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## Pre-emptive live donor kidney transplantation-moving barriers to opportunities: An ethical, legal and psychological aspects of organ transplantation view

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### Abstract

Live donor kidney transplantation (LDKT) is the optimal treatment modality for end stage renal disease (ESRD), enhancing patient and graft survival. Pre-emptive



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LDKT, prior to requirement for renal replacement therapy (RRT), provides further advantages, due to uraemia and dialysis avoidance. There are a number of potential barriers and opportunities to promoting pre-emptive LDKT. Significant infrastructure is needed to deliver robust programmes, which varies based on socio-economic standards. National frameworks can impact on national prioritisation of pre-emptive LDKT and supporting education programmes. Focus on other programme's components, including deceased kidney transplantation and RRT, can also hamper uptake. LDKT programmes are designed to provide maximal benefit to the recipient, which is specifically true for pre-emptive transplantation. Health care providers need to be educated to maximize early LDKT referral. Equitable access for varying population groups, without socio-economic bias, also requires prioritisation. Cultural barriers, including religious influence, also need consideration in developing successful outcomes. In addition, the benefit of pre-emptive LDKT needs to be emphasised, and opportunities provided to potential donors, to ensure timely and safe work-up processes. Recipient education and preparation for pre-emptive LDKT needs to ensure increased uptake. Awareness of the benefits of pre-emptive transplantation require prioritisation for this population group. We recommend an approach where patients approaching ESRD are referred early to pre-transplant clinics facilitating early discussion regarding pre-emptive LDKT and potential donors for LDKT are prioritized for work-up to ensure success. Education regarding pre-emptive LDKT should be the norm for patients approaching ESRD, appropriate for the patient's cultural needs and physical status. Pre-emptive transplantation maximize benefit to potential recipients, with the potential to occur within successful service delivery. To fully embrace preemptive transplantation as the norm, investment in infrastructure, increased awareness, and donor and recipient support is required.

**Key Words:** Pre-emptive; Kidney transplantation; Living donor; Ethics; End-stage renal disease

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**Core Tip:** Live donor kidney transplantation (LDKT) is the optimal treatment for end stage renal disease (ESRD), particularly pre-emptively, prior to requirement for renal replacement therapy. There are a number of potential barriers and opportunities to promoting this: (1) National frameworks; (2) Health care providers and transplant programmes; (3) Societal norms/cultural expectations; (4) LDKT donors; And (5) Patients with ESRD. We recommend an approach where: Patients approaching ESRD are referred early; potential donors are prioritized; education regarding pre-emptive LDKT should be the norm; pre-emptive transplantation maximize benefit to potential recipients. Investment in infrastructure, increased awareness, and donor and recipient support is required.

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## INTRODUCTION

Live donor kidney transplantation (LDKT) remains the optimal modality for treatment of end stage renal disease (ESRD). It has been demonstrated to provide improvements in both graft and patient survival in comparison to transplantation from a deceased donor<sup>[1]</sup>. Pre-emptive transplantation, which occurs prior to the recipient's requirement for dialysis, has demonstrated improvements in patient and graft survival in

comparison to implantation after the commencement of dialysis<sup>[2,3]</sup>. The cumulative benefit of pre-emptive live donor transplantation should provide tangible benefits. However, there remains a paucity of data to support this attitude to transplantation, although it appears logical based on existing data to promote this form of live donor transplantation.

The mechanisms for improved outcomes, both in terms of patient and graft longevity, with pre-emptive transplantation are not well understood although it is hypothesized that it may be a consequence of reduced co-morbidity burden due to avoidance of uraemia and dialysis, or due to improved patient selection<sup>[4]</sup>. It is also thought that the greater residual renal function improves patient resilience to a major intervention and an attenuated immune response in the recipient<sup>[4-6]</sup>.

There is concern as to the timing of pre-emptive transplantation in general. There remain international variations with respect to the timing of deceased organ transplantation. However, historically pre-emptive transplantation is considered when the glomerular filtration rate (GFR) approaches ESRD to optimize both patient and graft survival<sup>[7]</sup>. Recent studies have postulated, however, that this should occur shortly prior to the need to initiate dialysis, when uraemic symptoms become prevalent, although the data for this remains equivocal in randomized trials<sup>[8-10]</sup>. This will usually occur at a GFR between 7-10 mL/min, albeit with consideration regarding the rate of decline of renal function<sup>[11]</sup>. However, the optimal timing ultimately for transplant is currently recommended to be shortly or a few months prior to the need to commence dialysis<sup>[12,13]</sup>.

The debate over pre-emptive transplantation is relevant almost exclusively to renal transplantation. This is because of the evolution of durable renal replacement therapy (RRT), which allows more structured planning of transplant timing<sup>[14]</sup>. This hasn't been mirrored in other organ transplants where pre-emptive approaches, by necessity, remain the norm, due to the absence of viable organ replacement therapies. The ethical considerations regarding pre-emptive transplantation are relevant almost exclusively in the context of renal transplantation, where these choices exist.

Pre-emptive transplantation is, however, not without controversy, as there remain significant challenges to the provision of an equitable and sustainable service for all service users, without priority being given to certain aspects of the transplant process, particularly at the expense of deceased donor transplantation. These reflect potential challenges in both the systematic provision of pre-emptive live donor transplantation due to obstacles from health care providers (HCP) as well as societal challenges. The potential impact on both donor and recipient, particularly with extended exposure to immunosuppression and its associated deleterious effects also require consideration. The transplant community has historically engaged with and provided innovative solutions to ethical dilemmas that expand the boundaries of clinical practice, but there remains a paucity of data that unequivocally demonstrates a solid foundation for pre-emptive transplantation. These studies are urgently needed to provide robust support for engagement with this process, as the current patient load and clinical pressures mandate continued engagement in pre-emptive transplantation.

LDKT, which has evolved and now largely underpins the success and progression of the majority of transplant programmes, has to strike the balance between success, whilst minimizing acceptable risk to both the transplant donor and recipient. This has particularly resonated with increased awareness of the potential long term risk to organ donors<sup>[15,16]</sup>.

This has inevitably increased focus on providing sustainable, safe LDKT programmes that maintain public confidence in the robustness and safety of the entire process. There is a requirement for accountability to both the profession and society as a whole.

There are therefore a number of potential barriers and opportunities with respect to promoting and evolving pre-emptive LKDT, both individually and as a systematic process. We classify and characterize these, specifically focusing on opportunities with respect to the various stakeholders in the process: (1) National Frameworks; (2) HCP and transplant programmes; (3) Societal norms/cultural expectations; (4) LKDT donors; and (5) Patients with ESRD (including family and social networks).

Each of these groups has distinct areas of concern and influence in ensuring access to pre-emptive LDKT, and these will be examined in more detail. We particularly aim to examine factors influencing and understand the potential cause of variability in access and adoption of pre-emptive transplantation.

## NATIONAL FRAMEWORKS AND SOCIETY

The delivery of a successful pre-emptive living donor programme requires an established and efficient transplantation infrastructure. There is significant variability internationally in the maturity of living donor programmes, predominantly linked to prevailing national socioeconomic standards<sup>[17]</sup>. This results in varying priorities with respect to emphasis for development and progression. This is particularly true with increasing emphasis on the potential and deliver of paired exchanged and immunologically complex transplants, which require the existence of significant infrastructure and clinical input.

There is also a requirement supporting primary care facilities for early identification of patients with evolving chronic kidney disease (CKD), to allow identification and optimization of patients increasing the chances of achieving transplantation pre-emptively. There are a number of methods to improve cohesion between referring centres and the transplant team to facilitate this. This is largely coupled with education programmes for patients, their relatives and HCP's, which highlight the benefit of live donation, and particularly pre-emptive transplantation<sup>[18,19]</sup>. There is also a need for local and national regulatory authorities to provide infrastructural and financial support to allow these initiatives to flourish.

This approach has to be balanced against the confines of limited capacity in most programmes and should not be seen to adversely affect other aspects of the service delivery by impinging on the capacity of local systems to provide unrelated aspects of the programme for patients who may not have the benefit of pre-emptive live donor options to enable RRT.

## HCP/INDIVIDUALIZED TRANSPLANT PROGRAMMES

HCP's have to balance competing concerns in delivering safe and efficient healthcare in modern society. These include the overriding objectives of beneficence (doing good for the individual patient), and justice (ensuring fairness for all patients) that may require medical interventions across a wide variety of services and significant ethical considerations<sup>[20]</sup>.

This is particularly relevant in a financially contracting health economic model, which is currently evident in both Europe and North America. In addition, there are significant shifts in national health care priorities in the developed world, with an aging population and an emphasis on treatment and support of this as well as a focus on services with high priorities or profiles. This includes a culture where there has been, and remains, an expectation for continued improvements in areas such as cardiovascular and cancer services. This has to be balanced against the challenges of designing, innovating, and continuing to deliver high quality transplantation services.

LDKT has the added overriding responsibility of minimising risk to the potential donor. This has been focused by recent data regarding long term risks that has resulted in significant re-evaluation of the donor pool<sup>[15,16]</sup>. This is particularly highlighted in pre-emptive LDKT, where the urgency and benefit of transplantation may not yet be obvious.

The potential significant recipient benefit of pre-emptive live donor transplantation is countered by the need to ensure that this does not impact on investment, both in terms of resources and finance in the live donor pathway as a whole for all patients, ensuring continued equity of access to services. It is particularly important that access to transplantation for those who are already on dialysis cannot be compromised. These concerns are already being addressed in the development of strategies to promote LDKT in the United Kingdom amongst other countries<sup>[21]</sup>. These highlight the need to maximize patient benefit by ensuring that all suitable recipients have appropriate resources invested in their care. This should ensure that no other patients in 'conventional' work-up (particularly those who have commenced dialysis) are perceived to have been disadvantaged. In addition, it highlights the importance of embedding the principle of 'transplant first' initiative in clinical practice for all potential LDKT recipients. This initiative focuses on increasing patient transition to transplantation prior to the need for dialysis<sup>[22]</sup>.

Data demonstrates inequity in access to all transplant services amongst varying population groups. These are particularly prevalent across geographical distribution in ethnic minorities and potential recipients with socioeconomic deprivation in both North America and Europe<sup>[23,24]</sup>. This is once again further evident when potential barriers to access of live donation services are characterized<sup>[25]</sup>. This demonstrates that

a significant barrier to pre-emptive live donor transplantation may develop along both ethnic and socio-economic boundaries, and appropriate education needs to be embedded as a preventative measure within the healthcare community as a whole<sup>[19,26]</sup>.

There are also regional variances both within national and international programmes with respect to referral for transplantation by nephrologists and this is mirrored in the context of pre-emptive transplantation<sup>[27,28]</sup>. There are multiple contributing factors, including whether the potential recipient is receiving treatment in a dedicated transplant centre, coupled with the attitude of the referring nephrologist. There have been suggestions that there is a lack of consistency in the practice of 'transplant first' by referring nephrologists<sup>[29]</sup>. This in turn may result in unacceptable delays in referral for transplant assessment, and the subsequent lost opportunity for pre-emptive transplantation.

It could also be postulated, although this remains controversial, that in areas where practice or remuneration is linked to the volume of patients on dialysis, that there may be a conscious or unconscious bias on the part of the nephrologist with respect to referral for LDKT. This is due to the potential impact of loss of patients or finance, although this requires further clarification. There are data to support this worrying finding, though from North America<sup>[30]</sup>. This could potentially be counteracted by a provision of financial incentive to the referring physician with preferential options for transplant follow up to ease the financial obstacles to potential referral for pre-emptive LDKT.

It has also been shown that patients receiving pre-emptive transplants have significantly better socio-economic conditions and higher education levels<sup>[8,22]</sup>. The onus is therefore on HCP's to ensure that these potential barriers are overcome by highlighting potential pre-emptive live donor options to less advantaged groups of patients with ESRD, and improving education and access to information to promote these work streams. There should also be attempts to promote early identification and referral to allow timely donor screening and workup. This could remove significant temporal barriers and improve the equality of access to transplantation.

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## SOCIETY

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Society may provide potential barriers that are an extension of those faced by HCP's in provision of high quality care. However, there remains a susceptibility to the cultural attitudes and norms of society. The transplant community is required to identify and confront these challenges to ensure equity of access to all services. These challenges are not unique to deceased or live donor, or more specifically, pre-emptive transplantation but may be exacerbated by the unique challenge that the latter provides.

The emergence of data regarding long term live donor safety has provoked significant debate amongst HCP's regarding its acceptability<sup>[15,16,30]</sup>. There is the ongoing challenge of ensuring non-maleficence whilst supporting the acceptability and progression of treatment options and healthcare as a whole. The balancing of these two aims requires significant ethical debate. However, HCP's are required to balance these concerns with the individual patient that they are treating rather than the utilitarian challenge of driving progression or overcoming limitations in health care. It remains imperative that initiatives such as 'transplant first' as well as live donation are promoted to ensure optimal patient outcome. However, the corollary to this is to ensure that HCP's pastoral role ensures that patients, and in this scenario particularly donors, have their long-term health protected and preserved during this process. This is best evidenced by the commitment to donor follow up life long, or even prioritisation of donors with subsequent ESRD to transplant options in national programmes<sup>[31]</sup>.

There remain significant ethnic disparities in access to both deceased and LDKT<sup>[32,33]</sup>. These, on the whole, reflect socioeconomic inequalities and ultimately impacts as longer waiting times and decreased frequency of live donation proceeding due to a shortage of suitable and willing donors. Factors identified include both identification and recruitment of live donors as well as subsequent conversion of potential donors to actual donors<sup>[34]</sup>. This has a further impact when including the fact that the pool of deceased donors translates into patients from ethnic minorities having a prolonged wait time in this context. Pre-emptive LDKT is unlikely to prosper in this scenario. It is therefore essential that education programmes continue to focus on live donor promotion within these communities, relying on both formal systems as well as more individualised perspectives if appropriate. The success of formal education programmes has been well documented<sup>[25,26,35]</sup>.



These challenges are further highlighted in the context of pre-emptive LDKT. The time critical nature of performing pre-emptive LDKT means that any potential delays, as previously highlighted, impact significantly on the ability of ethnic minorities to benefit from pre-emptive LDKT.

The ethnic and socio-economic barriers are mirrored in certain cultural environments, and particularly those with religious influence, that impact on the ability of kidney donation to proceed and therefore proportionately affect pre-emptive LDKT. Transplantation, and particularly deceased organ donation remain controversial in certain religious and cultural environments, particularly Judeo-Islamic faiths, where the focus on preservation of the integrity of the physical body after death is predominantly considered sacrosanct. This occurs despite official support for organ donation by religious leaders<sup>[36]</sup>. This in turn has fuelled conservative attitudes to transplantation in general within these communities. The reduced rates of live donation, due to religious views, mirror those seen with socio-economic deprivation, and in turn are likely to impact on proceeding to LDKT in a timely fashion, although this context remains poorly characterised.

The final societal barrier predominantly concerns potential financial impact, particularly to the donor in terms of lost income. This is well described in the context of overall LDKT, but also applies to pre-emptive transplantation<sup>[36,37]</sup>. A recent survey identifying patient perceptions, and predominantly focused on barriers to pre-emptive transplantation, identified financial concerns as a significant stressor<sup>[37]</sup>. This corroborates previously reported findings that patients who received a LDKT had a significantly higher annual income, thereby again potentially initiating bias against those from lower socio-economic groups. There was also increased out of pocket costs for both donor and recipients. All of these factors can create disparities in access to transplantation based on financial means. The onus is on society as a whole to provide greater support for LDKT mechanisms to progress. This is particularly because of the well-proven financial benefits of successful transplantation to society as a whole, both in terms of on-going health care costs on RRT and the opportunity for successful recipients to return to employment. This may be overcome in situations where, although controversial in certain environments, reimbursement of live donors is facilitated at an appropriate level to act as an incentive<sup>[38]</sup>. This is counteracted by the obvious financial benefits of avoiding RRT and improved recipient longevity, both of which provide significant benefit to the national health economy.

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## DONOR FACTORS

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Donor willingness to engage in the LDKT is integral to the success of any durable live donor programme. The legal frameworks that govern the process aim to protect the donor and minimise potential opportunities for solicitation of organs. In addition, it is difficult to extrapolate emotions or barriers in donor to coming forward for pre-emptive LDKT, as each case will have individualised circumstances, challenges and opportunities.

As previously noted, recent data highlighting higher than previously perceived risk associated with live donation has had a significant impact on counselling and consent processes for organ donation. Although the relative risks remain very low, this may impact on donor willingness to volunteer<sup>[15,16]</sup>. This is especially pertinent in light of the fact that, unlike any other procedures, a donor nephrectomy is being performed on a patient with no pre-existing pathology, thereby strengthening the desire to ensure optimal outcomes<sup>[15]</sup>. The primary obligation of responsible clinicians caring for the donor is their outcome, thereby aiming to exclude any emotional pressures between donor and recipient or medical factors that may promote pre-emptive transplantation in the latter. This must obviously be in the context that, in a significant proportion of cases, there will already be a strong emotional bond between the donor and recipient pair.

The consent process should inform donors of potential risk, particularly based on these recent data, which may result in donor dropout, although this risk requires further clarification<sup>[39,40]</sup>. This is particularly relevant in extended criteria donors, where pre-existing comorbidities, and particularly Diabetes Mellitus and hypertension, may further heighten perceived or relative risk for the donor based on recent evidence. HCP's may also be resistant to pre-emptive LDKT if they feel that it is unwise to place any donor in a position of perceived or higher than expected risk when the potential recipient may not yet demonstrate all of the severe physical and psychological effects of ESRD, even in situations where voluntary consent has been established.

Within the context of pre-emptive LDKT, live donation also has to demonstrate that the earlier time frame for donation doesn't adversely affect the potential donor in any way. This is especially pertinent in light of the potential time pressures to achieve donation prior to the potential recipient receiving dialysis. This should not allow any unnecessary acceleration or dereliction in live donor work up, which may in turn impact compromise donor's long-term safety. However, an additional value to the entire process may be the improved psycho-social benefit to the potential donor by providing additional advantage to their recipient at an earlier time point.

Recipients receiving pre-emptive LDKT may not have experienced dialysis, increasing the risk of non-adherence and this may be mirrored in donors where the vicarious emotional distress of a family member or friend on dialysis has not yet been experienced<sup>[41]</sup>. This may act as a barrier to donors who are not yet aware of the potential for the patient with ESRD to undergo significant physical and emotional stress once dialysis commences. In addition, similar circumstances may occur if the transplant subsequently fails due to either technical or immunological reasons<sup>[41]</sup>. Previous data demonstrate short-term transient deteriorations in mental health that recovers over months<sup>[42,43]</sup>. These findings could be extrapolated to pre-emptive donors where the mitigating emotions of a recipient experiencing dialysis are not experienced vicariously by the donor.

Pre-emptive transplantation may, conversely, also provide improved convenience for the potential donor because the process, once commenced, is not halted to allow deterioration of renal function to a predetermined threshold. This approach may streamline the process of donor assessment and progression to donation. This prevents potential delays for the recipient commencing dialysis, thereby placing the potential donor's life on hold. There is a need for careful pragmatism of what best fits the convenience of the donor with balancing the ideal timing to maximize the longevity of the graft for the recipient's benefit. Definitive processes will need to be defined to ensure the timing of the transplant procedure, between all involved parties.

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## TRANSPLANT RECIPIENTS

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There are a number of pre- and post-surgical factors that result in variation in access to and outcomes for pre-emptive transplantation for patients with ESRD. This has to be countered with the view that any exposure to dialysis has a detrimental effect both on patient and graft survival. Longer pre-transplantation dialysis exposure is an independent risk factor for progressively higher risk of all cause transplant failure from any cause, including death<sup>[44]</sup>.

Pre-emptive transplantation provides the best option for patients with ESRD in terms of durable RRT. However, there may be barriers to ensuring adequate access and acceptability of this option. The predominant cause for these is socioeconomic or societal barriers, as previously noted. However, there also needs to be consideration regarding optimisation of the potential recipient and ensuring that no medical contraindications exist to preclude successful outcome. A recent meta-analysis and position statement highlighted a number of potential medical barriers that might impact on this process<sup>[41]</sup>.

In addition, concern remains regarding a perceived lack engagement with the possibility of pre-emptive LDKT, mimicking the features seen in non-adherent patients after transplantation<sup>[41]</sup>. This is predominantly seen in young recipients and largely occurs as the result of patients who have not yet experienced the deleterious effects on quality of life that are characteristic after commencing dialysis treatment<sup>[45]</sup>. However, there remains an absence of robust data to substantiate this, and this phenomenon may therefore be overestimated, as does the potential harmful effects of prolonged immunosuppression exposure<sup>[11,46]</sup>. There is, however, evidence to support that quality of life on dialysis is lower than patients with less advanced chronic kidney disease, the general population and individuals suffering from other chronic medical conditions<sup>[47-49]</sup>.

These factors highlight the importance of education for the potential transplant recipient regarding the benefits of pre-emptive transplantation and to manage the expectations of the recipients with respect to their experiences around the time of transplant. This may also include focus on the benefits of transplantation and associated experiences in comparison to RRT. This should include recognition of the importance of quality-of-life benefits for patients, which may supersede metrics such as graft and patient longevity, which predominate medical outcome measures. However, the former remain difficult to quantify and provide valid reproducibility

across various patient groups, although there are data to support their value and current potential for improvement in uptake<sup>[50-52]</sup>.

Another barrier to pre-emptive LDKT is the success and progression of dialysis treatment in terms of quality of life and durability for the patient, particularly intensive or nocturnal home haemodialysis. However, this method of RRT has shown conflicting benefits in terms of improvements in quality of life whilst LDKT has overwhelming favourable evidence<sup>[53]</sup>. In addition, mortality data regarding intensive haemodialysis is equivocal whilst transplantation again has shown significant and sustainable benefit, particularly in the context of pre-emptive transplantation<sup>[54]</sup>. However, in certain circumstances, consideration also needs to be given to the fact that intensive or home haemodialysis may provide a better option than further attempts at pre-emptive transplantation. This is particularly valid in situations such as recurrent focal segmental glomerulosclerosis, which may have caused recurrent disease in a previous transplant, necessitating delays and careful consideration of the benefit of further transplantation<sup>[54]</sup>. However, this approach should be seen as an exception rather than the norm.

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## CONCLUSION

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The overwhelming responsibility of HCP's is to ensure beneficence whilst minimising the chances of harm. Pre-emptive LDKT, if timed appropriately, maximises benefit to the potential recipient. However, within the context of modern healthcare it remains vital that both the individual and the entire service's requirements are fulfilled. This provides a number of barriers and opportunities that may prevent access to full adoption of this process.

These include a number of fundamental areas that underpin this process and that have been evaluated in some detail relevant to both the individuals involved in the process, namely the HCP's, potential donor and recipient but also the system and society into which they are integrated.

The progression of pre-emptive LDKT requires significant investment into education programmes early in the ESRD pathway, to ensure continued empowerment of individuals to represent and promote their interests. Transplantation has the benefit of well-informed patients who have chronic involvement in health care prior to requiring interventions due to the chronic nature of ESRD. There is therefore the opportunity to promote initiatives such as 'transplant first' but, more importantly, to particularly focus on LDKT, thereby potentially increasing pre-emptive numbers. This will require earlier discussion of these options with patients by HCP's.

Pre-emptive transplantation offers the potential benefit of improving patient outcome. By improving knowledge of the entire transplant community improving access to this initiative will have a significant impact on transplant programmes worldwide. Further work is also needed to understand potential differences in attitudes to pre-emptive transplantation between recipients receiving their first organ and those who may have had the experience of previous transplants.

This group therefore has a number of specific recommendations: Patients approaching ESRD should be directed to a pre-transplant clinic and not be prepared for dialysis as the norm. The discussion regarding pre-emptive live donation should occur and be the norm. This should be supported with live donor advocates and active promotion of pre-emptive LDKT in a multidisciplinary setting. On this basis, approaching and preparing potential donors for LDKT should be prioritised.

Education regarding pre-emptive LDKT should be the norm for patients approaching ESRD. This should be appropriate for the patient's cultural needs and physical as well as psychosocial status. Adequate resources are required at both a regional and national level to allow pre-emptive LDKT to be facilitated.

Transplantation requires an approach that promotes live donation, with specific focus on the benefit of a pre-emptive approach. Societal and transplantation structures need to be designed with this aim prioritised. This is particularly important in view of some of the cultural and societal challenges that occur regarding deceased donation, which in turn heighten the importance of live donation. There should be focus on early education and increased acceptance of this beneficial approach for prospective donors and recipients and HCP's. This will ensure the best use of valuable donated live donor organs and, in turn, improved outcomes for recipients.

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