, LL: Liver Left Lobe
*: Pediatric Patient

Supplementary Materials for

"The First 4-Way Liver Paired Exchange from an Interdisciplinary Collaboration between Healthcare Professionals and Design Economists"

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Appendix A. Differences between KPE and LPE matching algorithms and match runs

Although the LPE procedure uses similar optimization methodologies with KPE algorithms developed in (S1, S2), there are several notable differences. We outline these differences in this appendix.

1. The LPE matching procedure finds all possible matchings, while this is typically computationally hard for large KPE pools. Patients are expected to remain on the LPE pool in shorter periods than KPE since dialysis is an alternative (though inferior) treatment to transplantation, and such an alternative does not exist for end-stage liver disease. Thus, the time interval between match runs for KPE can be larger than LPE match runs, which are typically executed as soon as new patients and their co-registered donors enter the system. All of these factors cause the KPE

pools to be typically larger and more new patients to be enlisted between match runs in the USA. Therefore, computationally it can be difficult to calculate all matchings for KPE.

2. While a KPE donor can only donate a whole kidney, a LPE donor can donate different grafts. Thus, in every LPE, there can be multiple ways a donor can donate to the various recipients; these are all found and output in the LPE algorithm. The transplant committee determines which LPEs should be carried out using the ethical framework outlined in Section 4.1.
3. Compatible pairs are given the option to participate in LPE. Given different risk factors associated with different grafts of the donor, the LPE algorithm embeds the ethical Pareto principle that no donor should donate her RL graft if she can feasibly donate her Seg 2-3 or LL graft to her co-registered patient (S3).
4. Although altruistic donor domino chains are incorporated with most KPE pools in the USA, our program does not consider these domino chains as altruistic liver donation is not common in Türkiye.
5. This last difference between our LPE algorithm and standard algorithms for KPE is an artifact of the large, unusual simultaneous transplant capacity of the Institute that can conduct up to 5-way exchanges (S4). The LPE procedure does not have a built-in size constraint for exchanges, given the relatively small size of the LPE pool. This can easily be added to implementing the LPE algorithm in other programs; for example, when the largest exchange size is capped at 3-way. Imposing no constraint is practical in that, it enables a computationally fast implementation of the algorithm, which also enables to compute all matchings in

the pool very fast. Having an exchange size constraint makes the problem computationally hard even to find one maximum-cardinality matching (S5).

Appendix B. Attitude toward ABO incompatible LDLT at the Institute

Since 2013, the transplant team at Inonu University have been reluctant to practice ABOi LDLT for adult patients because of the risk of infection from potent immunosuppressive drugs despite outcomes show improvement after a series of specific management steps. ABOi LDLT for adult patients is still regarded as a challenging treatment modality because of inferior long-term survival (S6, S7). In a meta-analysis, the short-term and long-term outcomes were worse after ABOi LDLT than after ABOid or ABOc LDLT (S8). After ABOi LDLT, infection and antibody-mediated rejection remain to be resolved (S9).

Appendix C. Reasons for LPE Pool Participation at the Institute

Transplantation laws in Türkiye require that all living donors and their co-registered patients be within the fourth degree of consanguinity. All donors met this legal requirement.

Patient-donor pairs join LPE for the following three main reasons:

1. ABO incompatibility

2. Parenchymal problems such as small GRWR, insufficient remnant volume after RL donation and anatomical variations
3. Voluntary participation from compatible pairs

So far, voluntary participation from compatible pairs have been rare in our Institute. One such pair participated to LPE, resulting in a 2-way exchange in June 2022.

Table 1 gives the list of twelve patients who were in the LPE pool in the first week of July 2022. Six of these patients joined the LPE pool due to ABO incompatibility with their co-registered donors. The remaining six patients all had ABOid or ABOc co-registered donors, but they joined the LPE pool due to parenchymal problems. Of those six patients with parenchymal problems,

- Four of them had co-registered donors with RL GRWR < 0.8%,
- one of them had a co-registered donor with LL GRWR < 0.8% and remnant LL volume < 30% of the whole liver volume, and
- one of them, a pediatric patient, had a co-registered donor with RR GRWR > 4% and unsuitable LL or Seg 2-3 grafts due to risky anatomical variation, specifically multiple left hepatic arteries with very thin diameters.

Appendix D. Clinical Outcomes Post LPE Operations:

The median age for the twelve living donors from the four 2-way LPEs and one 4-way LPE is 28. With a range of 6-9 days, the median hospital stay after donor hepatectomy was 7 days. There was no donor mortality or morbidity. Three of the recipients were children.

With an average follow-up time of one year as of March 2023, with one exception, other recipients are alive and in good health.

One recipient (patient R6 in Table 1) died from cardiac arrest. This recipient had suffered from a Covid-19 infection prior to the LT. He had completed the appropriate treatment and gone through the recommended waiting time after the infection. He developed an acute portal vein thrombus complication the day after LT and was treated with surgical thrombectomy and portal vein reanastomosis. In the following days, he progressed with hyperbilirubinemia. Even though he received biliary stenting with endoscopic retrograde cholangiopancreatography, his hyperbilirubinemia did not improve. With the antibody-mediated rejection diagnosis in his biopsy, he was subsequently treated by IVIg, plasmapheresis, and rituximab. Response to treatment was finally achieved, and the recipient was discharged. However, the recipient was later readmitted to our center with chest pain and dyspnea. Sepsis with pericardial tamponade was detected, and it was drained nonoperatively. Suffering from multiorgan failure, the recipient died from cardiac arrest 4 months after LDLT.

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