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INVITED COMMENTARY

Do you really know what you get: the benefits and doubts of domino liver transplantation

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Liver transplantation (LT) has perhaps been the first long-term clinically successful gene-therapy to provide patients with an in-born error of metabolism a near normal life. Some of these metabolic defects with an indication for liver transplantation are associated with an otherwise structurally and functionally complete normal liver. With these scenarios, the concept of domino liver transplantation (DLT) has been established. The liver of the recipient with a liver-based metabolic disease can be "recycled" and transplanted into another recipient instead of being sent off to pathology. Eventually, this is the only setting were live donor liver transplantation with a whole organ is possible. It is a surgically, and logistically demanding procedure that has been shown to be successful in well-selected cases. As has been reported recently, it may even be performed when the first donor is a living donor [1]. However, little is known about long-term outcome in a larger, multicenter population.

In this issue of the journal, two distinct papers address the question of long-term outcome in recipients of domino liver transplants.

Geyer *et al.* analysed data from the United Network of Organ Sharing (UNOS) registry for the time period 2002–2016. Patients with an age under 12 years at LT, with high urgency status (UNOS Status 1) and missing data were excluded. During this 15-year period, 126 DLT were registered compared to 62 835 deceased donor liver transplantation (DDLT) (split grafts and donation after cardiac death (DCD) grafts were excluded) [2]. Thus, in the US, domino grafts accounted for approximately 0.2% of all transplants. While this seems small it deserves consideration as one further viable source of donor organs. Of note, recipients of a DLT were statistically significantly older, with a lower MELD score, more often at home awaiting a transplant, and with a waiting list time more than twice as long compared to recipients of a DDLT. Allograft cold ischaemia time was significantly shorter for DLT recipients. After propensity matching 123 DLT recipients were compared to 123 matching DDLT controls. Outcome of both groups was comparable. With DLT no increased risk of mortality or graft failure was observed. On the surface, these data confer a comforting and reassuring message regarding the use of DLT grafts. However, no data on specific donor disease or long-term functional metabolic data were available.

Familial amyloidotic polyneuropathy (FAP) has been the disease model with which the concept of DLT was

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developed. The mutation of the transthyretin gene (TTR) leads to misfolded amyloid which accumulates in extracellular deposits leading to neurologic, gastrointestinal and cardiac symptoms and is ultimately fatal. It is often believed that recipients of FAP domino grafts will rarely develop symptoms of FAP either because of the considerable lag time or because of extrahepatically normal transthyretin or both. Vollmar *et al.* [3] have closely examined progression of TTR amyloidosis in donors and recipients of a DLT graft in a prospective single-centre cohort study. They followed 24 FAP recipients and 23 FAP-DLT recipients over a more than 18-year period from 1998 to 2016 with a prospective protocol including nerve conduction velocity, quantitative sensory testing, heart rate variability, sympathetic skin response and orthostatic reaction. Biopsies were obtained from multiple sites in case of clinical suspicion of *de novo* amyloidosis. Biopsy-proven *de novo* amyloidosis occurred in 4 of 23 DLT (17%) recipients after a mean observation time of 10 years. In two domino graft recipients with the Val30Met variant in the donor, symptoms of peripheral neuropathy were observed as early as 4 and 5 years after transplant. In both these recipients, gastrointestinal symptoms attributable to amyloidosis began to appear 4.5 and 8 years after transplant. This careful prospective study demonstrates convincingly that not all FAP grafts are alike.

Because of the rarity of domino liver transplantation, little is known about the time course and severity of disease transmission to the recipient of the domino graft. A recent overview of liver transplantation using grafts with rare metabolic disorders has been compiled by Schielke *et al.* [4] which may serve as a useful reference. They have suggested the following scenarios when to consider acceptance of a domino graft from a donor with a metabolic disorders: (i) normal (extrahepatic) enzyme activity in the host which can compensate the metabolic disorder transmitted by the graft, (ii) the interval until development of metabolic symptoms is likely to be longer than the life expectancy of the recipient of the domino graft post-transplant and (iii) in exceptional cases as a bridging treatment while waiting for a second healthy graft.

In the setting of domino transplantation, the transplant team caring for the donor will have detailed knowledge about the disease characteristics and the potential risk for the recipient of the domino graft. They may thus give adequate advice to the recipient team which should be used when obtaining informed consent from the recipient. On the other hand, in the setting of deceased donor transplantation transmission of metabolic disease is a greater challenge. A recent overview by Tan *et al.* [5] provides valuable information about various metabolic diseases that have been transmitted by liver transplantation. They range from the relatively common and unproblematic such as Gilbert's syndrome to the rare and fatal such as previously undetected urea cycle disorders, in particular ornithine transcarbamylase deficiency. Given the time constraints and logistics of deceased donor liver transplantation, the identification of undetected metabolic disease of the graft, the estimation of risk to the recipient and the need for informed consent of the recipient will remain challenging.

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Conflicts of interest

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