Organ Transplantation from Deceased Donors: Eligibility Criteria and Allocation Protocols

Background review

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Preamble

This document presents a range of guideline and literature reviews and related data analyses intended to support the revision of Australian eligibility criteria and allocation protocols for deceased donor organs, on behalf of the Transplantation Society of Australia and New Zealand (TSANZ). The objectives of this review are (i) to provide information on the outcomes of existing allocation policies, based on analyses of local registry data, and (ii) to review international guidelines and evidence on specific topics pertaining to candidate eligibility, donor eligibility and the allocation of deceased donor organs. The scope of each organ-specific chapter was determined in consultation with the respective TSANZ Advisory Committee: only those topics that were identified as being of special interest at the time of writing are discussed. This review therefore does not cover every aspect of candidate/donor eligibility and organ allocation, and additional topics may subsequently arise during the development of the revised TSANZ guidelines. This review should be regarded as a useful resource, but not as a definitive document. It should also be noted that this document focuses on Australian eligibility and allocation policies: although organs are routinely shared between Australia and New Zealand, New Zealand has its own eligibility and allocation policies that are not discussed here.

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1. Introduction

Organ transplantation is a two-step process. First, the potential recipient is evaluated according to current eligibility criteria and – if determined to be a suitable candidate – added to the relevant transplant waiting list. Second, potential donors are assessed for eligibility to donate one or more organs, and – if consent is obtained and organ(s) deemed suitable – their organs then allocated according to organ-specific allocation protocols. This report considers the clinical aspects of each of these steps of the organ transplantation process, although the emphasis on recipient eligibility versus donor eligibility/allocation protocols varies from chapter to chapter (consistent with the topic priorities of the advisory committees).

Compared to 198 deceased donors Australia-wide in 2007, in 2012 the number of deceased donors was 354 – an increase of 80% (1). The number of kidney, pancreas, liver and lung transplants performed in Australia increased by 78%, 36%, 50% and 88% over this interval (heart transplant numbers did not increase, Figure 1). These trends are attributable to a combination of improved organ procurement practices, increased utilisation of circulatory death donors (DCDs), and expanded organ-specific donor eligibility criteria. Another important trend has been the steady aging of the deceased donor pool. The median age of deceased donors in Australia in 2012 was 50.5 years – the highest since records began (1). These factors have potential implications for both recipient eligibility criteria (greater availability of deceased donors may affect waiting list access) and organ allocation policies (changing donor characteristics raise important questions for allocation policies).

Ultimately, revisions to current wait-listing or allocation protocols need to be based on (i) identified shortcoming of the existing system, (ii) clearly articulated principles of what the system is supposed to achieve, and (iii) evidence that proposed revisions will be effective in achieving their intended aim. The purpose of this report is to examine the outcomes of existing wait-listing and allocation protocols, to consider the implications of a shifting donor and recipient case mix, and to summarise international practices and outcomes as they relate to selected eligibility and allocation policies. International guidelines are reviewed in detail to compare how different jurisdictions have dealt with specific issues of interest. Chapter 7, which discusses protocols for vascularised composite allotransplantation (VCA), is distinct in that local protocols for candidate and donor eligibility are still under development and only one VCA transplant has so far been performed in Australia. Therefore this chapter discusses key considerations for VCA policies, with reference to the international experience.

This report is intended as a reference document to the development of a revised TSANZ Consensus Statement on Eligibility and Allocation Protocols. The TSANZ is the body responsible for developing and updating eligibility criteria and allocation protocols in Australia and New Zealand. As part of the implementation of the National Reform Agenda for organ and tissue donation in Australia under the direction of the Organ and Tissue Authority (OTA), TSANZ received funding to develop nationally uniform criteria for patient eligibility and organ and tissue donation and allocation across Australia. The Consensus Statement on Eligibility Criteria and Allocation Protocols (Version 1.1) was released in June 2011 following comprehensive professional and community consultation. However several issues were raised
during the development of the original Consensus Statement document that remain unresolved, including (2):

- Governance issues: the respective roles of TSANZ, the Organ and Tissue Authority (OTA) in the process of developing and updating eligibility criteria and allocation protocols, and mechanisms for auditing adherence to agreed protocols;
- Use of likelihood of survival as a recipient eligibility criterion: This policy enforces rationing at the point of acceptance onto the waiting list, however the impact of this criterion on equity of access for difference patient groups is not known, and no clear rationale exists for why different survival thresholds should be applied for different organs. Importantly, a growing number of expanded criteria organs are being retrieved that are of insufficient quality to be acceptable for recipients with a long post-transplant expected survival, but may confer survival and other benefits to patients falling below the expected survival threshold for waiting list entry;
- Alternate listing: this concept involves the utilisation of organs considered to be unsuitable for patients on the general waiting list, by offering these organs to patients on an alternate waiting list. Patients on the alternate list would generally be those whose age or comorbid status precludes them from the standard waiting list on the basis of low expected post-transplant survival. The purpose of such a policy would be to gain utility from organs that otherwise might be discarded, and to improve quality of life for a larger number of end-stage kidney disease (ESKD) patients. The ethics of this policy and its impact on demand for ICU and overall hospital resources were issues that were flagged as needing further consideration;
- Logistics in allocation and equal right of access: the need to audit the frequency and type of logistical issues that impact on allocation decisions was raised;
- The role of HLA matching in allocation: on one hand, HLA matching discriminates against those with less common HLA antigens; on the other hand, for a subset of patients – particularly sensitised patients – transplant outcomes are significantly better if they are transplanted with a well-matched kidney;
- Pancreas allocation: as combined kidney-pancreas allocation is given priority, there is a need for an audit of patients wait-listed for and patients receiving combined kidney pancreas transplants;
- Re-transplantation: the question raised was whether there should be blanket policies regarding how many transplants an individual should be eligible to receive, and what implications this would have for patients transplanted as children and for patients that accept a marginal organ that subsequently fails;
- Appeals mechanism: patients have a right to a second opinion if assessed as unsuitable for organ transplantation. Authority with regards to appeals processes lies with the respective state and territory health departments, or their advisory committees.

Several of these issues are addressed in the present document, however the focus throughout is on those specific clinical aspects of eligibility and allocation that were identified as of particular interest by each of the respective TSANZ Advisory Committees following
consultation in June 2014. Ethical aspects of eligibility and allocation of organs from deceased donors are the subject of a separate NHMRC Guideline.

Finally, while not explicitly discussed in this document, community preferences with respect to the allocation of deceased donor organs are highly relevant to the TSANZ Consensus Document development process. Focus group studies have shown that the Australian community values a utilitarian approach to allocation – whereby organs are allocated to maximise life years saved – tempered by priority for medical urgency and for length of time on the waiting list (3). In addition to expert opinion and international evidence, community and patient preferences will need to be consulted in detail and incorporated into policy development.

Figure 1: Deceased donors in Australia, 1992 and 2012. Source: ANZOD Annual Reports (1).
2. Kidney Transplantation

2.1. Current eligibility and allocation criteria

In order to be wait-listed for a kidney transplant from a deceased donor, candidates must meet the criterion of an expected 80% 5-year survival post-transplant. This criterion is intended to set a single target so that all transplant units are using the same benchmark for assessing patients, and to facilitate the audit of centre wait-listing practices (2). Criteria for inclusion on the kidney transplant waiting list are: (i) end-stage kidney disease (ESKD) requiring dialysis, (ii) anticipated low perioperative mortality, and (iii) 80% likelihood of surviving for at least 5 years after transplantation. The current 5-year survival rate for kidney transplant recipients in Australia and New Zealand is close to 90% (4).

Exclusion criteria for kidney transplantation are:
1. An expected likelihood of less than 80% of surviving at least 5-years post transplant, taking into account comorbidities including cardiac disease, vascular disease, diabetes mellitus and malignancies;
2. Substantial, non-correctable cardiovascular disease (although lesser levels of disease would be considered a relative contraindication, taking into account expected 5-year survival);
3. Uncontrolled infection;
4. Active malignancies other than non-melanoma skin cancer;
5. Inability to comply with complex medical therapy.

Other medical conditions such as cardiac failure, chronic obstructive pulmonary disease, cirrhosis of the liver, peripheral vascular disease, cerebrovascular disease and complicated diabetes are considered on a case-by-case basis. Although advanced age in the absence of significant medical comorbidities is not necessarily a contraindication to kidney transplantation, less than 2% of the 5751 dialysis aged 65+ in Australia at the end of 2012 were actively wait-listed for a kidney transplant after taking into account the exclusion criteria above (4).

The major criteria by which the National Organ Matching System (NOMS) currently allocates deceased donor kidneys to waitlisted candidates are:
1. Blood group compatibility;
2. Waiting time on dialysis;
3. Tissue-type match with the donor;
4. Sensitisation;
5. Paediatric status – paediatric patients who are under 18 years and have been on dialysis for more than 12 months receive priority.

Kidneys are allocated first through the National Interstate Exchange program, designed to improve outcomes for sensitised patients by facilitating timely access to a well-matched kidney. If a sensitised patient (PRA>50%) is identified in NOMS as a close match to the donor kidney (0, 1, or 2 HLA mismatches), this kidney can be transported from anywhere in Australia. The Interstate Exchange Program also allocates kidneys to patients who are a zero HLA mismatch.
with the donor (even if they have no antibodies), with provision to allow reciprocal transfers between states to maintain a balance in the exchange of organs. About 20% of kidneys are allocated through the Interstate Exchange Program; the majority of kidneys (80%) are allocated within the state in which they were recovered. NOMS matches donors to recipients within each state, according to the state’s allocation algorithm (each state uses a slightly different algorithm). The algorithm looks first at tissue-type match: if no candidates are a good match then tissue-type is ignored, and the kidney is allocated to the patient with the same blood group who has been waiting the longest. All states ensure that their algorithm results in a minimum of 30% of locally allocated kidneys (i.e. those kidneys not allocated through Interstate Exchange) being allocated according to waiting time. Waiting time is calculated from the commencement of dialysis (not the date of wait-listing). In the case of retransplantation, if the first graft fails within 6 months of transplantation, then accumulated wait-time prior to first transplant is counted towards waiting time for a second transplant. Where failure of the primary graft occurs later than 6 months post-transplant, waiting time is calculated from (re)commencement of dialysis after graft failure. Kidney transplant candidates <18 years who have been on dialysis for more than 12 months are eligible for priority on the state-based waiting list, although this paediatric bonus is applied differently from state to state. Finally, in the rare event that there are not enough patients in a given state to accept the available kidney (for example if the donor has a rarer blood group), then a national override list is run including patients from across the country, to ensure that the kidneys do not go to waste.

An issue raised by the previous TSANZ Consensus Statement was the anticipated ongoing decline in donor quality as a consequence of population aging, increased prevalence of comorbidities such as diabetes, and consequent increased reliance on expanded criteria donors (2). The Renal Transplant Advisory Committee (RTAC) has been considering the question of how to utilise expanded criteria kidneys fairly, while maximising outcomes for all donors.

Major concerns with the current system include the following:

- Extreme age mismatches between deceased donors and recipients are permitted - as a consequence, poor quality organs are offered to young, healthy candidates and vice versa – high quality kidneys from young deceased donors may be offered to candidates with low life expectancy;
- Lack of an explicit consent process for acceptance of high-risk donor kidneys;
- The 80% rule is no longer useful in an era when an increasing number of marginal kidneys are being retrieved that may be inappropriate for allocation to a candidate with a long expected lifespan, but may be suitable for a marginal candidate;
- The current system for prioritizing sensitised candidates is not effective;
- The current system does not account for how many transplants an individual is likely to receive across their lifetime, and therefore the potential for sensitisation in young recipients is not accounted for in the allocation of the primary kidney graft;
- Geographic disparities in donor rates and organ sharing;
- Geographic disparities in waiting list access and waiting times;
There is a need for a formal examination of the impact of priority in allocation for multi-organ transplants (e.g. combined kidney-pancreas, combined kidney-liver). The outcomes for single organ and for multi-organ recipients need to be formally reviewed to better assess the utility outcomes for both types of transplantation.

2.1.1. Outcomes of the current allocation system in Australia

The number of deceased donor kidneys recovered in Australia has increased significantly since 2008/2009. Compared to 258 kidneys recovered from deceased donors in 2007, the number recovered in 2013 was 636 – an increase of 78% (1). Figure 2 shows the impact of this increased supply of deceased donor kidneys on access to kidney transplantation for candidates waitlisted in 2007 through 2012. Overall, the rate of deceased donor transplantation among waitlisted candidates has more than doubled over this interval (from 24 to 52 donors per 100 active patient years). Queensland and Western Australia showed the highest increases in the rate of deceased donor kidney transplantation, with smaller increases seen in New South Wales and Victoria. By comparison, the number of candidates active on the waiting list at December 31 2012 versus 2007 declined by 23% in New South Wales/ACT (2007, n=700; 2012, n=526), 3% in Victoria/Tasmania (2007, n=348; 2012, n=336), 17% in Queensland (2007, n=128; 2012, n=106), 18% in South Australia/Northern Territory (2007, n=67; 2012, n=55), and 53% in Western Australia (2007, n=90; 2012, n=42) (4).

Access to deceased donor kidney transplantation increased for waitlisted candidates of all age groups between 2007 and 2012 (Figure 2). Rates of deceased donor kidney transplantation in 2012 were 100 (95% CI 56-164), 52 (95% CI 48-57) and 45 (95% CI 34-60) transplants per 100 active patient years for candidates aged <18, 18-64 and 65+ years respectively. The increase in the rate of deceased donor kidney transplantation was smaller for blood type B and O candidates than for type A and AB candidates. For candidates with a PRA of 20-80%, the mean rate of deceased donor kidney transplantation increased from 24 transplants per 100 active patient years (95% CI 19-30) in 2007, to 42 (95% CI 34-51) in 2012: for candidates with a PRA of >80%, the mean rate of deceased donor kidney transplantation increased from 17 transplants per 100 active patient years (95% CI 10-27) in 2007, to 30 (95% CI 21-41) in 2012. By comparison, the mean rate of deceased donor kidney transplantation for candidates with a PRA <20% increased from 24 (95% CI 21-28) to 60 (95% CI 54-66) transplants per 100 active patients years over the interval from 2007 to 2012. This growing disparity in access to deceased donor kidneys by sensitisation status might partly explained by improved profiling of HLA antibodies following the introduction of luminex technology – clinicians might be declining kidney offers more frequently on the basis of antibody profile. Another likely explanation is that this trend relates to the changing characteristics of the donor pool. Much of the increase in donor availability has been in marginal donors, which are less likely to be accepted for sensitised patients for whom the longevity of the kidney is of particular importance.

The increase in the rate of deceased donor kidney transplantation in Australia since 2009 has corresponded with a simultaneous decline in the rate of living donor kidney transplantation (Figure 3). A report by Australian Healthcare Associates to the Department of Health and Aging concluded that, while there is no definitive explanation for the decline in rates of living organ donation in Australia, the principle hypotheses are that there was a temporary spike in living
Figure 2: Trends in the rate of deceased donor kidney transplantation, expressed per 100 active patient years, among waitlisted candidates from 2007 to 2012. Source: ANZDATA (personal communication, P Clayton).

donors in 2008, and that increased rates of deceased donation from 2009 onwards caused a drop in the waiting list and took the pressure off the need to pursue living donation. Other factors related to this decline in living donors may be an aging candidate population (fewer available living-related donors) or an upper threshold of capacity to perform kidney transplants within the
existing system (deceased donors displacing living donors) (5). Given this experience, it will be necessary to carefully evaluate any possible impact on living donation when considering potential revisions to policies for the allocation deceased donor kidneys in Australia. International precedents exist whereby allocation policy has possibly had unintended consequences for rates of living donor transplantation; for example the introduction of the OPTN Share 35 policy, which prioritised allocation of organs from donors younger than 35 to paediatric candidates, was accompanied by a 20% decline in the rate of living donor kidney transplantation (6).

Figure 3: Annual number of kidney transplants, by donor type, in Australia from 2007 to 2012. Source: ANZDATA 2013 Report.

There were 74 kidney regrafts from deceased donors in 2012. Figure 4 shows the distribution of age at primary graft for these 74 patients. Thirteen (18%) were less than 18 years of age at the time of their primary graft. Twenty-six were aged 18-34 years; therefore, 53% of regrafts in 2012 were in patients who were aged <35 years at the time of the primary transplant. Eight regraft recipients (11%) were aged 50 years or older at the time of their primary graft.

Figure 4: Age at receipt of first kidney transplant, all regrafts from deceased donors in 2012 (n=74). Source: ANZDATA (personal communication, P Clayton)

Retransplantation raises important issues of equity and utility. To a large extent, the question of retransplantation is an ethical one: on one hand, the decision to list for transplantation should be based on medical need – if the patient is able to benefit from
transplantation then they should be considered as a candidate; on the other hand, there is an opportunity cost to a patient receiving a second (third or forth) transplant. Paediatric patients are particularly affected: in the United States for example approximately half of all paediatric kidney transplant recipients will receive a second transplant in their lifetime (7). Of all paediatric recipients of primary kidney grafts (deceased or living donor) transplanted in Australia since 1990, the proportion retransplanted within 15 years was 28% (95% CI 24 to 33%; personal communication P Clayton). The corresponding proportion of paediatric primary graft recipients that died over the same interval was 11% (95% CI 8% to 15%). Figure 5 shows time to retransplantation or death for recipients transplanted as children with subsequent failure of their primary graft over the era from 1990 to 2012.

From a clinical perspective, allocation policies should ideally minimise the need for retransplantation, but also maximise the outcomes for recipients of second and subsequent transplants. Timely transplantation of paediatric candidates with a well-matched primary kidney graft will not only reduce subsequent need for retransplantation, but will also result in better outcomes after first graft failure. Recent analysis of paediatric kidney transplant recipients in the United States found that a higher number of HLA-DR mismatches at first transplant was associated with HLA sensitisation, longer waiting time, lower rate of retransplantation, and lower regraft survival (8). The other issue is that a high proportion of candidates for retransplantation will be sensitised, and would therefore derive the most benefit from a well-matched kidney with an appropriate expected lifespan. It might therefore be appropriate to consider allocation protocols in retransplantation separately to protocols for primary kidney transplantation.

![Figure 5: Time to retransplantation or death after primary kidney graft loss for paediatric recipients of kidney only transplants (from living or deceased donors) in Australia from 1990 to 2012. Source: ANZDATA (personal communication, P Clayton)](image-url)
2.2. Age in kidney allocation

2.2.1. Trends in deceased donor, candidate and recipient age

Median donor age in Australia was 51 years in 2012 (interquartile range 36 to 61 years), compared to 46 years in 2007. Median recipient age in 2012 was 51.5 years, compared to 49 years in 2007, and median candidate age in 2012 was 52 years compared to 50 years in 2007 (Figure 6). The median age of the deceased donors has therefore converged on median candidate and recipient age, as a consequence of the deceased donor pool aging at a more rapid rate than the candidate pool.

In 2012, 76% of deceased donors were under 60 years of age: 24% were 60 years or older (Figure 7). In 2007, by comparison, 83% of donors were less than 60 years of age and 17% were 60 years or older. The proportion of candidates aged older than 60 years has similarly increased over this interval, from 21% to 27%. The proportion of recipients of deceased donor kidney transplants aged 60 years and older increased from 14% in 2007 to 24% in 2012.

**Figure 6:** Median deceased donor, recipient (deceased donor), and active waitlisted candidate age and interquartile range, 2007-2012. Source: ANZDATA (personal communication, P Clayton)
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Figure 7: Distribution of deceased donor, recipient (deceased donor) and active waitlist age in Australia from 2007 to 2012. Source: ANZDATA (personal communication, P Clayton).

To put the age of the deceased donor pool in Australia in context, Figure 8 shows a comparison of international trends in the mean age of deceased donors from 2005 to 2012. Compared to the Australian deceased donor pool, the mean age of deceased donors in Norway and Catalonia was higher, the mean age of donors in the United States significantly lower, and the mean age of donors in the UK similar (although with recent divergence).

Figure 8: International trends in the mean age of deceased donors, 2005-2012. Sources: ANZDATA Registry Report, SRTR data request, OCATT (personal communication, J Twose), University Hospital Norway (personal communication PA Bakkan and A Foss), NHSBT data request.
Figure 9: Age distribution of deceased donors and patients added to the kidney transplant waiting list, 2008 to 2012. Waiting list age distribution is calculated as age at listing for on all patients who commenced RRT between 2007 and 2012 and were subsequently waitlisted for transplantation. Source: ANZDATA (personal communication, P Clayton).

2.2.2. International policies for retrieval of organs from older donors and allocation to older recipients

Within European countries in particular, aging candidate populations and the aging deceased donor pool have led to the introduction of specific policies for allocation of older kidneys to older recipients. Although donor and recipient populations in Australia are still relatively young, these demographics are shifting over time; furthermore, as a consequence of increasing rates of kidney transplantation and falling waiting lists, access to the kidney transplant waiting list may be expanded in the future to meet the treatment needs of a greater proportion of older ESKD patients (9).

The Norwegian system provides an example of how the needs of older candidates might be met in a context of relatively unconstrained access to kidney transplantation and high rates of kidney donation. There is no upper age limit on eligibility for kidney transplantation in Norway (personal communication A Foss); 80-90% of ESKD patients will receive a kidney transplant in their lifetime. Many are extremely sick – there is a high prevalence of arteriosclerosis and heart failure - however, on the basis that it is more cost-effective from a societal perspective that ESKD patients be transplanted rather than remain on dialysis, kidney transplantation is offered to all patients. Dialysis is considered a bridge to transplantation only. The prevalence of treated
ESKD in Norway was 874 pmp in 2011 (compared to 893 pmp in Australia), with 72% of this population living with a functioning graft (compared to 45% in Australia) (10). Relative to the size of the dialysis population, Norway by far performs the most kidney transplants per year worldwide (22 per 100 dialysis patients, compared to 7.5 in Australia and 4.1 in the United States) – see Figure 10 (11,12).

Despite the fact that Norway has one of the highest rates of transplantation relative to population size in the world (>90 transplants per million population in 2013; >50 kidney transplants per million population), the number of living donors has been declining slightly and average waiting times are increasing. For this reason, all deceased donor kidneys are used if they have urine production and an eGFR of at least 60 ml/min/1.73m$^2$. There is no upper age limit for the retrieval of DBD donor organs in Norway. Based on outcomes with deceased donors with age >75 years and eGFR <60 ml/min/1.73m$^2$ (13), donor organs with less than ideal kidney function will also be retrieved. There will be a few organs each year with primary no-function or poor function; however, if the creatinine is close to normal or only slightly elevated, and the eGFR is approximately 60 ml/min/1.73m$^2$, all kidneys with these characteristics will be used. There is similarly no eGFR-based exclusion criterion for donors in Australia, although eGFR, proteinuria, history of hypertension and diabetes, and biopsy findings are all taken into account in the donor evaluation. If kidney function impairment is long standing then the donor will be excluded, however acute kidney injury is not a contraindication to donation. Recent data demonstrate that kidneys retrieved from deceased donors with acute kidney failure have similar graft function and survival compared to kidneys without acute renal failure at 1 year post-transplant (14).

In Norway waiting time is given primary emphasis in the allocation of kidneys. However age matching is always considered, with a general rule that kidneys should not be matched beyond a 20-year age difference (for example, an 85 year old kidney will not be transplanted into a 45 year old patient). Allocation in order of consideration (personal communication, A Foss):

1. Waiting time;
2. Age match (assessed on a case by case basis, but a general rule that kidneys should be matched within 20 years of age, particularly in the case of older donors to younger recipients);
3. Tissue typing;
4. BMI of the recipient (the allocation of marginal kidneys to patients with a large BMI is avoided where possible).

In Catalonia, there is similarly no upper limit of age for retrieval of donor organs. In the case of donation after circulatory death (DCD) the original age limit for recovery of 55 years has been increased to 65; however, age is always considered a relative, not absolute, contraindication to organ recovery. This aggressive recovery of donor organs corresponds to inclusive eligibility criteria – only medical contraindications are considered, otherwise any patient is considered for kidney transplantation (i.e. an 80 year old can be considered for waitlisting – if an age appropriate donor appears, they will be transplanted). Despite this inclusiveness, 5-year patient and graft survival (primary kidney transplant, deceased donor) are
87% and 72% respectively (compared to 91% and 81% in Australia) (15). Discard rates, however, are high: about 17% of kidneys retrieved in 2013 were not transplanted. There is an effort to retrieve the maximum number of organs possible and to make the decision later about discard – based on the philosophy that the more organ retrieval performed, the more routine the process. This discard rate is also affected by the older age distribution of the deceased donor pool in Catalonia.

Catalonia is in the process of introducing a new points-based system for the kidney allocation (see APPENDIX A). Under the new system, allocation decisions will be made in the following order:

1. ABO group;
2. Regional priorities (paediatric, combined, sensitised);
3. Only one kidney is shared (i.e. allocated to other hospitals in the region), the other is retained for use by the transplant centre (if applicable);
4. Allocation according to candidate score, which is calculated based on waiting time, HLA match and age combined, donor-recipient age difference, location of patient relative to donor, HLA-DR homozygosity, HLA-B homozygosity, blood group match (score applied both regionally and within the center).

Both Norway and Catalonia, therefore, incorporate age matching in allocation policies in the context of world’s best donation rates but rapidly aging populations. Eurotransplant has addressed the issue of population aging in its kidney allocation policies through the introduction of the Eurotransplant Seniors Program (ESP) in 1999 (16). This program allocates kidneys from

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1 The transplant rate expressed per 100 dialysis patients does not take into account international variation in dialysis acceptance practices. Countries with high rates of dialysis acceptance (e.g. United States) will have a relatively low kidney transplant rate by this calculation.
deceased donors aged >=65 years to ABO compatible recipients aged >=65 years without the use of HLA typing. Kidneys are allocated locally to minimise cold ischaemia time. The intention of the ESP is to match kidneys to recipients based on their expected life-span (i.e. “old-for-old”). The ESP has reduced waiting times for older candidates (from a median of 943 days for candidates >=65 in 1998, to 707 days in 1999), and improved access to younger donor kidneys for younger candidates (17). Recipients of “old-for-old” kidneys through the ESP experience a lower risk of delayed graft function (as a consequence of local allocation and shorter cold ischaemia times), but higher rates of biopsy-proven acute rejection and late rejection compared to “old-to-any” or “any-to-old” allocation (18). This is likely to relate to HLA mismatching under the ESP protocol. Patient survival was lower in the ESP compared to “old-to-any” allocation (5-year survival 71%) or “any-to-old” allocation (5-year survival 60%, 71% and 74% respectively). Five-year death-censored graft survival under ESP, “old-to-any”, and “any-to-old” allocation models was 67%, 67% and 81% respectively (18). Therefore, allocation under the ESP disadvantages some elderly patients who would have otherwise received kidneys from younger donors; on the other hand the allocation of older kidneys to younger recipients is minimised, conferring a survival benefit on this recipient group.

2.2.3. Expanded criteria donors: policies and outcomes

An expanded criteria donor (ECD) kidney is defined by the United States Organ Procurement and Transplantation Network (OPTN) as a kidney recovered from a donor of age 60 years or greater, or a donor between 50 and 59 years of age who meets at least two of the following criteria: a terminal pre-recovery serum creatinine > 1.5 mg/dL (133 umol/L), a cerebrovascular accident as the cause of death, or a history of hypertension. These criteria were selected on the basis of SRTR data analyses indicating an associated relative risk of graft failure 70% greater than that of kidneys transplanted from an “ideal” reference group of non-hypertensive donors between the ages of 10 and 39 years with a terminal serum creatinine of less than 1.5 mg/dl and death from a cause other than a cerebral vascular accident (19). A study of outcomes of ECD kidney transplants in Australia and New Zealand – applying the OPTN definition of an ECD kidney - reported that, compared to donors <50 years, adjusted hazards of graft failure (including death with a functioning graft) 1-5 years post-transplant were 1.34 (95% CI 0.87 to 2.07) for ECD kidneys from donors aged 50-59 years, and 2.52 (95% CI 1.97 to 3.23) for ECD kidneys from donors aged >=60 years (20). These results indicate that donor age >=60 years is the most significant determinant of poor outcomes observed with ECD kidneys.

The ECD concept was developed in the United States in response to the very high rate of discard of kidneys recovered from donors over the age of 60 (approximately 50% in 2000). A working group convened in 2001 recommended the expedited placement of kidneys from donors older than 60 years, with allocation based on waiting time alone (19). The standardised definition of an ECD given above was adopted by the OPTN/UNOS Board in 2001, and was incorporated into allocation algorithms in October 2002.

Under the current OPTN kidney allocation policy, candidates must give consent prior to being listed for ECD transplantation. Candidates who agree to be listed to receive an ECD are also eligible to receive a standard criteria donor (SCD) kidney according to the usual allocation policy (i.e. “dual listing”). Active candidates who have agreed to receive an ECD kidney and
are ABO compatible with the donor are prioritised according to waiting time. Priority in the allocation of ECD kidneys is given to zero mismatch and sensitised (cPRA>=80%) candidates (21).

Theoretically, the principal advantage of dual listing for an ECD kidney lies in the potential to expedite kidney transplantation for candidates who are less able to tolerate a lengthy wait on dialysis (22). Higher rates of morbidity and mortality among older candidates in particular make transplantation with an ECD kidney a preferable option to remaining on dialysis, whereas younger, healthier candidates benefit from waiting for a higher quality kidney, despite longer dialysis exposure (23). Marginal donor kidneys have been shown to increase life expectancy for recipients compared to waiting on dialysis with no transplant (24). Further, long term mortality is reduced for recipients of ECD kidneys compared to waiting for transplantation with an SCD kidney, with the magnitude of this benefit increasing with older recipient age, longer expected waiting time, presence of diabetes or hypertension, and moderate sensitisation (22). Older recipients derive the greatest survival benefit from ECD kidneys: in their study of 3000 kidney transplants performed in France, Savoye et al found that – compared to remaining on the waiting list – recipients aged 60 years and older who were transplanted with ECD grafts had multivariate-adjusted rates of survival 2.3 times higher than patients remaining on dialysis (25). Ultimately whether or not to accept an ECD kidney depends on (i) the likely outcome of accepting that kidney, and (ii) the likely waiting time for a better offer, the likelihood of surviving on the waiting list for that long, and the likely outcome of that better offer. Therefore the optimal decision for an individual patient involves a complex calculation based on waiting time, expected graft outcomes, and expected dialysis outcomes. The experience of the United States has been that the percentage of candidates that would be predicted to benefit from an ECD kidney that are actually listed for ECD offers varies widely across transplant centres (26).

Despite the intent of the ECD classification to minimise discard of organs from older donors, rates of discard of ECD kidneys remain high in the United States and also vary widely across OPOs. Generally, OPOs with longer waiting times tend to procure and transplant more ECD kidneys than OPOs with shorter waiting times: this suggests that demand drives decision making on whether to utilise these kidneys, more so than clinical utility. As an ECD classification connotes increase risk of graft failure, a “labelling effect” has been suggested whereby the ECD designation itself may adversely affect utilisation of these kidneys. Hirth et al reported that, although the rate of recovery of kidneys from donors >=60 years increased in the post-ECD era, rates of utilisation fell (27). Subsequent analysis of kidney discard rates by Woodside et al found that ECD kidneys were not more likely to be discarded than SCD kidneys of similar quality, however the ECD label does affect perception of organ quality and may lead to unnecessary biopsies (28).

Another major critique of the ECD classification has been the inappropriate classification of kidneys as ‘marginal’ despite a longer expected survival than a proportion of kidneys classified as SCD (29). The kidney donor profile index (KDPI) was developed to improve risk scoring of deceased donor kidneys and is central to the new United States Kidney Allocation System that will be operational by the end of 2014 (see sections 0 and 2.3.3). In the new U.S. Kidney Allocation System, the ECD definition in use since 2002 will be replaced with a definition of a high-risk kidney that is based on KDRI score.
2.2.4. Priority for paediatric patients

Kidney transplant candidates <18 years of age who have been on dialysis for more than 12 months are currently eligible for bonus points in the national deceased donor allocation algorithm (from November 2011), and in NSW (from November 2011) and in Victoria (from December 2013). Other states currently do not have NOMS-based paediatric bonus points available, although some have informal priority arrangements for paediatric patients. As a consequence of these state-by-state differences in the application of paediatric priority, differences exist in time to deceased donor transplantation (30).

After accounting for living donor transplantation and death on dialysis in a competing risks model, and censoring for age >=18 years, median months to deceased donor transplantation for paediatric candidates (<15 years) waitlisted between 2002 and 2011 were 14.3, 21.5, 11.8, 15.3, and 24.7 in NSW, VIC, QLD, SA, and WA respectively (personal communication A Le Page, data from ANZDATA). Interstate variation in living donor transplantation for paediatric recipients (excluding preemptive transplantation) was similarly variable: in a competing risks model, median months on dialysis prior to living transplantation were 6.2, 12.2, 8.1, 16.3, and 19.8 in NSW, VIC, QLD, SA and WA respectively (personal communication A Le Page, data from ANZDATA). Shorter median wait times to deceased donor transplantation thus correlate with lower median wait times to living donor transplantation for paediatric candidates. Whilst paediatric priority differences are likely to significantly account for deceased donor transplant waiting times, other possible explanations include differences in access to paediatric surgical expertise for both living and deceased donor transplantation, and interstate variation in waiting list management such as the practice of listing candidates for deceased donor transplantation while living donors are being worked-up. International policies with respect to paediatric priority are detailed in APPENDIX A.

2.3. Incorporation of utility in allocation policy: age-matching, longevity-matching, and life-years from transplantation

The strongest critique of the current system for allocation of deceased donor kidneys in Australia is that substantial age mismatches are permitted. Figure 11 shows donor versus recipient age for all deceased donor kidney transplants performed between 2010 and 2012. Although the majority of donor-recipient pairs were matched within 20 years of age, a large proportion of recipients received kidneys from donors more than 20 years older or younger. Of recipients aged <18 years, 60% received a kidney from a donor >20 years older (n=29). Of recipients aged 65 years and above, 33% (n=68) received a kidney from a donor >20 years younger (personal communication P Clayton). Allocating younger donor kidneys to older recipients may result in a loss of utility due to the discrepancy in the life expectancy of the kidney versus the life expectancy of the donor. For example, Australian data show that recipients >=55 years have a risk of death with a functioning graft more than 2.5 times that of recipients aged <55 years (31). Allocating older donor kidneys to younger recipients may result in inefficiency and potentially to unnecessary discards where the offer is not accepted, or – where the offer is accepted – to poorer recipient outcomes and the requirement for
retransplantation. Allocation policies that explicitly match donors and recipients on the basis of age and/or expected survival post-transplantation are widely applied internationally. Within Europe, donor-recipient age-matching is widely used: the United States is currently transitioning to a system that matches donors and recipients on the basis of respective predicted outcomes post-transplantation (longevity-matching). These different approaches to utility in allocation policy, and their relevance in the Australian context, are discussed here.

Figure 11: Donor versus recipient age for all donor-recipient pairs (deceased donor) transplanted between 1 Jan 2010 and 31 December 2012. Source: ANZDATA (personal communication, P Clayton)

2.3.1. Age-matching policies

The UK NHSBT incorporates age-matching into its kidney allocation policy by awarding points for recipient age and for donor-recipient age difference (see APPENDIX A). HLA match and age are combined in determining point scores, such that the maximum points go to zero mismatched candidates <18 years of age and diminish thereafter as age increases (32). Points are also awarded for donor-recipient age difference according to the formula:

\[-\frac{1}{2}(\text{donor-recipient age difference})^2\]

The greater the age-mismatch between donor and recipient, the greater the number of points subtracted from the total score for the potential recipient. By comparison, Eurotransplant does not age-match below 65 years, however recipients >=65 years are allocated kidneys from deceased donors also >=65 years through the Eurotransplant Seniors Program (see 2.2.2) (33).
The current kidney allocation system in Catalonia age-matches donors and recipients as follows: (i) old for old - kidneys from donors aged 65 and older are allocated to recipients aged 65 and older, (ii) young for young - kidneys from donors aged less than 40 years are allocated to recipients less than 40 years, (iii) all others - kidneys from donors between 40 and 65 years are age matched to recipients within 10 years of age (sensitised patients are matched within 30 years of age). However, Catalonia will soon transition to a points-based allocation system (based on the NHSBT system) that similarly awards points based on a combination of HLA match and age, permits a maximum age mismatch of 15 years (or 30 years if the recipient is highly sensitised), and gives priority in allocation to paediatric candidates for kidneys from donors younger than 40 years.

Lim et al have previously modelled the impact of broad young-for-young/old-for-old donor-recipient matching (donors <60 to recipients <55 years; donors >=60 to recipients >=55 years) on total graft years from transplantation for the Australian population (31). Under an optimal scenario of best-case age-matching (reallocating young kidneys to young recipients and old kidneys to old recipients) applied to the 4616 kidney transplants performed in Australia between 1991 and 2006, it was estimated that a total of 262 graft years would be gained (equating to $12-$22 million in cost savings from dialysis avoided). At the level of the individual, younger recipients of younger donor kidneys would experience on average three more graft years than older recipients of younger kidneys. In a scenario of an aging donor pool, the graft years gained by matching young-for-young and old-for-old kidneys would increase (assuming recipient age distribution remains relatively constant). Further, Lim et al have subsequently reported a lack on an association between donor age and recipient survival for recipients aged 60 years and older: that is, based on the outcomes of transplants performed in Australia between 1995 and 2009, preferential allocation of kidneys from donors 60 years and older to recipients 60 years and older potentially would not significantly reduce the life expectancy of these patients, though further modelling is warranted (34).

Figure 12 shows the percentage of deceased donor kidneys that would be available to candidates of each age under different scenarios of age-matching, based on the age distribution of the Australian deceased donor and kidney transplant candidate pools. Given the symmetry in the age distribution of donors and waitlisted candidates in Australia, any of a range of age-matching policies (+/- 5, 10, 15 or 20 years) would be associated with similar equity outcomes for all candidates, with the exception of sensitised patients.

### 2.3.2. Longevity matching

In 2013, the Organ Procurement and Transplantation Network (OPTN) in the United States approved a new kidney allocation system based on “longevity-matching” of donors and recipients (35). Details of the development of the new system are given in APPENDIX B. The new kidney allocation system was designed in response to inequity, inefficiency and suboptimal utility in existing allocation protocols. There was particular concern regarding the potential years of life lost from the existing donor pool, as a consequence of policies that allocated kidneys with a long potential life span to recipients that do not (due to the emphasis on waiting time and, to a lesser extent, HLA match). This is particularly relevant to the United States, where the donor pool is relatively young but the waiting list is aging rapidly. After the adoption
of the MELD system for liver allocation, the OPTN kidney Advisory Committee was interested in whether more a biologically-based allocation system might be feasible for kidneys.

![Diagram](image.png)

**Figure 12:** The percentage of donor kidneys available to candidates of each age, under different age-matching scenarios. Curves are based on utilised deceased donors between 2008 and 2012. The bars show the number of candidates of each age actively waitlisted for a kidney transplant in 2012. Source: ANZDATA (personal communication, P Clayton)

Longevity matching in the new kidney allocation system will operate as follows:

1. Deceased donors kidneys will be assigned a kidney donor profile index (KDPI)\(^1\), ranking all recovered kidneys on a scale from zero to one, based on expected survival in a hypothetical “modal” recipient: the lower the numeric score, the longer the expected survival. Kidneys are then allocated within 4 bands of the KPDI: <0.2 (best kidneys), 0.2 to <0.35, 0.35 to <0.85 and >=0.85 (worst kidneys);
2. Kidneys with a KDPI<0.2 (i.e. the kidneys with the longest survival potential), will be matched with the top 20% of candidates by estimated post transplant survival (EPTS);
3. EPTS for waitlisted candidates is calculated based on 4 variables: patient age, time on dialysis, prior organ transplant, and diabetes status;
4. Paediatric candidates limited to kidneys with a KPDI<0.35, and prior living donors to kidneys with a KPDI <0.85;
5. Within each band of longevity matching, current priority for waiting time, HLA similarity and prior living donors are maintained.

---

\(^1\) The kidney donor profile index (KDPI) is derived from the kidney donor risk index (KDRI), and expresses the quality of a given donor kidney relative to other donors. A donor with a KDPI of 90% has a KDRI higher than 90% of donor from a given reference population (http://optn.transplant.hrsa.gov/ContentDocuments/Guide_to_Calculating_Interpreting_KDPI.pdf)
Although age-matching of the donor to recipient (within 15 years +/-) was proposed during the development of the new U.S. kidney allocation system, explicit age-matching was ultimately impermissible on the basis of age discrimination laws. Instead, priority is assigned according to the biological effect of recipient age, in combination with time on dialysis, prior organ transplant, and diabetes status. The 20% of kidneys with the longest estimated function (relative to the national case mix) will be allocated to the group of candidates with the longest EPTS. The use of the EPTS will not change how the majority of kidney candidates are assigned priority for transplant – only those expected to benefit from the transplant the longest. Approximately 97% of candidates aged 18-25 years would fall into the top 20% of candidates for longevity, 81% of 26-35 year olds, 43.8% of 36-45 year olds, 10.1% of 46-55 year olds, and 0% from age 56 onwards.

In order to improve procurement and transplantation rates for kidneys with a high KPDI (i.e. marginal kidneys), kidneys with a KDPI >85% will be allocated to a combined local and regional list, making available with less cold ischemic time those kidneys that would be discarded in one OPO due to shorter candidate waiting times but utilised in a neighbouring OPO with longer waiting times. In the same way that candidates formally had to consent to being waitlisted for an ECD kidney, candidates will have to consent to being waitlisted for a KDPI >85% kidney. The KDPI>85% kidneys will also still be allocated based on waiting time alone, with the difference compared to the old system being that they will be allocated regionally rather than locally to prevent unnecessary discard of marginal organs.

Simulations comparing the current U.S. allocation policy to the new kidney allocation system have shown that the new allocation system results in slightly more transplants for candidates aged 18 to 49 years, slightly fewer kidney transplants for candidates older than 50 years, and overall better matching of expected patient and graft longevity (36). The new allocation system is predicted to increase median recipient life years by 7%, and median graft years by 3% (Table 1). In absolute terms, from 1000 transplants the new allocation system could lead to a gain of 830 life years and 250 graft years. Further, the new kidney allocation system is predicted to yield more life years for kidney transplant recipients, without increasing waiting list mortality. It should be noted, however, that simulations cannot account for changes in organ retrieval, acceptance, or wait-listing behaviours that may arise under the new system: if the new kidney allocation system results in significant shifts in practices with respect to organ retrieval, organ acceptance or waitlisting, then the outcomes of the new system may differ from predictions.

Table 1: Outcomes of 10 simulations off current and new systems for the allocation of deceased donor kidneys in the United States (36)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Simulated current system</th>
<th>Simulated new system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of candidates on the waiting list</td>
<td>122,669</td>
<td>122,669</td>
</tr>
<tr>
<td>Number of primary transplant recipients</td>
<td>11,531</td>
<td>11,599</td>
</tr>
<tr>
<td>Median lifespan posttransplant</td>
<td>11.82</td>
<td>12.65</td>
</tr>
<tr>
<td>Median allograft-years</td>
<td>8.82</td>
<td>9.07</td>
</tr>
<tr>
<td>Median extra life-years from transplant v. waitlisting</td>
<td>5.01</td>
<td>5.24</td>
</tr>
<tr>
<td>Number of deaths on the waiting list by age group:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>18-34</td>
<td>223</td>
<td>221</td>
</tr>
<tr>
<td>35-49</td>
<td>927</td>
<td>926</td>
</tr>
<tr>
<td>50-64</td>
<td>2353</td>
<td>2367</td>
</tr>
<tr>
<td>&gt;=65</td>
<td>1330</td>
<td>1338</td>
</tr>
</tbody>
</table>
2.3.3. The KDRI and the EPTS

The kidney donor risk index (KDRI) was introduced to address the limitations of the binary ECD/SCD classification system for risk stratification of deceased donor kidneys. The KDRI expresses the risk of graft failure for a given donor kidney on a continuum of quality, relative to the rate of failure of a kidney from a healthy, 40-year-old donor (37); values of the KDRI exceeding 1.0 indicate a higher expected risk of graft failure than the reference donor. The formula for calculating the KDRI, as derived for the U.S. population, is given in Table 2. Donor characteristics included in the calculation of the KDRI are age, height, weight, ethnicity, hypertension, diabetes, cause of death, serum creatinine, HCV status, and DCD status. The relationship between current ECD classification and KDRI score is shown in Figure 13. As the KDRI considers additional factors compared to the ECD definition, the ECD/non-ECD classification does not correspond to a sharp cut point on the KDRI scale. Instead, a proportion of ECD kidneys would be considered lower risk according to KDRI, and a proportion of non-ECD kidneys would be considered higher risk. Figure 14 shows how the KDRI performs for the Australian donor pool as a discriminator of graft survival outcomes.

A donor risk index has also been derived for the UK population (38). Based on an analysis of data from 7620 adult deceased donor transplants performed between 2000 and 2007, Watson et al determined that donor age, history of hypertension, weight, days in hospital and adrenaline were significant predictors of post-transplant survival. A simplified donor risk index (the UK KDRI) based on these 5 factors predicted outcomes in a validation cohort with a concordance statistic of 0.62. The UK KDRI is calculated as follows (38):

\[
UKKDRI = \exp \left\{ -0.245 \times (\text{donor age} < 40) + 0.396 \times (\text{donor age} \geq 60) \\
+ 0.265 \times (\text{hypertension}) + 0.0253 \times (\text{donor weight (kg)} - 75) / 10 \\
+ 0.00461 \times (\text{days in hospital}) + 0.0465 \times (\text{adrenaline}) \right\}
\]

![Figure 13](image_url): Overlap of SCD and ECD classification by KDRI index (37).

The OPTN calculates expected post-transplant survival (EPTS) score based on kidney transplant candidate age, diabetes status, years on dialysis, and prior organ transplant status, as shown in Table 2 (39). Evaluation of the performance of the EPTS score in the United States
recipient population indicated moderate ability to discriminate between recipients with good versus poor survival outcomes (c-statistic 0.69). Validation of the EPTS score in the Australian population demonstrated similar results for discriminating post-transplant survival among adult recipients (40). The EPTS will therefore correctly predict which of two kidney transplant candidates will live the longest 69% of the time. Although this result indicates the existence of unmeasured factors affecting post-transplant survival, it is not necessarily desirable for the EPTS score to account for all factors that may potentially influence recipient outcomes. Only characteristics that might feasibly be known at the time of kidney donation may be included; the score should also be based on objective, measurable and ethically sound criteria (compliance and race are therefore excluded). In terms of the implementation of the EPTS calculation in the new US Kidney Allocation System (APPENDIX B), waitlisted candidates with missing or unverified EPTS factors will be assumed to have an EPTS outside of the top 20% of candidates

<table>
<thead>
<tr>
<th>Calculation of KDRI Score*</th>
<th>Calculation of the EPTS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.013*(Age – 40) *</td>
<td>0.047*MAX(Age - 25.0) +</td>
</tr>
<tr>
<td>1.25*(serum creatinine – 1) *</td>
<td>-0.015<em>Diabetes</em>MAX(Age - 25.0) +</td>
</tr>
<tr>
<td>1.13*(hypertensive=yes) *</td>
<td>0.398*Prior Organ Transplant +</td>
</tr>
<tr>
<td>1.14*(diabetic=yes) *</td>
<td>-0.237<em>Diabetes</em>Prior Organ Transplant +</td>
</tr>
<tr>
<td>1.09*(cause of death=CVA) *</td>
<td>0.315*log(Years on Dialysis +1) +</td>
</tr>
<tr>
<td>0.96*(height in cm/10) *</td>
<td>-0.099<em>Diabetes</em>log(Years on Dialysis + 1) +</td>
</tr>
<tr>
<td>0.98*(weight in kg/5) *</td>
<td>0.130*(Years on Dialysis=0) +</td>
</tr>
<tr>
<td>1.14*(DCD=yes) *</td>
<td>-0.348<em>Diabetes</em>(Years on Dialysis=0) +</td>
</tr>
<tr>
<td>1.27*(HCV=yes) *</td>
<td>1.262*Diabetes</td>
</tr>
</tbody>
</table>

* For a non-African American, weighing <80kg, aged >=18 and <=50 years, with serum creatinine <=1.

Figure 16 shows the extent to which the current allocation system in Australia matches high-quality kidney donors with recipients with long expected post-transplant survival, and vice versa. KDRI and EPTS are calculated according to the U.S. OPTN formula. Under Australia’s current kidney allocation system, a substantial number of high quality kidneys are transplanted in recipients with low expected survival. A smaller number of low quality kidneys are transplanted into recipients with long expected survival post-transplant.

Figure 17 shows the distribution of KDRI values by recipient age group, for all donor recipient pairs transplanted between 2010 and 2012. The vast majority (85%) of paediatric recipients of deceased donor transplants were transplanted with a kidney with a KDRI score below the median value. Of recipients aged 18-34, 35-64 and 65+, the proportions transplanted with a deceased donor kidney in the top 50% for KDRI were 60%, 48% and 42% respectively. Based on deceased donor kidney transplants performed from 2010 to 2012 (excluding multi-organ transplants) the proportion of paediatric recipients transplanted with a deceased donor kidney in the top 20% for KDRI was 48%. The proportions of recipients aged 18-34, 35-64 and 65+ receiving a deceased donor kidney in the top 20% for KDRI were 25%, 19% and 13%

1 http://optn.transplant.hrsa.gov/ContentDocuments/Guide_to_Calculating_Interpreting_EPTS.pdf
respectively. Therefore, based on current practice, younger recipients are receiving a greater proportion of high quality deceased donor kidneys.

**Figure 14:** Death-censored graft survival by KDRI quintile, for Australian adult kidney-only deceased donor grafts transplanted between 2000 and 2012. Adjusted for HLA mismatch, ischaemic time and EPTS. Source: ANZDATA (personal communication, P Clayton)

**Figure 15:** Unadjusted post-transplant patient survival by EPTS quintile, adult recipients (20+ years) of deceased donor kidneys transplanted between 2003 and 2012 in Australia (kidney grafts only, no combined transplants). Adapted from Clayton et al, Am J Transplant, 2014 (40)
Figure 16: Kidney donor risk index (KDRI) versus expected post-transplant survival (EPTS) score for all donor-recipient pairs transplanted in Australia between 2010 and 2012. Source: ANZDATA (personal communication, P Clayton).

Figure 17: Distribution of KDRI values (based on donor characteristics only) within recipient age groups, for all donor-recipient pairs transplanted in Australia between 2010 and 2012. Source: ANZDATA (personal communication, P Clayton).
2.3.4. Life-years from transplantation (LYFT)

In the early phase of the OPTN review process, there was interest in creating a kidney allocation system based on the concept of “life-years from transplant” (LYFT). This approach was informed by the introduction of the MELD score in liver allocation, which prioritises liver transplant candidates on the basis of medical need. The proposed LYFT-based allocation system would allocate kidneys on the basis of the additional life years that a potential recipient would be expected to gain as a result of transplantation, compared to remaining on the waiting list. Expected graft outcomes and expected patient survival are estimated based on historical experience with donors and recipients with similar characteristics (41). The proposed LYFT-based allocation system would match the kidneys with the longest survival potential to younger candidates with the longest expected LYFT. Older candidates and those with lower expected LYFT would be allocated kidneys with shorter expected survival on the basis of waiting time and CPRA.

An advantage of the LYFT system over longevity matching is that LYFT privileges vulnerability – i.e. priority is given to those with the most to gain by transplantation, who would be harmed the most by remaining on dialysis – whereas candidate vulnerability is not incorporated into longevity matching (this system instead allocates the best organs to those who would be injured the least by remaining on dialysis). Allocation of organs to those who would be harmed the most (lose the most potential life years) by not receiving a timely transplant is closest to a “fair innings” approach to resource distribution. These two alternatives advantage very different groups of people. For example:

<table>
<thead>
<tr>
<th>Candidate</th>
<th>60 year old DM</th>
<th>20 year old non-DM</th>
<th>20 year old DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifespan without transplant</td>
<td>4 years</td>
<td>16 years</td>
<td>9 years</td>
</tr>
<tr>
<td>Lifespan with transplant</td>
<td>9 years</td>
<td>22 years</td>
<td>16 years</td>
</tr>
<tr>
<td>Incremental survival (LYFT)</td>
<td>5 years</td>
<td>6 years</td>
<td>7 years</td>
</tr>
</tbody>
</table>

- Allocate to the 60 year-old diabetic to maximise waiting list survival;
- Allocate to the 20 year-old non-diabetic to maximise post-transplant survival;
- Allocate to the 20 year-old diabetic to maximise incremental survival.

However, critiques of LYFT-based allocation are that it is conceptually and logistically complex, and that patient groups with low expected survival have diminished access to kidney transplantation. Whereas longevity matching allocates 52% of donor kidneys to recipients >50 years old, the proportion of kidneys going to older recipients under the LYFT system would be less than 30% (Table 3).

<p>| Table 3: Outcomes of allocation systems based on life-years from transplant, age-matching, and/or longevity matching, modelled for the United States population (29) |
|---------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Gain in life years</th>
<th>National Sharing +LYFT</th>
<th>LYFT Longevity Matching</th>
<th>Age Matching Longevity Matching</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gain in life years</td>
<td>34,026</td>
<td>25,794</td>
<td>15,223</td>
</tr>
<tr>
<td>Proportion of kidneys transplanted into recipients &gt;50 years old</td>
<td>10%</td>
<td>29%</td>
<td>46%</td>
</tr>
</tbody>
</table>
2.4. Utilisation and allocation of kidneys donated after circulatory death

Donation after circulatory death (DCD) is the fastest growing source of deceased donors in Australia. The number of DCD donors increased from 23 in 2008 to 77 in 2012, representing more than half of the overall growth in utilised deceased donors over this interval (1). Relative to international benchmarks, donation after circulatory death (DCD) donors now constitute a large proportion of utilised deceased donors in Australia (Figure 18). In 2012, the rate of DCD in Australia was 3.4 donors per million population (pmp) – accounting for 22% of all deceased donors (1). Internationally, the highest rate of DCD is observed in the UK (8 DCD donors pmp, 43% of all deceased donors), followed by the Netherlands (7.7 pmp, 50% of deceased donors), Latvia (6.8 pmp, 40% of deceased donors), and Belgium (6.6 pmp, 22% of deceased donors). The rate of DCD in Australia is equivalent to that observed in the United States and Spain, though DCDs constitute a greater proportion of deceased donors overall in Australia.

![Figure 18: International comparison of the rate of DCD and DBD (donors per million population). Source GODT.](image)

With increasing international experience with DCDs, more evidence is now available regarding the long-term outcomes of DCD kidney transplantation. Despite concerns regarding a high incidence of delayed graft function (~50%) as a consequence of warm ischaemic injury acquired during circulatory death, 5-year graft and patient survival data indicate that kidneys from controlled DCDs are equivalent to DBD kidneys with respect to long-term outcomes for first-time transplant recipients (42). Graft and patient outcomes following transplantation with DBD versus DCD kidneys, for all transplants performed in Australia between 2001 and 2012, are shown in Figure 19. Recipients of second grafts who are transplanted with a DCD kidney experience significantly worse graft and patient survival compared to recipients of a second DBD kidney (42). Increasing donor age is associated with poorer transplant survival for all deceased donor kidneys, however – for donors aged >60 years - there is no evidence of additional risk of graft loss for recipients of older DCD compared to older DBD kidneys (43). Cold ischaemic time greater than 12 hours is strongly associated with poorer graft survival for recipients of DCD but not DBD kidneys, and minimisation of cold ischaemia time remains an important consideration for allocation policies (43).
Under current Australian protocols, DCD kidneys are allocated according to the same algorithm as DBD kidneys (2). Eurotransplant protocols similarly treat DCD and DBD kidneys as equivalent (in those countries where DCD is legally and ethically allowed) (33). Current OPTN policy allocates DBD and DCD kidneys according to separate algorithms: whereas the algorithm for DBD kidneys prioritises waiting time, HLA match sensitisation and then local allocation, the algorithm for DCD kidneys prioritises allocation within the donor hospital’s donor-service area, then waiting time and HLA match (44). Under the new U.S. Kidney Allocation System, DCD and DBD kidneys will be allocated by the same algorithm, however the KDRI score will assign a high-risk value to DCD kidneys (36).

Similar to current OPTN policy, the UK NHSBT policy gives local priority in the allocation of DCD kidneys (32). Whereas kidneys from DBD donors are allocated through the National Allocation Scheme, kidneys retrieved from DCD donors are allocated locally.
Review of Eligibility and Allocation Protocols in Deceased Donor Transplantation

according to local kidney transplant centre policies (ref NHSBT guidelines). In a recent policy change designed to minimise the potential for discard, DCD donors were added to the NHSBT Kidney Fast Track Scheme in March 2013. DCD kidneys are offered through the Kidney Fast Track Scheme to participating centres if any of the following criteria are met:

- If, at any point, the kidney is deemed to be unusable by a specialist organ donation nurse or member of the retrieving or transplanting team;
- Three kidney transplant centres decline the kidney for either donor or organ quality reasons. The reasons given may differ between centres but must relate specifically to the donor or the organ quality;
- The organ has accrued three hours of cold ischaemic time and has not yet been accepted for transplantation;
- If the kidney has been offered and accepted for a transplant but is subsequently declined by the accepting centre after treatment withdrawal, but before organ retrieval has begun.

In part the NHSBT policy serves to minimise cold-ischaemia time for DCD kidneys: however the main reason for separate allocation of DCD kidneys in the UK is the historical lack of evidence regarding donor and recipient factors affecting outcomes in DCD transplantation, and therefore the difficulty in developing an evidence-based national allocation algorithm (42). Given the implications for equity inherent in local-only allocation of DCD kidneys, especially as DCDs emerge as the majority source of deceased donor kidneys in the UK, the NHSBT is currently considering the feasibility of a national organ-sharing scheme for DCD kidneys. National allocation would compensate for regional variation in rates of DCD donation, however longer transport distances increase the duration of cold ischaemia time. Given the evidence that longer cold storage time is associated with poorer graft survival for recipients of DCD kidneys, the benefits of a national allocation system will need to be weighed against the risks of increased cold-ischaemia time (43).

2.5. ABO incompatible transplantation using deceased donors

None of the allocation guidelines reviewed currently permit blood group incompatible kidney transplants using deceased donor organs – a few policies do, however permit blood group-compatible (but not blood group-identical) transplants. Under the NHSBT guideline, blood group O donors can be transplanted into blood group A and AB recipients, and blood group B donors into AB recipients, if the recipient is a zero HLA mismatch and highly sensitised or <18 years, or a zero HLA-DR homozygous match with the donor. Donors with blood group subtype A2 can also be allocated to recipients of blood group B as part of a pilot scheme in London. Similarly the OPTN policy requires that blood type O kidneys be transplanted only into blood group O recipients, and blood group B kidneys to blood group B recipients, except in the case of a zero HLA mismatch. Under the new kidney allocation system being implemented in the United States, blood type A2 and A2B donors may be allocated to blood type B recipients who meet certain titre requirements (set by each individual transplant program and monitored every 90 days). Transplant programs will be required to obtain written informed consent from candidates stating their willingness to receive an A2 or A2B blood type kidney. The purpose of
this policy change is to reduce disparities faced by minority candidates - approximately half of all blood type B candidates in 2013 were black (45). Eurotransplant permits non-identical blood group matches within the acceptable mismatch program only. Under this program blood group A donors may be transplanted into blood group A and AB recipients, blood group B donors can be transplanted into blood group B and AB recipients, and blood group O donors can be transplanted into A, B, AB and O recipients.

Australian states are heterogeneous in their application of blood group compatibility rules (Table 4). South Australia permits O donors to be transplanted into A, AB and B recipients; Queensland and Western Australia permit O to B transplants, and Western Australia additionally permits O to AB. A to AB and B to AB transplants are permitted in all states (personal communication, P Clayton). This non-uniformity potentially raises issues of equity of access for recipients of different blood groups across the states and territories.

Table 4: Current blood type compatibility rules in Australia

<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient</th>
<th>Australia</th>
<th>NSW</th>
<th>VIC</th>
<th>SA</th>
<th>QLD</th>
<th>WA</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>A</td>
<td>AB</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>AB</td>
<td>AB</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>B</td>
<td>AB</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>O</td>
<td>A</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>O</td>
<td>AB</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>O</td>
<td>B</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>O</td>
<td>O</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

2.6. Access to kidney transplantation for sensitised patients

Given the difficulty of finding a suitable donor and the extremely poor waiting list outcomes for highly sensitised kidney transplant candidates, international allocation protocols typically award priority (often the highest level of priority) to highly sensitised kidney transplant candidates. However, waiting list priority alone is not necessarily effective at improving equity of access to kidney transplantation for highly sensitised patients. An alternative approach is to allocate kidneys to highly sensitised patients on the basis of acceptable HLA mismatches, as opposed to broad antigen matching. The advantage of this approach is that the donor pool available to certain highly sensitised candidates is increased. Acceptable mismatch programs have been adopted by Eurotransplant, Scandiatransplant, France, Greece, Switzerland and Canada (46).

Eurotransplant introduced its Acceptable Mismatch program in 1999. Patients eligible for this program (for full details of eligibility criteria and allocation protocols see APPENDIX C) are given the highest priority in the allocation of kidneys compatible with their antibody profile. Positive identification of all antibody specificities in highly sensitised patients is not possible, therefore the Eurotransplant Acceptable Mismatch Program defines and registers the HLA-A, -B, and –DR antigens towards which the patient has never formed antibodies with the
aim of predicting negative cross match (46). About 60% of candidates are transplanted within 2 years of inclusion in the Acceptable Mismatch program, and experience short term graft survival comparable to nonsensitised patients (47).

The Scandiatransplant Acceptable Mismatch Program (STAMP) was introduced in April 2009, and is available to patients with a PRA >=80%. Full details of STAMP guidelines are given in APPENDIX C. In the first 3 years of the STAMP (April 2009 to May 2012), 115 candidates were accepted into the program. Of this number, 31 (27%) received kidney transplants through STAMP exchange obligations. In addition, 12 patients accepted into the program received a local transplant without a STAMP match. Weinreich et al suggest these additional transplants were likely the result of increased awareness and more extensive HLA analysis of these highly sensitised patients (48). From 2008 to 2011, the mean waiting time to kidney transplantation for highly sensitised patients in Scandinavia fell from 42 to 37 months.

Not all highly sensitised patients will find a compatible donor through an Acceptable Mismatch program, however. Eurotransplant and Scandiatransplant both therefore assess the likelihood that an individual Acceptable Mismatch program candidate will find a compatible donor from within their respective donor pools. If the probability of finding a donor is very low, then alternative options such as desensitisation or paired donor exchange may offer the best outcome for that particular patient (46,48). Significantly for Australia, the probability of finding a compatible donor in the context of an acceptable mismatch program will be dependent on the size of the donor pool.

The costs and benefits of including acceptable mismatches in the existing deceased-donor allocation model have been modelled for the Western Australian population (49). Inclusion of acceptable mismatches improved transplantation access for 4 out of 28 identified highly sensitised candidates, reducing waiting time for these candidates by 34 months (from 86 to 52 months) and achieving a lifetime gain of 0.034 QALYs along with cost savings of $4,000 per highly-sensitised patient. On the other hand, the acceptable mismatch model was also associated with a loss of 0.005 QALYS and additional costs of $800 for every reallocated patient. At the level of the overall candidate population, the acceptable mismatch model increased life years by 1.3 days (1.8 quality-adjusted days) and saved $622 per highly sensitised recipient; the rest of the waiting list would lose 0.1 days and incur an additional cost of $66 per patient. Nguyen et al concluded that the application of an acceptable mismatch allocation model would be an equitable approach for improving access to transplantation for highly sensitised candidates in Australia, without compromising health benefits for the overall candidate population awaiting deceased donor kidney transplantation (49). However this model does not cost the administrative resources required to make such a change to the existing allocation system: taking the full costs into account it is unlikely that an acceptable mismatch program would be cost-neutral for Australia and New Zealand.

Priority in allocation of sensitised candidates, and the measurement and definition of sensitised status are areas of ongoing debate. Eurotransplant, the UK and the US have moved towards utilisation of “calculated” or “virtual” PRA, a measure which more accurately reflects the fraction of the donor pool that a given recipient may have a positive cross-match against. The benefits of the calculated or virtual PRA are a reduction in the number of organs accepted...
for candidates ultimately determined to have a positive cross match (and hence reduction in cold ischaemia time), and access to a greater proportion of the donor pool for sensitised patients. In the future, eplet matching and allelic matching will likely lead to more sophisticated allocation protocols, including for sensitised patients, although this is beyond the scope of the current report.
3. **Pancreas Transplantation**

3.1. **Current eligibility and allocation criteria**

Pancreas transplantation is performed as a treatment for type 1 diabetes mellitus in Australia and New Zealand. Pancreas transplantation can be undertaken as the transplantation of the whole solid pancreatic organ, or of insulin producing islets. Solid pancreas transplantation only is discussed in this chapter. The vast majority of solid organ pancreas transplants in Australia and New Zealand are performed as simultaneous pancreas and kidney transplants in recipients with both type 1 diabetes and ESKD. Potential candidates for simultaneous kidney pancreas transplantation must first meet minimum eligibility criteria for referral to a National Pancreas Transplant Unit, and then meet the inclusion criteria for entry to the pancreas transplant waiting list (2).

Criteria for referral to a National Pancreas Transplant Unit:

1. Type 1 diabetes with insulin dependence;
2. GFR <30 mL/min/1.73m²;
3. Absence of significant cardiac disease or adequately treated cardiac disease;
4. Patent iliac vessels bilaterally;
5. BMI <35 kg/m²;
6. Age <50 years (individual subjects >50 years may be eligible if otherwise very fit medically).

Criteria for waitlisting for pancreas transplant:

1. Insulin dependence deemed by the National Pancreas Transplant Unit to be reversible by pancreas transplantation;
2. GFR <15 mL/min/1.73m² and dialysis impending;
3. Absence of significant cardiac disease or adequately treated cardiac disease;
4. Patent iliac vessels bilaterally;
5. BMI <30 kg/m² (BMI 30-35 is a relative contraindication);
6. Non-smoker or permanent cessation for more than 3 months.

Pancreas allocation is based on recipient referral patterns and geographical considerations regarding retrieval teams and acceptable ischaemic times. At the individual level, patients are transplanted in order of referral for assessment (i.e. waiting time) within each blood group, within each transplant unit. The decision about each individual transplant offer and transplant list management are the responsibility of the recognised Pancreas Transplant Unit. There is no urgent classification for pancreas transplant candidates. A national pancreas transplant waiting list exists for highly sensitized candidates who have been active on the waiting list for more than 2 years, with at least 1 year on dialysis.
3.2. Trends in pancreas transplantation

Of the three types of solid pancreatic transplantation – simultaneous pancreas-kidney transplantation (SPK), pancreas after kidney transplant (PAK) and pancreas transplant alone (PTA) – rates of chronic and acute rejection are highest for PTA recipients (50). PTA recipients also experience higher rates of lymphoproliferative disorder post-transplant (51). For pancreas transplant candidates with nephropathy, SPK is the best option: PAK is associated with the same kinds of immunological problems as PTA, but is a reasonable option if necessary. Figure 20 shows, for the U.S. population, the graft survival curves for each of these three types of pancreas transplants. In Australia, 97% of the 613 solid organ pancreas transplants performed between 1984 and 2013 were SPK transplants (52). In 2013, all 36 pancreas transplants performed were SPK transplants (Figure 21).

Figure 22 places the rate of pancreas transplantation performed in Australia in the international context. The balance of SPK, PAK and PTA transplants performed in a given country is partly influenced by the availability and the age distribution of donors, relative to the number and case-mix of candidates wait-listed for a pancreas transplant. In Catalonia, for example – whereas the number of indications for pancreas transplantation is increasing but the availability of young deceased donors is decreasing – pancreas after living kidney transplantation has become increasingly important (personal communication, J Ferrer). In the United States, falling rates of both living and deceased donation are reflected in declining pancreas transplantation of all types, though PAK transplants have been particularly affected (51). In response to falling rates of pancreas transplantation in and significant geographic disparities in access, the OPTN Board approved in 2010 a policy change to create a combined list for SPK, PAK and PTA transplants, giving equal priority at the local level for each transplant type. Other factors influencing the demand for each of the three types of pancreas transplantation include improved insulin delivery systems, and an increasing role for islet transplantation (51).

![Figure 20: Graft survival among adult recipients of deceased donor pancreas transplants in the United States in 2007. Source: SRTR & OPTN Annual Data Report 2012](image-url)
This international experience of falling rates of pancreas transplantation is, however, occurring in the context of continuing improvements in outcomes (50). For Australian recipients of SPK transplants between 1984 and 1999, rates of 5-year patient, pancreas graft and kidney graft survival were 89%, 73% and 86% respectively; for recipients transplanted between 2005 and 2009, corresponding 5-year survival rates were 95%, 88% and 97% (52). Trends toward improved outcomes are likely to be attributable to the combination of improvements in donor and recipient selection, pretransplant recipient evaluation (cardiac evaluation in particular), immunosuppression protocols, and surgical techniques.
3.3. Donor eligibility criteria: International guidelines and evidence

Selected international criteria for pancreas donor eligibility are summarised in Table 5. European countries consider BMI >30kg/m\(^2\) as an absolute contraindication to pancreas donation, with upper age limits ranging from 45 (non-trauma cause of death) to 55 years. In contrast, United States policy does not consider obesity an absolute contraindication to pancreas donation; however, pancreases from donors with a BMI>30 kg/m\(^2\) are allocated according to a separate algorithm. The UK National Pancreas Allocation Scheme uses a points scheme to determine whether a donor pancreas would be suitable for solid organ or islet cell transplantation (for details see APPENDIX D).

By comparison to international policies, upper age thresholds for pancreas donor eligibility in Australia are relatively conservative. The mean age of pancreas donors in Australia from 1984 to 2013 was 27.3 years (median=25 years) with a range of 4 to 61 years. Maximum weight criteria in Australia are similar to those applied in Europe. The median BMI of pancreas donors in Australia from 1984 to 2013 was 24.2 kg/m\(^2\): and 25.8% and 5.4% of pancreas donors over this interval were overweight and obese respectively (52).

There is consistent evidence showing older donor age is associated with increased risk of technical failure and of inferior short- and long-term graft and patient outcomes in SPK (53-56). In a recent study of donor and recipient age-matching in pancreas transplantation, Kayler et al reported that recipients transplanted with organs from donors older than 40 years had survival outcomes that were only equivalent to remaining on the waiting list – with the important exception of candidates resident in OPOs with the longest waiting times (54). In this study, recipients <40 years who received an SPK from a donor >40 years had increased risks of patient death and death-censored pancreas and kidney graft failure of 73%, 53% and 63% respectively compared to young donor SPK. Recipients >40 years who received an SPK from a donor >40 years had increased risks of patient death, pancreas graft and kidney graft failure of 91%, 124% and 85% respectively (54). Overall, risk of patient death associated with donor age 45-49 years was increased 89%, compared to donor age 18-24 years. Risk of patient death associated with donor age >=50 years was more than two-fold greater than for recipients of organs from donors aged 18-24 years (54). It has been proposed that it is older age in the presence of other donor and transplant-related risk factors (hypertension, obesity, DCD, cold ischaemia time) that produces poor outcomes, rather than chronological age per se (57). The issue with age cut-offs is that chronological age is not always equivalent to biological age, and therefore strict donor eligibility criteria have the potential to underutilise biologically good organs. Overly strict donor eligibility criteria will also prolong waiting times, with implications for recipient outcomes. Therefore it generally recommended that age limits be applied in combination with the clinical judgement of the physician (57).

The question of whether older donors (50-60 years) are suitable for pancreas transplantation is currently being addressed by an ongoing Eurotransplant multicentre trial of extended criteria for pancreas donation (58). This trial will also examine the suitability of donors with a BMI >30 kg/m\(^2\). Higher BMI has similarly been associated with increased risk of technical failure and of pancreas graft loss and patient mortality following SPK in numerous studies (53,56), however other studies have concluded that similar results post-transplant results
can be achieved with obese as with normal BMI donors (59). The investigators of the EXPAND study hypothesise that organs from donors 50-60 years or with a BMI >30, based on local allocation with minimal ischaemic time, can be transplanted with similar results to standard criteria organs. Recipients will be required to consent to receive an extended criteria pancreas (simultaneously with a standard criteria kidney), with the idea that they will experience shorter waiting times and improved survival and quality of life (58).

Table 5: Current international suitability criteria for solid organ pancreas donation

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Min age</th>
<th>Max age</th>
<th>Min weight</th>
<th>Max weight</th>
<th>Other criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>3</td>
<td>45 (DBD)</td>
<td>25kg</td>
<td>100kg</td>
<td>No known diabetes or insulin dependence, no pancreatic trauma (may be considered separately for islets), no history of alcoholism or chronic pancreatitis. For DCDs, max ischaemic time from withdrawal of treatment to organ perfusion &lt;30 min.</td>
</tr>
<tr>
<td>Norway</td>
<td>5</td>
<td>55</td>
<td>20kg</td>
<td>90kg</td>
<td>Plasma glucose and HbA1c must be in the normal range (4.5 to 6.5%)</td>
</tr>
<tr>
<td>Catalonia</td>
<td>-</td>
<td>50</td>
<td>-</td>
<td>BMI 30kg/m²</td>
<td>Cold ischaemia time 10-12 hours</td>
</tr>
<tr>
<td>United States</td>
<td>0</td>
<td>65</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>The UK National Pancreas Allocation System incorporates patients listed for both vascularized pancreas and islet transplantation, and allocates pancreata on the basis of a points system. BMI weighting is applied such that below a BMI of 26 kg/m², the pancreas is more likely to be allocated to vasularized pancreas transplant; above a BMI of 28 kg/m², the pancreas will be more likely to be allocated to islet transplantation. Donor and recipient age matching is included in the scheme as a tie-breaker between patients with similar overall scores (see Appendix D).</td>
</tr>
<tr>
<td>Eurotransplant</td>
<td>5</td>
<td>50</td>
<td>BMI &lt;30kg/m²</td>
<td></td>
<td>Notes: donors with age &gt;50 and BMI&gt;=30 are considered extended criteria donors and are eligible for islet transplantation. The Pre-procurement Pancreas Allocation Suitability Score (P-Pass) is used to determine eligibility for pancreas donation (see Appendix D).</td>
</tr>
</tbody>
</table>

3.4. Recipient eligibility criteria: International guidelines and evidence

Again, European countries consider a BMI >30 kg/m² a contraindication to pancreas transplantation whereas the United States does not. Age is often a relative contraindication that is dependent on the overall cardiovascular status. Policies on the acceptability of type 2 diabetics for pancreas transplantation are variable. In Norway, type 2 diabetes is an absolute
contraindication to pancreas transplantation: at the other extreme, 8% of candidates waitlisted for pancreas transplantation in the United States have type 2 diabetes, and approximately 20% are obese (51). Only a very small number of pancreas transplants have been performed in type 2 diabetics in Australia (0.5% of all transplants between 1984 and 2013).

Recipient age >50 years has been shown to be a risk factor for graft failure and patient death in several studies (54,60,61). Most recently, a UNOS database review of all 20,854 pancreas transplants performed in the United States between 1996 and 2012 found patient age to be inversely proportional to patient survival (62). In this study, rates of 1, 3, 5, 10 and 15 year patient survival among recipients aged 50-59 years were 93%, 88%, 82%, 62% and 42% (among recipients >=60 years these rates were 91%, 80%, 71%, 43% and 0%); by comparison, among recipients 18-29 years, 1, 3, 5, 10 and 15 year rates of survival were 95%, 91%, 86%, 74% and 65% respectively (62). However – with increasing demand for pancreas transplantation from older patients – there is little international consensus on how recipient age should be incorporated into eligibility criteria, and age >50 is generally interpreted as a relative contraindication (54). The authors of the UNOS database study note that age-related differences in recipient survival may related to confounders such as comorbidities or type of treatment, and recommend that recipient age not be used as a contraindication to pancreas transplantation (62).

Table 6: Current international eligibility criteria for solid organ pancreas transplantation

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Max age</th>
<th>Max BMI</th>
<th>Diabetes type</th>
<th>Other criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia and New Zealand</td>
<td>50</td>
<td>&lt;30kg/m²</td>
<td>Type 1 only</td>
<td>GFR&lt;15 mL/min and dialysis impending. Absence of significant/inadequately treated cardiovascular disease, patent iliac vessels bilaterally. Non-smoker or permanent cessation &gt;3 months.</td>
</tr>
<tr>
<td>Individual subjects &gt;50 years may deemed eligible if otherwise medically fit, taking into account a waiting time to SPK of approximately 2-3 years. BMI &lt;30 kg/m² is preferred, but BMI 30-35 kg/m² is a relative contraindication.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td></td>
<td></td>
<td></td>
<td>C-peptide &lt;=0.3 nmol/L. Good cardiovascular status (particularly arterial status) based on an overall assessment. DSA+ transplants not permitted</td>
</tr>
<tr>
<td>SPK=55</td>
<td></td>
<td>&lt;30kg/m²</td>
<td>Type 1 only</td>
<td></td>
</tr>
<tr>
<td>PAT=60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAK=65</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notes: BMI&gt;30 kg/m² is an absolute contraindication for pancreas transplantation, though BMI &lt;28 kg/m² is desirable. BMI 28-30 kg/m² is permissible if there are no other significant risk factors present, particularly in young and muscular candidates. The PAT age threshold is going to be dropped to &lt;55 years because of the increasing number of single pancreas transplants in type 1 diabetics with intact kidney function, and because of a bolus of candidates around 20 years of age. There is also concern about arteriosclerosis in candidates from a surgical perspective, and from the perspective of post-transplant risks from generalized arteriosclerosis.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catalonia</td>
<td>50</td>
<td>&lt;30kg/m²</td>
<td>Type 1 (mostly)</td>
<td></td>
</tr>
<tr>
<td>Notes: Age &gt;50 is a relative contraindication – patients up to 55 years have been transplanted. Age-related eligibility depends on the state of the arteries and the anaesthetic risk of the patient. Although pancreas transplantation has been performed in patients with type 2 diabetes, there are not enough pancreas donors to do this routinely.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>75</td>
<td>None</td>
<td>Type 1 and Type 2</td>
<td>C-peptide &lt;=0.67 nmol/L (or, if C-peptide &gt;=0.67 nmol/L, on insulin with a BMI&lt;=28 kg/m²)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>-</td>
<td>30 kg/m²</td>
<td>Type 1 and Type 2</td>
<td>2 allowed</td>
</tr>
<tr>
<td>Notes: BMI&gt;30kg/m² is an absolute contraindication for PTA and type 2 diabetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eurotransplant</td>
<td></td>
<td></td>
<td></td>
<td>No global policy for recipient eligibility specified by Eurotransplant</td>
</tr>
</tbody>
</table>
International policies are also variable with respect to the eligibility of recipients with type 2 diabetes. A UNOS database study of 6756 SPK transplants comparing outcomes for type 1 and type 2 diabetic recipients found that kidney graft survival was inferior for type 2 recipients, but that there was no increase in the risks of death or pancreas failure compared to type 1 recipients (63). However, the results of this and other observational studies on this topic are likely to be confounded by significant selection bias, whereby only the best type 2 candidates are selected for SPK. Multivariate adjustment for age, race, weight, time on dialysis and cardiovascular disease in estimating hazard ratios may also over-correct for important differences between type 1 and type 2 candidate populations. With respect to BMI criteria for recipient eligibility, evidence regarding risks to patient and graft survival associated with recipient BMI $\geq 30$ kg/m$^2$ is not conclusive. Kayler et al found no association between recipient obesity and risk of mortality in 4636 SPK recipients in the United States (54). Fridell et al similarly reported, on the basis of a single centre study, that pancreas transplantation may be successfully performed in selected obese recipients (e.g. tall individuals with few prior abdominal surgeries and C-peptide $<0.67$ nmol/L) (64). Again, however, selection bias is likely to play a role in these findings.

3.5. Protocols for urgent listings

The Eurotransplant Pancreas Allocation System (EPAS) awards Vascularized Pancreas Special Urgency status to (i) recipients with vascularised pancreas graft failure within two weeks after combined vascularised pancreas transplantation, (ii) patients with a defective glycaemic counter regulation confirmed by a hypoglycaemic clamp test, and (iii) patients suffering from hypoglycaemia unawareness at least twice in one year, requiring medical assistance and hospitalization (in Germany: either suffering two or more hypoglycaemic episodes in one year requiring medical assistance or one confirmed episode of hypoglycaemic unawareness). Excluded from Special Urgency status are pancreas transplant candidates <18 years or >65 years, patients with a duration of diabetes mellitus <10 years, patients with creatinine clearance <60 ml/min, patients not under the supervision of a diabetologist, patients with a lack of diabetes education or with insufficient documentation of blood glucose values, and patients with other general contraindications to organ transplantation. Special Urgency status can also be requested for islet transplantation in non-German countries: Special Urgency status for islet transplantation is awarded according to the relevant national criteria (65). None of the other guidelines reviewed had specific policies with respect to emergency status/urgent listings for pancreas transplantation.
4. Liver Transplantation

4.1. Current eligibility and allocation criteria

To be eligible for a liver transplant in Australia or New Zealand, adult patients must have a Model for End-Stage Liver Disease (MELD) score of $>15^1$; paediatric patients must have a Paediatric End-Stage Liver Disease (PELD) score of $>17^2$ (except in the case of metabolic disease and tumour patients). Patients with hepatocellular carcinoma (HCC) are also eligible for liver transplantation regardless of MELD score if their HCC falls within University of California San Francisco (UCSF) criteria (no single tumour $>6.5$cm in diameter and total diameter of all tumours not more than 8cm). If the maximum tumour diameter is $\leq 2$cm then standard MELD score will apply. If the maximum tumour is $> 2$cm and within USCF criteria then a score of 22 will be allocated to the patient, with an additional 2 points allocated for every 3 months on the waiting list. Additional indicators for liver transplantation are listed in the TSANZ Consensus Statement document (2). Patients are excluded from liver transplantation if their medical condition or other circumstance make the probability of survival at 5-years post-transplant lower than 50%.

Any liver from a deceased donor that becomes available within Australia or New Zealand is liver is offered first to patients listed as urgent. If there is no recipient in the urgent category, then the local unit will allocate the liver to the ABO blood group identical recipient with the highest MELD or PELD score except in the following circumstances:

1. The presence on the waiting list of a patient with HCC whose HCC MELD score exceeds the MELD score of other patients on the list of the same ABO blood group;
2. The liver is of poor quality – poor quality donor livers may be utilised but may need to be transplanted into recipients with lower MELD scores to ensure success;
3. The presence of a paediatric patient on the waiting list in need of a split or reduced size liver, provided the donor liver is of suitable quality;
4. The donor is paediatric, in which case – for size reasons – paediatric recipients have priority;
5. Donor-recipient size mismatch – as overly large size discrepancies result in poor outcomes, size matching may result in patients without the highest MELD/PELD being allocated a liver;
6. Logistical considerations (e.g. transport, cold ischaemia time, surgeon availability etc) would affect the success of the transplant;
7. Presence of an urgent patient on the list who is not prioritised on the basis of MELD, PELD or HCC MELD (e.g. familial amyloidosis, oxalosis, protein C deficiency)

To place local eligibility and allocation criteria in context it is helpful to compare rates of waitlisting and liver transplantation in Australia and New Zealand against international

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$^1$ MELD score = $0.957 \times \log_{10}(\text{creatinine mg/dL}) + 0.378 \times \log_{10}(\text{bilirubin mg/dL}) + 1.120 \times \log_{10}(\text{INR}) + 0.643$
Multiply score by 10 and round to the nearest whole number. Max serum creatinine is 4.0 mg/dL.

$^2$ PELD score = $0.480 \times \log_{10}(\text{bilirubin mg/dL}) + 1.857 \times \log_{10}(\text{INR}) - 0.687 \times \log_{10}(\text{albumin g/dL})$
$+ 0.436$ if patient is $<1$ year old, $+ 0.667$ if the patient has growth failure ($< -2$ standard deviations)
Multiply score by 10 and round to the nearest whole number
benchmark (Figure 23 and Figure 24). Recipient eligibility criteria tend to correlate with organ availability – that is, the higher the availability of donor organs, the less restrictive eligibility criteria tend to be. In terms of additional allocation priority for HCC candidates, for example, the appropriate degree of priority depends on the overall size of the waiting list and average waiting times.

**Figure 23:** International deceased donor liver transplantation activity in 2012, expressed as rate per million population. Source: GODT (66)

**Figure 24:** International rates of waitlisting for liver transplantation (active candidates per million population) versus access to liver transplantation (liver transplants per million population). All data are for 2012. Source: GODT (66)
4.2. Eligibility criteria and allocation of livers to candidates with hepatocellular carcinoma

Of the 4244 patients who received a liver transplant in Australia between 1985 and 2013, 298 (7%) had a primary diagnosis of HCC (67). The proportion of transplanted candidates with a primary diagnosis of HCC has increased steadily in Australia since the late-1990’s. In 2013, 14% of liver transplants were in patients with a primary diagnosis of HCC, compared to 3% in 1999.

Eligibility and priority for HCC patients were identified as key topics of interest with respect to liver allocation policy in Australia. International protocols for determining eligibility, down staging (salvage liver transplantation), and priority for HCC recipients are therefore reviewed here.

4.2.1. Eligibility criteria in patients with hepatocellular carcinoma

Liver resection or locally ablative treatment is the most appropriate treatment for patients with small, solitary tumours that occur in the background of chronic liver disease Child’s A with preserved synthetic function and no evidence of portal hypertension. However, for patients with HCC not amenable to these approaches or tumours associated with more advanced chronic liver disease, liver transplantation may offer the best chance of survival (68). The Milan criteria were proposed in 1996 as a means of identifying which HCC patients would derive a suitable level of benefit from liver transplantation (69). In the original study the actuarial survival at 4 years post-transplant of patients meeting Milan criteria was 75%: the recurrence free survival was 83% (69). With growing experience and success in the transplantation of patients with HCC, an increasing range of expanded Milan criteria have been proposed (70). A wide range of criteria are now applied internationally, consistent with local organ availability, and/or perspectives on access to transplantation for HCC patients and what constitutes acceptable post-transplant risk (68). Table 7 shows a selection of international criteria used in the determination of HCC patient eligibility for liver transplantation. Five-year survival data give an indication of the trade-off between access to transplantation and outcomes.

Previously, Australian and New Zealand transplant centres had used Milan criteria, but approximately 5 years ago the national guidelines shifted to the adoption of the less restrictive USCF criteria on the basis of equivalent 5-year survival using these guidelines. For the 96 liver transplants with >5 years of follow-up performed since 1985 in recipients with a primary diagnosis of HCC (i.e. including individuals meeting either Milan or USCF criteria, and others outside of criteria), 5-year post transplant survival was 73% (where HCC was a secondary diagnosis, 5-year survival was 75%) (67).

By comparison, the relatively unconstrained supply of livers for transplantation in Norway allow for generous eligibility criteria for HCC patients, with the trade off of lower 5-year survival (Norway is also currently the only country to offer liver transplantation for...
unresectable metastases from colorectal primary cancers). In an alternative approach, Hospital Clinic in Barcelona applies the more conservative Milan criteria to determine eligibility for deceased donor liver transplantation; however, eligibility to receive a living donor liver transplant are based on the expanded criteria of a single lesion <7-8 cm, less than 5 lesions <3cm, or successful down-staging treatment (assessed at 6 months). The principle of this centre-specific policy is that it is possible to offer living donor liver transplantation to HCC patients outside of Milan criteria with good results. In Australia, patients being considered for living donor liver transplantation must meet the same eligibility criteria for inclusion on the deceased donor list. The rationale for this policy is to prevent high-risk transplants being performed for poor results and potential subsequent need for priority transplantation with a deceased donor liver.

Table 7: International criteria for eligibility of patients with hepatocellular carcinoma and cirrhosis for liver transplantation

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Reference</th>
<th>Eligibility criteria</th>
<th>5-year post-transplant patient survival</th>
</tr>
</thead>
</table>
| Milan    | Mazzaferro V et al. NEJM, 1996; 334: 693-9 | • One lesion smaller than 5 cm.  
• Up to 3 lesions smaller than 3 cm.  
• No extra-hepatic manifestations  
• No vascular invasion | 75% |
| UK       | NHSBT Liver Advisory Group, Selection Criteria | • A single tumour ≤5cm diameter  
• Up to 5 tumours all ≤3cm  
• Single tumour >5cm and ≤7 cm diameter where there has been no evidence of tumour progression (volume increase by <20%) and no extra-hepatic spread and no new nodule formation over a 6-month period.  
• Tumour rupture and AFP >10,000iu/ml are absolute contraindications to transplantation  
* tumour size determined as the widest dimensions on a MDCT or MRI scan | - |
| UCSF     | Yao F et al. AJT 2007; 7:2587 | • Single tumour ≤≤6.5cm  
• 2-3 tumours ≤≤4.5 cm and total tumour diameter ≤≤8cm | 82% |
| ELAS     | Eurotransplant Manual | • Single tumour ≥≥2cm and ≤≤5cm  
• 2-3 tumours ≥≥1cm and ≤≤3cm  
• No extra-hepatic manifestations  
• No vascular invasion | |
| Kyoto    | Takada Y et al. Dig Dis 2007; 25:299 | • Up to 10 tumours ≤≤5cm  
• Serum des-gamma-carboxy prothrombin (DCP) ≤≤400mAU/MI | 82% |
| Oslo     | Personal communication (A Foss) | • Single tumour <10cm  
• If 2-5 tumours, none should be larger than 5cm  
• If the tumour number is >5, none should be larger than 2cm | 50% |

1 Yet waiting times for liver transplantation have increased in Norway particularly over the past 5-10 years. In 1998 the median time to transplant was 20 days, in 2008 it was 60 days (71). The growing number of liver candidates is attributable to population aging and to immigration – an increasing number of foreign-born residents are presenting with liver failure, largely due to hepatitis. For this reason, the decision was made to begin MELD scoring in Norway in September 2014. Increased demand for livers might conceivably also affect protocols with respect to HCC.

2 Age eligibility for liver transplantation at Hospital Clinic in Barcelona: Age <68 for deceased donor transplantation, age <68-70 of living donor transplantation. Maximum age of eligibility has been increasing over time.
A difficulty with Milan, UCSF and similar eligibility criteria for HCC patients is that tumour size alone has relatively poor sensitivity and specificity as a predictor of HCC recurrence (72). The aggressiveness of the tumour and pre-transplant tumour management will affect the probability of post-transplant HCC recurrence regardless of whether a given patient is within criteria. For this reason there is growing interest in incorporating other markers associated with tumour progression in the evaluation of eligibility for liver transplant for HCC patients. Alpha-fetoprotein (AFP) is one such marker: an AFP ≥400 ng/mL is indicative of potential vascular invasion and has been shown to be a strong predictor of recurrence post-transplant (72,73). AFP is elevated in approximately two-thirds of HCC patients, and in this situation individuals are pended, awaiting reassessment. Once vascular invasion is confirmed or there is a further rise in AFP, that patient is invariably delisted.

In addition, three-dimensional tumour size (tumour volume) is a better predictor of post-transplant survival than HCC diameter (72,73). Tosso et al, in their analysis of over 6478 liver recipients in the United States, found that a score combining total tumour volume and AFP value was effective in predicting post-transplant survival: in this study, recipients that had a total tumour volume >115 cm$^3$ or an AFP >400 ng/mL had a 3-year survival of <50% (73). Notably, tumour volume and AFP are independently associated with post-transplant outcomes, and combining these markers in a single score captures both large HCCs and small HCCs with the potential for aggressive growth. A more recent report from the same Alberta group refined this approach by using an ellipsoid formula for calculating tumour volume, with the authors recommending eligibility criteria of total tumour volume (using ellipsoid formula) <100 cm$^3$ and AFP<400 ng/mL (72). The sensitivity and specificity of these proposed criteria in predicting HCC recurrence post-transplant were 52.6% and 86.9% respectively; sensitivity and specificity of UCSF criteria, by comparison, were 52.6% and 69.8%. The volume/AFP eligibility criteria were also more inclusive: In the Kashkoush study, 76.5% of patients would be eligible for liver transplantation on the basis of volume/AFP criteria, whereas only 66.1% would be eligible on the basis of UCSF criteria. More accurate determination of HCC recurrence risk therefore avoids the unnecessary exclusion of potential liver transplant candidates. It should be noted, however, that imaging in HCC remains prone to error – either missing small tumours entirely or over-calling benign lesions – and has relatively poor sensitivity (~30%) as a prognostic for identifying HCC transplant candidates at risk of recurrence. For this reason there has been a move in the United States towards standardized imaging protocols and minimum technical specifications for the acquisition of images\(^1\).

4.2.2. Down-staging and salvage liver transplantation

For HCC patients who fall outside of UCSF criteria, surgical resection to reduce the size and number of tumours to within acceptable limits (“down-staging”) may be an option. The down-staging process is intended to identify tumours outside of standard criteria but with a favourable biology, on the basis of a good response to down-staging treatments over a follow-up period of at least 3 months. Theoretically these patients should then be expected to do well post-transplant. There are concerns, however, that (i) down-staging protocols would flood the

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\(^1\) Proposal for improved imaging criteria for HCC exceptions: [http://optn.transplant.hrsa.gov/PublicComment/pubcommentPropSub_273.pdf](http://optn.transplant.hrsa.gov/PublicComment/pubcommentPropSub_273.pdf)
liver transplant waiting list with patients who are destined to drop out, and (ii) the application of Milan, UCSF or other criteria in the context of down-sizing uses tumour size in an overly literal way that does not take the history of the tumour into account (i.e. reducing the size of the tumour does not necessarily reduce the risk of recurrence post-transplant) (74). There is evidence, however, to indicate that down-staging can yield excellent post-transplant outcomes: Yao et al reported 4-year post-transplant survival among patients who had undergone down-staging of 92% (74).

Intention-to-treat analyses have been important in addressing the issue of waiting list drop-out in down-staging (Table 8). Intention-to-treat analyses have reported 5-year actuarial survival post down-staging treatment of 56%, compared to 5-year survival of 63% among controls within Milan criteria (75). Overall, however, down-staging studies are widely heterogeneous in their methods and data analysis, and it is difficult to generalise regarding potential benefits of down-staging protocols (76). This is particularly the case given that waiting time and case-mix are highly variable from jurisdiction to jurisdiction, and therefore the impact on the waiting list of increased access to liver transplantation for HCC patients will also vary. That is, increased access for HCC patients may increase waiting times – and therefore drop-outs – for all candidates, and this needs to be weighed against the benefits of down-staging.

### Table 8: Selected studies on down-staging treatment for hepatocellular carcinoma prior to liver transplant

<table>
<thead>
<tr>
<th>Ref (study size)</th>
<th>Eligibility criteria for down-staging</th>
<th>Loco-regional therapies used</th>
<th>Minimum follow-up interval*</th>
<th>Successful down-staging (transplanted)</th>
<th>Patient survival post HCC down-staging treatment**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yao, 2005 (N=30)</td>
<td>Single tumour &lt;8cm Total tumour volume &lt;8cm</td>
<td>TACE and/or RFA</td>
<td>3 months</td>
<td>70% (53%)</td>
<td>89% 82% - -</td>
</tr>
<tr>
<td>Yao, 2008 (N=61)</td>
<td>As above</td>
<td>As above</td>
<td>3 months</td>
<td>71% (57%)</td>
<td>88% - - 69%</td>
</tr>
<tr>
<td>Ravaioli, 2008 (N=48)</td>
<td>Single tumour &lt;8cm Bifocal tumours &lt;5cm Multiple (&lt;6) tumours, total diameter &lt;12cm</td>
<td>TACE, RFA, PEI and/or LR</td>
<td>3 months</td>
<td>90% (67%)</td>
<td>82% 73% 62% - 56%</td>
</tr>
<tr>
<td>Graziadei, 2003</td>
<td>Outside Milan, no vascular invasion, no extrahepatic disease</td>
<td>TACE</td>
<td>None</td>
<td>73%</td>
<td>- - - - 31%</td>
</tr>
<tr>
<td>Lewandowski, 2009 (N=43)</td>
<td>T3</td>
<td>TACE</td>
<td>None</td>
<td>31%</td>
<td>- - 19% - -</td>
</tr>
<tr>
<td>De Luna, 2009 (N=27)</td>
<td>Beyond Milan</td>
<td>TACI</td>
<td>None</td>
<td>63%</td>
<td>- - 84% - -</td>
</tr>
<tr>
<td>Jang, 2009 (N=386)</td>
<td>Beyond Milan, no lobar major vessel involvement or metastasis</td>
<td>TACE</td>
<td>None</td>
<td>42%</td>
<td>- - - - 25%</td>
</tr>
</tbody>
</table>

LR: liver resection; TACE: transarterial chemoembolization; RFA: radiofrequency ablation; PEI: percutaneous ethanol injection; transcatheter arterial chemoinfusion.

*Follow-up interval refers to the minimum length of time over which patients were followed post-down-staging before they were eligible for a liver transplant

**Survival is based on intention-to-treat analysis
Lastly, the limitations of tumour size and number as prognostic indicators of HCC recurrence post-transplant (as described in the previous section) also apply to down-staging. AFP level and macrovascular invasion must also be taken into account. For example, in their prospective study of down-staging outcomes, Yao et al found that the only factor that predicted treatment failure (waiting list drop out, all cause death, or HCC recurrence) was AFP >1000 ng/mL (74). If AFP level is high and there is macrovascular invasion then, despite a reduction in tumour size and number, the patient will not be eligible for liver transplantation. There is widespread national and international consensus that the number and size of active lesions must be reduced to within criteria, AFP must be <400 ng/mL, and individuals must have had no significant progression over a 6-month period based on imaging performed every 3 months.

4.2.3. Assigning priority for patients with hepatocellular carcinoma

Liver allocation according to MELD score puts HCC patients at increased risk of dropout from the transplant waiting list: HCC patients have relatively good liver function and therefore low urgency according to MELD score, however with longer waiting times comes increased risk of tumour progression. On the other hand, if HCC patients are given too much priority in order to prevent drop out, the risk of tumour recurrence post-transplantation is increased. Too much priority would also increase waiting times for all other candidates, and potentially cause drop out among non-HCC candidates. Indeed there is an argument that some amount of waiting time for HCC patients is desirable in that it screens for candidates with the highest risk of tumour progression/recurrence. In Australia, where waiting times to liver transplantation are longer relative to many European countries, there is more opportunity to observe individuals serially for tumour progression. The median time on the waiting list for all patients with a primary diagnosis of HCC listed between 2004 and 2013 was 137 days (personal communication G Balderson, data from ANZLTR). In Australia, therefore, HCC MELD is not universally applied as the priority points under the current national policy may not reflect the observed biology of the HCC.

Achieving this balance – between giving sufficient priority to HCC patients such that those candidates who would benefit from liver transplantation are transplanted in a timely manner, while not prioritizing patients destined to have recurrence post-transplant – is a critical challenge for liver allocation systems, particularly as the number of indications for transplantation of HCC patients increases (68). Currently the United Kingdom does not award any priority points for HCC patients awaiting liver transplantation, though the outcomes of this policy in terms of waiting list drop out are unknown (68). In Catalonia, 19 extra points are awarded to HCC patients when the size of the tumour is <3cm, when the AFP is less than 200, or after successful post down-staging treatment based on evaluation at 6 months (personal communication J Ferrer). The Eurotransplant policy is that candidates with HCC within Milan criteria are registered at a MELD score equivalent to a 15% probability of candidate death within 3 months (provided the recipient had no extra-hepatic metastases and no macrovascular invasion).

The United States introduced a priority MELD score for candidates with stage T1 (single lesion >=1cm and <2cm – 24 points) or stage T2 (Milan criteria: single lesion >=2cm and <=5cm or 2-3 lesion >=1cm of <=3cm – 29 points) HCC in 2002. This policy was based on
prior analysis of waitlist outcomes that showed candidates with multiple tumours or a single tumour larger than 3cm were at significantly increased risk of drop-out (78). However, after the introduction of the priority MELD score, time to liver transplantation for HCC patients dropped to such an extent that UNOS revised the policy in 2004, retaining priority only for candidates with T2 tumours – based on evidence that risk of dropout is not elevated for candidates with T1 tumours - and revising downward the number of points awarded to 22 (68). The current OPTN policy is that candidates with HCC who have T2 tumours (one lesion >=2cm and <=5cm, 2-3 lesions >=1cm and <=3cm) and meet specified imaging requirements receive an initial MELD/PELD score equivalent to a 15% risk of 3-month mortality (as in the Eurotransplant policy). A candidate receives additional MELD/PELD points equivalent to a 10 percentage point increase in the candidate’s mortality risk every three months after receiving an HCC exception until the candidate receives a transplant or is no longer suitable for transplantation because of disease progression. Candidates not meeting these criteria may continue to be considered for a liver transplant according to each hospital’s own policy, but the candidate must be registered at the calculated MELD/PELD score with no additional priority awarded for HCC diagnosis. All such candidates - including those with downsized tumours whose original tumour was greater than a stage T2 – must be referred to the applicable regional review board for prospective review in order to receive additional priority. Decisions of the regional review board may be appealed, but the candidate will not receive additional MELD/PELD until approved by the review board.

Waiting times for liver transplant candidates in the United States vary widely between donor service areas. Under the current system, longer waiting times result in HCV patients dying on the waiting list while HCC patients – with their priority MELD score – climb the list faster. A range of proposals have been put forward to address this situation. These include a proposal to cap HCC priority scores so that non-HCC candidates with MELD/PELD >=35 (who have a higher risk of drop-out) have better access to regional offers, and a proposal to delay the assignment of priority to HCC candidates for 6 months, to allow observation of candidates with rapidly growing tumours, and to address geographical disparities in drop-out as a result of variable waiting times.

In the future, incorporation of biomarkers such as AFP may improve the prediction of dropout and therefore enable more accurate determination of the need for waiting list priority for HCC candidates (79).

4.3. Paediatric priority in liver transplantation

The number of paediatric candidates ever active on the liver transplant waiting list during 2013 was 71: of this number, 46 (65%) received a liver transplant, 3 patients died on the list, and 1 became too sick and was delisted. There were 19 paediatric patients still on the liver transplant waiting list at 31 December 2013 (67). Of the 46 paediatric candidates who were transplanted,

1 http://optn.transplant.hrsa.gov/PublicComment/pubcommentPropSub_330.pdf
2 http://optn.transplant.hrsa.gov/PublicComment/pubcommentPropSub_331.pdf
median waiting time to transplant was 56 days – compared to a median waiting time of 114 days for adult candidates (personal communication G Balderson).

Paediatric recipients of liver transplants are reported to have increased likelihood of cognitive deficits, poorer academic outcomes, difficulties with executive functioning, and ADHD (80-83). Although a small number of pre- and post-transplantation studies have been performed, they generally suffer from methodological issues and small sample sizes and have shown no evidence of improved cognitive outcomes associated with receipt of a liver transplant (81). It is therefore unclear at present what impact liver transplantation has on cognitive outcomes in paediatric candidates or what, if any, implications this would have for allocation policies. Several studies have, however, linked pre-transplant nutritional status, growth retardation, and operative complications with cognitive and intellectual outcomes (81), and it is plausible that psychoeducational outcomes for paediatric liver transplant recipients would be optimal where waiting time is brief. Most international liver transplant allocation policies contain provision for paediatric priority.

4.3.1. International policies for paediatric priority in liver transplantation

Under liver allocation policies in Australia and New Zealand, urgent listing categories specific to paediatric patients include:

1. Paediatric candidates with severe acute or chronic liver disease who have deteriorated and are in a paediatric intensive care unit (Status 2a);
2. Paediatric patients suitable for transplantation who suffer from severe metabolic disorders or hepatoblastoma, for whom a limited time period exists during which liver transplant is possible (status 2b).

Patients meeting these criteria are offered any liver that becomes available from a deceased donor within Australia or New Zealand. Non-urgent paediatric patients will be allocated livers according to PELD score. Paediatric candidates have priority for livers from paediatric donors, and adult livers are split where possible.

International policies with respect to paediatric priority for liver transplantation are fairly consistent, generally incorporating similar elements of urgency, organ sharing and splitting of eligible livers. The US OPTN policy includes similar categories for paediatric urgency (covering fulminant liver failure, primary non-function of a liver transplant, hepatoblastoma etc), with urgent candidates receiving offers from the regional pool (adult donors), and from the regional and national pool (paediatric donors) (44). Several policies require eligible donors be mandatorily offered for splitting if an appropriate paediatric recipient exists. For example the NHSBT policy requires that all DBDs <40 years, weighing more than 50kg, and in ITU for <5 days be offered for splitting if there is an appropriate paediatric recipient (unless a super-urgent, hepatoblastoma, multivisceral or combined lung/liver patient is waiting) (84). The Nordic countries have a policy whereby all paediatric candidates are placed on the joint Scandiatransplant waiting list, with the aim of offering part of a deceased liver as soon as possible. To incentivise sharing of split livers for the transplantation of paediatric patients in other countries, a payback system is in place whereby a center that ships liver segments 2 and 3 for paediatric candidates on the joint waiting list is paid back with a whole liver (personal
communication A Foss). The volume of paediatric liver transplants in the whole of Scandinavia is approximately 15-20 recipients per year (~ 5 per year in Norway), mostly these recipients are transplanted with segment 2 or 3 from adult donors (living donor liver transplantation is not performed). Catalonia similarly has a plan to begin to split livers from young, healthy adult donors for allocation to paediatric recipients (personal communication J Ferrer).

4.4. Expected post-transplant survival in determining waiting list eligibility

Current eligibility criteria for liver transplantation in Australia and New Zealand specify that patients must have a 5-year expected post-transplant survival of 50% or higher to qualify for the liver transplant waiting list. This threshold rules out a lot of patients with HCC, all cholangiocarcinoma patients, but also some with recurrent liver disease affecting their grafts and other groups (older patients for example). Age is not an explicit exclusion criteria but the cumulative incidence or peri-operative risk (particularly from cardiovascular disease and diabetes) means that individuals >70 years old are unlikely to routinely satisfy the 5-year 50% survival rule. Likewise, patients with neuroendocrine tumours are excluded from transplant despite international reports that in highly selected cases the results can be good. Cholangiocarcinoma is currently receiving experimental therapy at the Mayo Clinic but remains an absolute contraindication in Australia.

Five-year survival of liver recipients transplanted in Australian and New Zealand between 2005 and 2009 was 85% - far exceeding the current 50% 5-year survival requirement(67). This suggests that current eligibility criteria are applied too rigorously. To answer the question of whether a policy change with regards to eligibility criteria is warranted would require an audit of access to the liver transplant waiting list in Australia and New Zealand by age and primary disease.
5. Heart Transplantation

5.1. Current eligibility and allocation criteria

In 2013, 77 heart and 2 heart-lung transplants were performed in the 5 heart transplant centres across Australia (9 heart transplants were performed in New Zealand). There were 78 patients active on the heart transplant waiting list as at 1 January, 2013, and a total of 105 new additions during the year. Eighty-six patients were removed from the waiting list for reason of transplantation, 12 were removed because their condition worsened or they developed contraindications to transplantation, and 15 waitlisted individuals died. The total number active on the heart transplant waiting list at 31 December, 2013, was 58 (85).

Currently, heart transplantation in Australia is only offered to patients who have:

1. End-stage heart disease, manifested as:
   a. irreversible cardiogenic shock,
   b. intractable symptomatic heart failure (NYHA Class III-IV) despite maximally tolerated evidence-based therapy,
   c. need for permanent mechanical cardiac support,
   d. frequent discharges from an automatic implanted cardioverter defibrillator,
   e. intractable angina despite optimal treatment;
2. Exhausted all alternative treatment options; and
3. A life expectancy of at least 10 years post-transplant, with a reasonable prospect of returning to an active lifestyle.

The vast majority of patients referred for heart transplantation have chronic heart failure. Before referral for transplant, patients should be established on optimal medical therapy including maximally tolerated doses of angiotensin-converting enzyme inhibitors and beta-blockers. Patients with poor tolerability of this therapy have a poor prognosis and, in the absence of contraindications, should be referred for heart transplant assessment. Patients requiring repeat hospitalisation for decompensated heart failure and who need repeated or chronic administration of intravenous diuretic or inotropic therapy should also be referred for heart transplant assessment, if suitable candidates. Further, patients implanted with an automatic implanted cardioverter defibrillator and patients receiving cardiac resynchronisation therapy who experience complications or technique failure may be candidates for heart transplantation.

Approximately 5% of heart transplant candidates present with cardiogenic shock complicating acute myocardial infarction, cardiac surgery, or myocarditis. Some will recover following mechanical circulatory support; where the heart shows no sign of recovery, heart transplantation becomes the only treatment option. Finally, a small proportion of referred patients present with disabling angina due to coronary heart disease that is not amenable to revascularisation.

All patients listed for heart transplantation have severely impaired quality of life and most have a survival or less than 2 years without a transplant. There is no hard age cut-off for eligibility for heart transplantation (the oldest patient to undergo heart transplantation in
Australia was 71 years or age), however the presence of comorbidities would likely exclude the majority of potential candidates aged older than 70 years.

Exclusion criteria for heart transplantation are as follows:

1. Active malignancy – active malignancies other than non-melanoma skin cancers are an absolute contraindication, however ‘cured’ patients with long disease-free survival may be eligible;
2. Complicated diabetes – patients with established microvascular complications, HbA1c >7.5 or diffuse peripheral vascular disease are generally unsuitable;
3. Morbid obesity – potential candidates should reduce their BMI to below 30kg/m^2 (or under 140% ideal body weight) before being considered for heart transplantation;
4. Uncontrolled infection – decisions to be made on a case-by-case basis in consultation with an infectious disease specialist. HIV, HBV, or HCV infection is not an absolute contraindication, nor is colonisation with MRSA or VRE (however active systemic infection is still considered an absolute contraindication);
5. Inability to comply with complex medical therapy;
6. Active substance abuse – includes smoking, excessive alcohol consumption and illicit drug use;
7. Irreversible degeneration/damage of other organ systems that precludes rehabilitation after heart transplantation – e.g. advanced neurodegenerative disease, advanced rheumatoid arthritis, severe peripheral vascular disease. Combined organ transplantation may be considered for failure of multiple transplantable organs in carefully selected individuals, provided a low risk of perioperative mortality and reasonable post-transplant life expectancy;
8. Relative contraindications include eGFR <40 ml/min/1.73m^2, hyperbilirubinaemia >50 mol/L, intractable ascites with hypoalbuminaemia, and fixed pulmonary hypertension with transpulmonary gradient >15 mm/Hg or pulmonary vascular resistance (PVR >4 Woods Units after pulmonary vasodilator challenge. Patients with evidence of renal and/or hepatic decompensation who otherwise meet eligibility criteria should be considered for mechanical circulatory support (‘bridge to transplant’). Patients with fixed pulmonary hypertension should be considered for heterotopic heart transplantation or long-term mechanical circulatory support.

Waitlist management for heart transplant candidates in Australia is the individual responsibility of each of the six heart transplant units. Donor hearts are allocated according to the following criteria (2):

1. ABO compatibility
   a. Except paediatric patients aged <24 months
2. Negative T & B cell cross-match
a. Sensitised recipients for whom there are no other options may require transplantation in the setting of a positive T and B cell cross-match, followed by augmented immune suppression

3. Size and weight compatibility
a. +/- 20% of donor body weight
b. Greater variability in the ratio of donor:recipient weight may be acceptable depending on the age of the donor and recipient, especially in paediatric cases.

4. Urgency status
a. When the heart transplant candidate has developed a condition where their expected survival is less than 2 weeks, the Unit Directors communicate with the other Heart Transplant units to get a consensus view of urgent listing. It is the responsibility of the Transplant Unit Director to notify the cardiothoracic transplant units and the organ donor coordinators when a patient is placed on or removed from the urgent list. Re-notification is required every two weeks until the patient dies or is transplanted. Heart Transplant Units are limited to 3 urgent listing per year, and a yearly audit is undertaken.

b. In a situation of simultaneously listed urgent patients, donors from the same state as the urgently listed recipient go to that recipient, and donors from outside the state will go to the patient waitlisted first.

5. ABO identity

6. Recipient waiting time

7. Logistical considerations (e.g. coordination with donor retrieval team, transport, type of transplant operation, number of transplants to be performed, availability of ICU beds.

<table>
<thead>
<tr>
<th>Country</th>
<th>Allocation algorithm</th>
<th>Tx in status, %</th>
<th>Median wait time, days</th>
<th>Ever active on the WL in 2012, N</th>
<th>Transplant rate 2012, %</th>
<th>MCS at transplant, % (VAD/ECMO)</th>
<th>Heart transplants, per million</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>Urgent Non-urgent</td>
<td>60 40</td>
<td>14 293</td>
<td>116 352</td>
<td>33 54</td>
<td>19 (16/3)</td>
<td>2.1</td>
</tr>
<tr>
<td>France</td>
<td>High urgency 1 High urgency 2 Regional urgency Non-urgent</td>
<td>39 8 8 46</td>
<td>9 102 219 189</td>
<td>397 830 48 75</td>
<td>27 (13/14)</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>Urgent status 0 Urgent status 1 Elective status</td>
<td>14 21 65</td>
<td>8 7 80</td>
<td>247 433 57 74</td>
<td>15 (9/6)</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>1 high urgency 2A 2B</td>
<td>14 86</td>
<td>3 292</td>
<td>231 1100 32 59</td>
<td>9 (9/0)</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>1A high urgency 1B intermediate 2 low urgency</td>
<td>64 31 5</td>
<td>78 224 618</td>
<td>2378 6669 36 76</td>
<td>40 (39/1)</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>ANZ</td>
<td>Urgent Non-urgent</td>
<td>8 92</td>
<td>15 120</td>
<td>85 186 46 79</td>
<td>40 (40/0)</td>
<td>3.3</td>
<td></td>
</tr>
</tbody>
</table>

Table 9: International comparison of allocation systems and waiting list outcomes, data from the ISHLT International Registry for Heart and Lung Transplantation in 2012 [86]
Table 9 compares allocation systems and waiting list outcomes in 2012 for 5 countries including Australia and New Zealand. Median waiting time to heart transplantation is relatively low in Australia and New Zealand (120 days for non-urgent listings, 15 days for urgent listings). Only 8% of heart transplant recipients were transplanted in urgent status – versus 60% of recipients in the UK for example – reflecting differences in the definition and application of urgency status (86).

5.2. Allocation policies for sensitised heart transplant candidates

Figure 25 shows the increase in the proportion of pre-transplant heart candidates in Australia treated with a VAD over the past decade: compared to 5% in 2003, the proportion of pre-transplant candidates on VAD in Australia had increased to 40% by 2013. This is consistent with international trends: the overall proportion of candidates worldwide who were being treated with a VAD at the time of transplant in 2010 was 32% (87). The increased use of VAD has resulted in more patients surviving to heart transplantation; however, this is complicated by an increased rate of sensitisation among the candidate population (88). Approximately half of all patients develop de novo sensitisation, as measured by single bead antigen assays, after VAD implant (89). Studies have indicated that sensitised heart transplant recipients have increased risks of cellular and humoral rejection, early rejection, more severe rejection episodes, cardiac allograft vasculopathy, and mortality (90). However, the evidence for increased mortality in highly sensitised candidates bridged to heart transplant is based on older-generation devices, and is refuted by more recent evidence. In their analysis of 1544 heart transplant recipients bridged to transplant with a HeartMateII or HeartMateXVE device, Arnaoutakis et al found no difference in 30-day or 1-year survival by PRA level, nor in rates of early rejection (91). An association was observed, however, between higher PRA level and incidence of primary graft dysfunction. Outcomes of heart transplantation by sensitisation status in Australia (not accounting for treatment with VAD) are shown in Figure 26. The second issue arising from the increased prevalence of sensitisation among heart transplant candidates is that the available donor pool is diminished, and therefore time to transplantation is increased. In the Arnaoutakis study, average waiting time for recipients with PRA >25% were 65% longer than for patients with PRA <25% (91). Prolonged waiting time increases the risk of mortality pre-transplant, however these deaths would not be reflected in recipient survival statistics (90).

Existing international policies for heart allocation tend to share the following features: priority of medical urgency, preference for local distribution, allocation according to waiting time – all other factors being equal, and some degree of paediatric priority (92). However, given the steady increase in the proportion of heart transplant candidates who are sensitised and the inferior waiting list outcomes for these patients, whether heart allocation policies can (and should) the incorporate the needs of sensitised candidates is a topic of current debate (90). A number of heart transplantation policies – including Germany, Canada and the United States - give priority to sensitised candidates (44,93,94). In 2010 the Canadian Cardiac Transplant Network endorsed modifications to its heart allocation policy that included the introduction of a new national priority category (Status 4S - defined as PRA >80% or PRA>20% with 3 prior positive cross-matches) to specifically address waiting list outcomes for sensitised heart
transplant candidates (94). The OPTN policy does not give national priority, but allows a transplant program to allocate a heart out of sequence to a sensitised candidate within the donor service area if:

- The candidate’s transplant surgeon or physician determines that the candidate’s antibodies would react adversely to certain human leukocyte antigens;
- All heart transplant programs and the OPO within the donor service area agree to allocate a heart from a compatible deceased donor to the sensitised candidate;
- The candidate’s transplant program, all heart transplant programs, and the OPO within the donor service area agree upon the level of sensitisation at which a candidate qualifies for the sensitisation exception.

However, the benefits of prioritising sensitised heart transplant candidates in allocation policies are not clear. For example, it has not been established that the Canadian policy revision has had the intended impact on waiting times for sensitised candidates, and preliminary analysis of the impact of the policy change found significant waiting list mortality persists for Status 4S listed patients (95). The majority of patients wait-listed as Status 4S across Canada between January 2010 and June 2011 who were subsequently transplanted received a heart from a non-local donor procured from a median distance of 1,050km, with a median cold ischaemia time of 338 minutes (95). Further, whether a stable but sensitised candidate should receive priority over a candidate with high-dose or multiple inotropes who are not candidates for VAD is debatable (92).

In terms of the relevance of these policies to Australia, it must be noted that OPTN and the Canadian Cardiac Transplant Network are examples of systems that incorporate multiple heart transplant programs, large waiting lists and a large donor pool. Priority for sensitised heart transplant candidates would not necessarily improve waiting list outcomes for candidates in Australia and New Zealand, given the relatively small population, and the small number of transplant centres separated by large distances.

Beyond awarding waiting list priority status, alternative strategies that might improve access to heart transplantation for sensitised candidates include policies that expand the available donor pool, or, possibly, desensitisation therapies. For example, a factor limiting the available donor pool for a given candidate is the requirement for a time consuming cytotoxic cross match with the potential donor to be performed. The introduction of virtual cross matching to determine histocompatibility lessens these time constraints and allows for geographically distant donors to be considered without compromising on cold ischaemia time (88). Desensitisation therapies, on the other hand, have been widely studied but with mixed results; protocols trialled so far have had only limited success and there is no consensus on an appropriate desensitisation strategy for heart transplant candidates (90). Desensitisation therefore remains an emerging area.

Lastly, any policies specific to sensitised patients require agreement on the measurement, definition and treatment thresholds for “sensitised” individuals. Currently there is a lack of consensus on the appropriate definition of a sensitised patient in the context of heart transplantation: whereas a PRA threshold of >=10% has been linked with increased mortality, other analyses have reported increased risk of recipient mortality at PRA>25% (90,96). Threshold-based definitions of sensitisation are themselves problematic, as PRA level is more
meaningfully interpreted on a continuum. Further, whether a given individual is defined as sensitised under any of these definitions is also highly depended on the sensitivity and specificity of PRA measurement (89,90). The calculated PRA (cPRA) was developed to introduce greater accuracy in the definition of sensitisation, and is expressed as the percentage of actual organ donors that express one or more unacceptable HLA antigens for a given recipient. Protocols for the allocation of kidneys to sensitised candidates in the United States now incorporate the cPRA, and a shift from a threshold-based system to a sliding scale of priority (see APPENDIX B).

Figure 25: Percentage of pre-transplant heart transplant candidates implanted with a ventricular assist device, and the number of heart transplant candidates in each year from 1996 to 2013 (Source ANZCOTR).

Figure 26: Cutler-Ederer survival, by peak panel reactive antibodies, all heart transplants performed between 1984 and 2013 (Source ANZCOTR).

5.3. Donor and recipient characteristics

Surveillance of international trends with respect to donor and recipient characteristics show an increase in the median age of heart donors worldwide from 20 years of age in 1983 to 32 years in 2011 (43 years in Europe), and a similar increase in the median age and comorbidity burden
(particularly diabetes and hypertension) of heart transplant recipients (86). Figure 27 shows the consistency between international and Australian trends with respect to the aging of donors and recipients of heart transplants.

In recognition of the need to adapt heart allocation protocols to these shifts in the epidemiology of donors and recipients, The International Society for Heart & Lung Transplantation has recently revised its guidelines for donor and candidate eligibility and allocation of heart and lung transplants. Notable changes include revised positions with respect to the criteria for recipient age, BMI and diabetes status, as well as HIV, HCV and the introduction of frailty assessment. Important revisions to donor eligibility – in particular the acceptability of DCD hearts – are also included in the revised guidelines. Although the revised ISHLT guidelines were not yet released at the time of writing this report, these guidelines will be a critical reference for the TSANZ Consensus Guidelines process.

Figure 27: Median age of heart donors and heart transplant recipients in Australia and internationally, from 1984-2012. Source: ANZCOTR and ISHLT Registry.

5.3.1. “Marginal” and DCD heart donors

One of the most important features of the revised ISHLT guidelines are the updated recommendations regarding the use of hearts from “marginal” brain dead donors and from DCD donors. The first three heart transplants from DCD donors were performed in Australia between July and October, 2014. This has important implications for the future availability of donor hearts in Australia, with DCD donors now accounting for 22% of all deceased donors. However, in the current absence of data on the outcomes of DCD heart transplantation, how DCD hearts should be incorporated into the existing heart allocation algorithm is yet to be determined. At present, DCD hearts are allocated under a research protocol with informed recipient consent. So far early outcomes appear equivalent to DBD hearts, however further experience and longer-term follow-up are obviously required.
5.3.2. Size and sex-matching of heart donors and recipients

In the context of increasing use of marginal donors and increasing recipient complexity, there is currently a renewed interest in the role of size and sex-match as modifiable factors affecting post-transplant outcomes (97). Current ISHLT guidelines recommend that adult donors be matched within 30% of recipient body weight, and that female to male matches be confined to +/- 20% of body weight (98). Australian guidelines require donors and recipients be matched within 20% of weight, regardless of sex. Recent evidence, however, indicates that weight-match is a poor predictor of post-transplant outcomes, largely because weight alone is an inaccurate measure of heart size. More accurate assessment of donor and recipient heart mass therefore has the potential to improve utility outcomes from heart transplantation.

Models for the prediction of heart mass based on magnetic resonance studies have previously been published (99,100). From these models, the following equations for the prediction of left ventricular and right ventricular mass are derived:

\[
\text{Predicted left ventricular mass (g)} = a \cdot \text{Height}^{0.54} \cdot \text{Weight}^{0.61} \text{(kg)}
\]

Where \( a = 6.82 \) for women and 8.25 for men

\[
\text{Predicted right ventricular mass (g)} = a \cdot \text{Age}^{-0.32} \cdot \text{Height}^{1.135} \cdot \text{Weight}^{0.315} \text{(kg)}
\]

Where \( a = 10.59 \) for women and 11.25 for men

In their recent analysis of the outcomes of heart size- and sex-matching in the United States, Reed et al applied these equations to a cohort of 31,634 heart recipients transplanted between 1989 and 2011 (101). The results of this study confirmed that donor-recipient matching according to weight difference performs poorly in terms of making optimal allocation decisions (survival hazard ratio for the most underweight quantile = 1.07, 95% CI 0.95-1.21). In contrast, donor-recipient difference in predicted heart mass was a good discriminator of mortality risk (hazard ratio for the most undersized donor quantile = 1.27, 95% CI 1.12-1.43). In addition, based on predicted heart mass, risks of graft failure in the first year and of recipient mortality at 1 and 5 years were increased for undersized donors – but not for oversized donors (101). This finding of an absence of significant risk associated with transplants performed using oversized hearts was similarly reported in a previous analysis of the UNOS database (102). Finally, the authors concluded that the survival differences associated with sex-mismatches were largely attributable to differences in heart mass. While this likely explains the increase in early post-transplant mortality observed for female-to-male transplants, in the case of male-to-female heart transplants, however, excess mortality is more likely to relate to increased rates of rejection or coronary allograft vasculopathy than to size mismatch (97).

New, more accurate, methods for predicting heart mass based on a combination of height, weight, age and sex therefore have the potential to improve utility outcomes from heart transplantation, and should be evaluated for inclusion in allocation algorithms. Alternatively, the use of echocardiographic measurements to assess cardiac volume has been proposed, although no studies have yet examined the association between echocardiographic measurements and transplant outcomes (97).
5.3.3. Ex-vivo perfusion (EVP) of donor hearts: outcomes and impact on the donor pool

Clinical experience with ex vivo perfusion of donor hearts is increasing rapidly, and hypothermic and normothermic ex vivo perfusion (NEVP) systems have been developed. The Transmedics Organ Care system (OCS) is the first commercially available device to provide NEVP, and has been approved for use in Europe, North America and Australia. The Transmedics OCS requires approximately 1.25 to 1.5 litres of donor blood to ‘prime’ the perfusion circuit; otherwise retrieval proceeds as normal except that a lower volume of short-acting cardioplegic solution is used as the initial cold ischaemia time is usually only 20-30 minutes. Two heart transplant programs in Australia (St Vincent’s and Royal Perth) have experience with the Transmedics OCS. Ongoing clinical trials in North America have compared early post-transplant outcomes of heart transplants from standard criteria donors during which the donor heart was preserved using NEVP versus conventional cold storage. Results to date suggest similar post-transplant outcomes (103).

The major clinical impact of EVP is likely to be in the increased utilisation of marginal donor hearts including hearts from DCD donors. A recently published case series suggests that NEVP increases the utilisation of donor hearts from marginal brain dead donors (104). The EXPAND Trial, an ongoing multi-centre study in the Nth America examining the use of NEVP to retrieve hearts from ‘marginal’ brain dead donors, will provide important data to inform this issue, Pre-clinical studies indicate that cold storage provides inadequate preservation of DCD hearts (105) and the 3 successful heart transplants reported to date have all been with hearts retrieved using NEVP. As previously discussed, average donor age has been rising steadily in Australia and it is expected that an increasing proportion of brain dead donors will fall into ‘marginal’ categories. Use of EVP will become increasingly important in maximising the opportunities for heart transplantation from marginal BD and DCD donors.
6. Lung Transplantation

6.1. Current eligibility and allocation criteria

Given the scarcity of donor lungs, lung transplantation in Australia and New Zealand is offered only to patients with a life expectancy <2 years where no other treatment options exist (2). Beyond this medical urgency criterion, inclusion criteria for lung transplantation are:

1. Respiratory failure despite optimal medical, interventional and surgical treatment, and/or;
2. Poor quality of life, potentially with intractable symptoms and repeated hospital admissions.

Exclusion criteria are more extensive, and include (but are not limited to):
1. Active malignancy;
2. Irreversible significant dysfunction of other organs or body systems (combined organ transplant is possible though patients must meet eligibility requirements for both);
3. Non-curable chronic infection;
4. Documented non-adherence, or inability to comply with complex medical therapy or follow-up;
5. Substance addiction (active within the last 6 months).

Lung donor suitability criteria are given in detail in section 6.3.1. Donor organs are offered first to the recognised lung transplant unit corresponding to the state where retrieval takes place. The home state unit then has 30 minutes to respond to the offer; if the home state declines the offer the donor organs are made to non-state units based on a rotalist, with 30 minutes to respond. Donor lungs are then allocated by the accepting lung transplant unit, based on consideration of the following criteria:

1. ABO compatibility;
2. Size compatibility;
3. Absence of a positive T-cell or B-cell cross-match, and absence of donor specific antibodies (even in the absence of a positive cross-match);
4. Clinical urgency (graded by level of support required and evidence of rapidity of deterioration of underlying indication);
5. Logistics;
6. Long-term outcome benefit (based on evaluation of comorbidities);
7. Recipient waiting time, all other factors being equal;
8. CMV matching is also considered (CMV mismatch is avoided where possible, especially for older recipients).
6.2. Recent trends in lung transplantation in Australia and New Zealand

In the decade from 2003 to 2013, the number of annual new additions to the lung transplant waiting list for Australia and New Zealand has increased by 48% - from 153 new listings in 2003 to 227 in 2013. Over the same interval, the annual number of lung transplants has more than doubled – from 91 lung transplants performed in 2003 to 188 in 2013 (Figure 28). The prevalent waiting list at 31 December each year and the annual number of permanent removals for reasons other than transplantation have remained relatively steady. Fourteen candidates died waiting for a lung transplant in 2013, and another 10 were removed from the waiting list because they were too ill or developed new contraindications (85).

The growing number of lung transplant candidates wait listed each year has therefore been met by an increasing rate of lung transplantation, while the number of candidates dropping out of the waiting list each year due to death or for other reasons has remained steady. Further, waiting time to lung transplantation has been falling since 2009. In 2013, the mean wait to lung transplantation was 161 days – lower than at any point in the past two decades (Figure 29). Given that the rate of lung retrieval has remained steady at between 0.4 to 0.5 lungs per donor since 1997, the observed increase in access to lung transplantation has been driven by the overall increase in the number of deceased donors in Australia (Figure 30). Given the rising average age of deceased donors over this period, high rates of lung retrieval and utilisation have therefore largely been maintained by an increasing rate of retrieval from expanded criteria lung donors (1).

![Figure 28: Stock and flow on the lung transplant waiting list, Australia and New Zealand. Source ANZCOTR (personal communication R Pettersson). *Permanent removals from the waiting list for reason that patient condition improved, patient condition worsened (too ill or new development of contraindications), patient declined transplantation, or for an unspecified reason.](image-url)
Donors and recipients of lung transplants in Australia and New Zealand over the past twenty years have aged roughly in parallel (Figure 31). The median age of recipients of bilateral lung transplants in Australia in 2013 was 49 years (min=14, max=67), compared to 34 years in 1993 (min=19, max=56). The mean age of bilateral lung donors in 2013 was 43 years (min=9, max=74), compared to 31 years in 1993 (min=18, max=24). Much of the increase in the mean age of lung donors is attributable to increased utilisation of lungs from donors older than 55 years. In 2008, donors older than 55 years accounted for 13.2% of lung donors in Australia and New Zealand: by 2013, the proportion of donors older than 55 years was 24.5% (Figure 32). This was very similar to the proportion of lung donors in 2013 older than 55 years in the Norwegian, Catalan and Eurotransplant systems (27%, 24% and 26% respectively), though significantly higher than the proportion of donors >55 in the United States (13%, Figure 33).
Figure 34 shows variation in lung retrieval rates across Australian states and territories. For the past 3 years, rates of lung retrieval have been highest for Victoria/Tasmania, and South Australia/Northern Territory. Victoria also had the largest numbers of deceased donors of any state/territory in each of these three years.

**Figure 31:** Mean age of utilised donors and recipients of bilateral lung transplants in Australia and New Zealand, from 1993 to 2013. Source ANZCOTR (personal communication R Pettersson)

**Figure 32:** Age distribution among utilised lung donors in Australia and New Zealand. Source: ANZCOTR (personal communication R Pettersson)
Figure 33: International comparison of the proportion of lung donors aged >55, 2009 to 2013. Sources: University Hospital Oslo (personal communication Per Arne Bakkan), SRTR data request, ANZCOTR (personal communication R Pettersson), OCATT report, Eurotransplant Registry Report.

Figure 34: Rate of lung retrieval in 2010, 2011 and 2012 (lungs retrieved per deceased donor), by donor state. Source: ANZOD

6.3. Utilisation of extended criteria lung donors

6.3.1. Extended criteria for lung donation: definition, allocation and outcomes

Standard criteria for lung donors, according to the 2003 guidelines of The Pulmonary Council of the International Society for Heart and Lung Transplantation, are as follows (106):

- Age <55 years;
- Less than 20 pack-years smoking history;
- Appropriate size matching with the prospective recipient;
- Ratio of pulmonary arterial oxygen to fraction of inspired oxygen (PF ratio) higher than 300 mm Hg;
- No evidence of pulmonary infection, absence of purulent secretions on bronchoscopy, and absence of organisms on sputum Gram stain;
- Absence of chest trauma, and no cardiopulmonary surgeries.
However, the need for lung donors, the changing characteristics of the deceased donor pool (e.g. increased utilisation of DCDs and older donors), and the successful transplantation of organs falling outside of standard criteria have prompted the expansion of the definition of an acceptable lung donor in Australia and elsewhere. A majority of the lungs currently transplanted in Australia fall outside of the criteria above, yet one-year recipient survival remains high at over 90% (85,107). Local analysis of outcomes using expanded versus standard criteria lungs found no significant difference in 5-year survival, regardless of whether the recipient was at high or low risk of mortality (108). In contrast, a number of international studies have reported that high-risk recipients are at increased risk of mortality when transplanted with expanded criteria donor lungs, whereas there is no evidence of contraindications to the use of expanded criteria lung donors in the transplantation of standard criteria recipients (109,110).

Most recently, a single-centre study of 365 lung transplants in Spain reported that high-risk recipients had worse survival outcomes following lung transplantation regardless of donor quality, and in fact the poorest survival outcomes in this study were observed for high-risk recipients transplanted with standard criteria donor lungs. In this study, no significant differences in survival were observed for recipients receiving standard versus expanded criteria donor lungs (111). Moreno et al conclude that expanded criteria lung donors can be safely used to increase the donor pool, but that strict selection of lung transplant candidates is warranted in the context of a scarcity of available organs. These results differ from earlier reports of poorer 10-year survival among recipients of lungs from donors aged 60 years and older, predominantly due to bronchiolitis obliterans syndrome (112). It has been argued – on the basis of this evidence suggesting poorer long-term survival of recipients of older donor lungs – that lungs retrieved from older donors should be preferentially allocated to older recipients, but avoided for high-risk recipients and where longer ischaemic time is anticipated (108). Although the evidence on outcomes of lung transplantation using expanded criteria donors is somewhat conflicting, the recent introduction of ex-vivo lung perfusion (EVLP) is likely to increasingly render many of these concerns obsolete (see section 6.3.2).

Current Australian criteria for suitability for lung donation are (2):

- Age 5-70 years;
- No significant untreated lung disease:
  - Also no known significant pleural disease in the case of DCD;
- Arterial blood gases on 100% fractional inspired oxygen (FiO2) and 5cm positive end-expiratory pressure >250 mmHg:
  - Or equivalent partial pressure of oxygen in the blood (PaO2:FiO2 ratio).
Table 10: Standard criteria for lung donors, and considerations for extending these criteria (113)

<table>
<thead>
<tr>
<th>Standard criteria</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;55 years</td>
<td>Lungs from donors older than 55 years have successfully been transplanted; Increased age is associated with borderline risk for increased 5-year mortality, increased 10-year mortality, and increased risk of bronchiolitis obliterans syndrome.</td>
</tr>
<tr>
<td>&lt;20 pack-years smoking history</td>
<td>No study has evaluated the number of pack-years that would preclude lungs from being transplanted; More than 20 pack-years is associated with longer time spent by recipient in intensive care, impaired early oxygenation and ventilation, but no difference in late outcomes; Study showed increased 3-year mortality associated with smoking donors compared with non-smoking donors, and an increased incidence of bronchiolitis obliterans syndrome; Crucial factor is assessment of lungs for evidence of emphysematous changes and malignancy.</td>
</tr>
<tr>
<td>Appropriate size match with recipient</td>
<td>Oversized lungs can undergo lung-reduction surgery to prevent thoracic compartment syndrome; Total donor lung capacity 75-125% of recipient capacity not associated with clinical problems.</td>
</tr>
<tr>
<td>PaO\textsubscript{2}:FiO\textsubscript{2} ratio &gt;300 mm Hg</td>
<td>Consider EVLP in borderline grafts with PF ratios &lt;=300 mm Hg (having already employed maximum organ procurement strategies at procurement).</td>
</tr>
<tr>
<td>No evidence of pulmonary infection</td>
<td>50% of donors are colonised with organisms; however, this should not present as purulence; Routine prophylaxis of every recipient with broad spectrum antimicrobials.</td>
</tr>
</tbody>
</table>

1 De Perrot, M et al. J Thorac Cardiovasc Surg 2006; 133:525-31
2 Oto T et al. Transplantation 2004; 78:599-606
4 Tamm M et al. Am J Respir Crit Care Med 1994; 150:403-407

By comparison, NHSBT guidelines on lung distribution and allocation suggest the following donor lung acceptance criteria (which are at the discretion of the recipient centre and must be consented to by the recipient):

- Age up to 70 years;
- No or minimal chest trauma:
  - Pneumothorax and/or a chest drain are not a contraindication,
  - No previous chest surgery on the retrieval side;
- Ventilated <10 days (tracheostomies are acceptable);
- Normal chest x-ray appearance reported on retrieval day;
- No evidence of respiratory infection as demonstrated on chest x-ray or the presence of purulent sputum and confirmed pathogens:
  - Purulent secretions do not necessarily rule out lung donation. Multiple organisms on gram stain may indicate normal flora and are unlikely to lead to infection. No donor should be rejected based on purulent sputum without bronchoscopy evidence of infection,
  - Heavy fungal infection of the bronchial tree may exclude donation. Candida infection should be treated with an azole;
- No systemic sepsis;
- Acceptable arterial blood gases:
  - On FiO\textsubscript{2} 100%, PaO\textsubscript{2} >=35kPa and on,
  - FiO\textsubscript{2} of 40%, PaO\textsubscript{2} >=14kPa,
PaO$_2$ should preferably be 35 x FiO$_2$ (i.e. PF ratio $\geq$350),

- PaO$_2$ of 25 x FiO$_2$ (i.e. PF ratio $\geq$250) may be considered at the discretion of the senior implanting surgeon;

- Normal ventilator parameters with normal compliance (the addition of 8cmH$_2$O of positive end-expiratory pressure is recommended);

- Mild asthma is acceptable (but may be transmitted);

- Current pulmonary oedema if associated with CXR changes and borderline ABG excludes donation. May consider if treated and resolved;

- No evidence of aspiration. The presence of a positive history, poor gasses and abnormal CXR and bronchoscopic findings suggesting aspiration will preclude donation. In cases of history suggesting inhalation, abnormal bronchoscopy should be established before donors are turned down;

- CMV mismatches acceptable unless specified in high risk recipients;

- Carbon monoxide poisoning is acceptable with caution as long as there is no smoke inhalation;

- Smoking history should not be the sole reason for refusal of a well-functioning organ. Acceptable up to 30 pack years (i.e. 1 pack per day for 30 years). If greater than this, other factors should be considered in conjunction with smoking history as reasons for refusal.

### 6.3.2. Ex-vivo perfusion of donor lungs: outcomes and impact on the donor pool

Steen and colleagues reintroduced the concept of ex-vivo lung perfusion (EVLP) in 2001, as a technique by which to evaluate lungs from uncontrolled DCD donors prior to transplantation (114). A decade later, the seminal study of Cypel et al demonstrated the feasibility of transplanting high-risk donor lungs (defined as PaO$_2$:FiO$_2$ $<$300 mm Hg, pulmonary oedema, poor lung deflation/inflation, blood transfusions exceeding 10 units, and DCD Maastricht categories III or IV) that have undergone EVLP, finding rates of primary graft dysfunction and 1 year patient survival comparable to those observed for standard criteria lungs (115). Subsequent analysis of a larger cohort of lung transplants confirmed the safety of transplantation of high-risk donor lungs after 4 hours of EVLP based on the Toronto protocol (116).

EVLP preserves lung cells and tissues in a metabolically active, viable state for several hours, allowing (i) time for thorough evaluation (e.g. bronchoscopy, radiography, haemodynamics, gas exchange, ventilatory mechanics, infectious disease screening) and (ii) potential reconditioning of previously unacceptable grafts via removal of waste products (blood clots, neutrophils, inflammatory cytokines), treatment of infection, and “recruitment of atelectatic areas resulting in better ventilation/perfusion” (117). Further, EVLP introduces the potential to limit ischaemic time and improve outcomes from donor lungs that are already considered acceptable for transplantation.

The great benefit of EVLP is therefore that the pool of potential lung donors is expanded beyond that of expanded criteria donors, without compromising on donor outcomes (116,118). There remains, however, a need for data on long terms outcomes of recipients of lungs that have undergone EVLP. The clinical potential of EVLP as a method for the normothermic
preservation of donor lungs and for reconditioning post-retrieval is the subject of several ongoing clinical trials – INSPIRE, NOVEL, DEVELOP and EXPAND (117). It is likely that protocols will continue to be improved in future, for example with the addition of biomarkers to protocols for EVLP assessment and donor selection (119).

In Australia, EVLP is currently available only at The Prince Charles Hospital. Local data on long-term outcomes are minimal - a total of ten transplants using lungs following EVLP have been performed in Australia since November 2011, with one death recorded at 2.5 years post-transplant. Significantly, the availability of EVLP at Prince Charles has increased the rate of lung retrieval from 37% to 50%, and net lung transplant numbers by 10-15% per annum (85). International single-centre experiences of the clinical impact of the introduction of EVLP have suggested the potential for an increase of between 20-50% in lung transplant procedures (116,118,120).

Andreasson et al note, however, that despite the potential of EVLP to increase the number of lungs available for transplantation, the technique is also expensive and time consuming (121). The outcomes of ongoing clinical trials of various EVLP protocols and systems will hopefully answer important questions related to the cost-effectiveness of the technique – questions such as whether to use cellular or acellular perfusate, optimal perfusion time, full or reduced perfusate flow, and appropriate antimicrobial protocols. At such a point as more data are available on the clinical outcomes of EVLP, economic evaluation of the costs and benefits of increased utilisation would be appropriate (121).

6.4. Urgent listings and sensitised patients

Current Australian protocols allocate donor lungs according to ABO compatibility, size compatibility, and absence of a positive T-cell cross-match. In cases where multiple potential recipients match with the donor, priority among these candidates is determined on the basis of clinical urgency, logistics, long-term benefits, and recipient waiting time (all other factors being equal). Clinical urgency is determined on the basis of the level of support required and evidence of rapid deterioration (2). Level of support includes use of extracorporeal membrane oxygenator (ECMO), mechanical ventilation, non-invasive ventilation, high-flow O₂ requirement, low-flow O₂ requirement, prolonged or recurrent hospitalization or other support devices such as continuous intravenous therapies. Rapid deterioration is defined as change in NYHA functional Class or MRC grade, significant fall in lung function, significant fall in PaO₂, significant rise in partial pressure of carbon dioxide in the blood (PaCO₂), significant fall in 6-minute walk test distance, need for escalation in level of support as above, time course of progression of radiological changes, development of symptomatic pulmonary hypertension, or development of refractory right heart failure.

In 2014, the TSANZ Lung Transplantation Advisory Committee ratified a new National Notification Protocol. Under this protocol, patients wait-listed for lung transplantation may be placed on a national list given the following indications:
1. Patient survival estimated to be days to weeks without transplantation as a result of or development of:
   - Requirement for ECMO;
   - New or worsening respiratory failure needing high flow oxygen, non-invasive ventilation or mechanical ventilation;
   - Rapid deterioration as indicated by, but not limited to a significant rise in partial pressure of carbon dioxide, marked reduction in functional capacity, acute irreversible fall in lung function parameters or refractory right heart failure.

2. The patient is highly sensitised – defined as multiple (>6) positive cross matches with high Panel Reactive Antibody or high titre anti-HLA antibodies.

These are for general guidance only rather than an automatic trigger for national listing, with institutional factors, prognosis and predicted outcome post transplantation influencing decision-making on a case-by-case basis. National listing for lung transplantation is at the discretion of the Transplant Unit Director. Lung donor allocation remains under the control of the home state as does the rotational non-home state offers as per standard practice. It will be the responsibility of the Transplant Unit Director (or his or her nominee) to notify all other cardiothoracic transplant units in Australia and New Zealand, and to notify the organ donor coordinators in all jurisdictions when a patient is placed on (and removed from) the national waiting list. It is expected that the majority of individuals placed on the national waiting list will either die or be transplanted within 4 weeks of notification (with the exception of highly sensitised patients). In the event that a person remains urgently listed beyond 4 weeks, re-notification of all cardiothoracic transplant units and donor coordinators is recommended at 2-weekly intervals (with the exception of highly sensitised patients). The operation of the national waiting list will be subject to annual audit by the Lung Advisory Committee of TSANZ and be listed as a standing agenda item at LAC meetings.

The OPTN protocol for lung allocation similarly includes an exception for sensitised patients, such that lungs may be allocated to sensitised candidates within a given donor service area out of the usual match run if the following requirements are met:

1. The candidate’s transplant surgeon or physician determines that the candidate’s antibodies would react adversely to certain HLA antigens;
2. All lung transplant programs and the OPO within the donor service area agree to allocate the lung from a compatible deceased donor to the sensitised candidate because the results of a crossmatch between the blood serum of that candidate and the cells of the lung donor are negative;
3. The candidates transplant program, all lung transplant programs, and the OPO within the donor service area agree upon the level of sensitisation at which a candidate qualifies for the sensitisation exception.

The Lung Allocation Score (LAS), originally developed in the United States but adopted by a number of international transplant programs (e.g. Eurotransplant), formalizes this assessment of clinical urgency and long-term outcome benefit. The LAS is based on the concept of ‘net benefit’, and gives the highest priority to candidates who are most urgently in need of a
transplant AND are expected to derive the greatest benefit. The LAS calculation is based on the following (ref OPTN guideline):

- **Waiting List Urgency Measure** – which is the expected number of days a candidate will live without a transplant in an additional year on the waiting list
- **Post-transplant Survival Measure** – which is the expected number of days a candidate will live during the first year post-transplant
- **Transplant Benefit Measure** – which is the difference between the Post-transplant Survival Measure* and the Waiting List Urgency Measure
- **Raw Allocation Score**, which is the difference between the Transplant Benefit Measure and the Waiting List Urgency Measure.

*Factors that predict survival after lung transplantation are age, forced vital capacity, PWC pressure, continuous mechanical ventilation, serum creatinine, functional status, and diagnosis.

The following recipient factors are included in the calculation of the LAS:

- Height (cm) and weight (kg)
- Age
- Lung diagnosis code
- Assistance level (none, some, total)
- Diabetes (no diabetes, insulin dependent, non-insulin dependent, unknown)
- Assisted ventilation
- Oxygen requirement
- Supplemental oxygen (FIO₂ in % or l/min)
- Forced vital capacity (% predicted)
- Pulmonary artery systolic pressure (mm Hg)
- Mean pulmonary artery pressure (mm Hg)
- Pulmonary capillary wedge mean (mm Hg)
- Current, highest and lowest PCO₂ (mmHg)
- Six minute walk distance
- Serum creatinine (mg/dl)

The Eurotransplant Thoracic Advisory Committee has introduced further requirements to report end saturation after six minute walk test, estimated right ventricular systolic pressure, presence of pneumothorax with drain, need for combined lung transplant, need for ECMO, IV-prostanoids, bilirubine and coagulopathy. These data will be incorporated into a future adaptation of the LAS system used by Eurotransplant (ref Eurotransplant Manual).

Both the OPTN and Eurotransplant allocation guidelines allow for exceptional LAS in individual cases: if a candidate’s transplant program believe that a candidates calculated LAS does not appropriately reflect the candidate’s medical urgency for a transplant, it is possible to apply for an exceptional LAS or exceptional priority. In the United States, the transplant program may request the approval of a specific priority or a specific LAS from the Lung Review Board. The transplant program can also ask the Lung Review Board to approve specific estimated values or diagnoses. In the Eurotransplant system, the transplant center may propose an alternative LAS value, accompanied by a detailed description of the underlying reasoning, with this proposal evaluated by a LAS Review Board.
Eurotransplant also conducts random audits of LAS scores, and routinely audits every high LAS case by checking submitted data against the original lab data. In the Eurotransplant system, lung transplant candidates are categorized as low LAS, high LAS or exceptional LAS. Low LAS status is valid for 180 days (90 in Germany): after the validation date has expired the LAS returns to zero unless updated patient information is received. A high LAS status is valid for 14 days: after 14 days, new data must be submitted to Eurotransplant. Exceptional LAS status is valid for 56 days. If a patient is still on the waiting list after 56 days, and the centre considers that patient still eligible for an exceptional LAS status, a renewed request for exceptional LAS status can be submitted to the LAS Review Board.

Within Scandiatransplant, all active heart, lung or heart-lung candidates in Scandinavian countries are registered in the Scandiatransplant database. Lungs are allocated locally, then nationally, then to the Scandiatransplant list to patients with priority - defined as those on ECMO or ventilatory support or with a rapid progression of lung failure with poor prognosis (defined by the responsible centre). For the fair exchange of organs across borders, offers to the Scandiatransplant list are made according to “rotalists” – each Scandiatransplant geographical division has a rank on the rotaist in decreasing order according to the most recent acceptance of organs from other Scandinavian centres (122). The UK NHSBT is currently assessing the impact of moving to national allocation for some categories of urgent patients. Currently, lungs are allocated to the transplant center within the allocation zone in which recovery occurs. If no recipient is found within the local zone, the organ is offered to other transplant centres using the “Transplant Centre Rota” (i.e. the offer sequence is in reverse-chronological order of the last transplant date when organs were accepted outside of their own allocation zone). The tradeoffs between the transparency and equity offered by national allocation, and the closer matching enabled by zonal allocation are the subject of close review.
7. Vascularised Composite Allotransplantation

7.1. Definition of vascularised composite allotransplantation

Vascularised composite allotransplantation (VCA) is the transplantation of a vascularised body part containing multiple tissue types as an anatomical/structural unit to a recipient. VCA is fundamentally more similar to organ transplantation than to tissue transplantation, as is recognised as such by the United States Department of Health and Human Services, and by the European Parliament (123). Body parts that meet the definition of VCAs include limbs, face, larynx and abdominal wall.

The OPTN policy defines a vascularised composite allograft as a transplant involving any body parts that meet all nine of the following criteria:

1. That is vascularised and requires blood flow by surgical connection of blood vessels to function after transplantation;
2. Containing multiple tissue types;
3. Recovered from a human donor as an anatomical/structural unit;
4. Transplanted into a human recipient as an anatomical/structural unit;
5. Minimally manipulated (i.e., processing that does not alter the original relevant characteristics of the organ relating to the organ's utility for reconstruction, repair, or replacement);
6. For homologous use (the replacement or supplementation of a recipient's organ with an organ that performs the same basic function or functions in the recipient as in the donor);
7. Not combined with another article such as a device;
8. Susceptible to ischemia and, therefore, only stored temporarily and not cryopreserved; and
9. Susceptible to allograft rejection, generally requiring immunosuppression that may increase infectious disease risk to the recipient.

7.2. Assessment of candidate and donor eligibility for VCA

As of September 2014, a single hand transplant has been performed in Australia. For the purposes of this first hand transplant, DonateLife in Victoria worked with Professor Wayne Morrison and the St Vincent’s Hospital Plastic Surgery and Nephrology Units to formulate local guidelines for donor selection, donor referral, the retrieval surgery and donor family support. St Vincent’s Hospital had consultation with overseas organ procurement agencies in Cleveland and Pittsburgh, as well as extensive ethics consultation both externally with The Caroline Chisholm Centre for Health Ethics and internally with their Clinical Ethics Committee. Approval was granted to proceed in May 2010; in 2011, the St Vincent’s Hospital team performed Australia’s first hand transplant (124). With a second potential hand transplant recipient currently being assessed, these initial guidelines are now under review. Questions for
future iterations of Australian VCA guidelines include single versus multiple centres, whether
to extend indications for VCA (in particular to unilateral amputees), provisions for other organs
in addition to face and hands (e.g. larynx, trachea, tongue), and the establishment of a VCA
waiting list.

As this is such a new field, protocols for assessing recipient and donor eligibility for
VCA are developed and applied at the institutional level. Efforts are currently underway to
generate international standard guidelines for candidate and donor eligibility for VCA, with a
particular focus on standardised psychosocial assessment tools (the ‘Chauvet protocol’) (125).
However, these efforts are limited by the small number of VCA transplants that have been
performed to date worldwide, and hence the small size and heterogeneity of the available cohort
from which to draw evidence-based guidelines. As the practice of VCA transplantation matures,
the capacity to generate standardised, evidence-based guidelines will increase.

7.2.1. Candidate eligibility criteria

Criteria for candidate eligibility for VCA have a number of unique requirements
compared to other forms of transplantation:

1. The recipient will experience both positive and negative changes to body image: the
   graft – and therefore rejection - is visible;
2. Risk of death or return to dialysis are not a factor in motivating adherence to
   immunosuppression;
3. Unlike the transplantation of other solid organs transplantation, VCA transplantation
   may decrease rather than increase life expectancy – the goal is not to extend life, but
   to increase quality of life alone;
4. The recipient is required to comply with lengthy and intensive rehabilitation to
   achieve function from their transplant, and may initially experience increased
   disability and/or a decrement in quality of life. For some patients, the only gain will
   be with respect to body image – there may be no functional gain. All patients should
   be advised of the potential risk of a worse outcome, including the possibility of graft
   explant.

The psychological evaluation of potential candidates and the informed consent process
(both for recipients and for donor families) are therefore of critical importance. With regards to
recipient eligibility, VCA will only ever be appropriate for a small minority. Indeed, a key role
of VCA units may be in educating and supporting patients through a process of self-exclusion.
With only one VCA transplant performed in Australia so far, poor choice of recipients and
associated poor outcomes carry the risk of discrediting the procedure. That said, there is as yet
no consensus concerning what would constitute a successful VCA, nor are there standardised
methods for measuring non-survival outcomes.

The inclusion/exclusion criteria for patient eligibility for hand transplantation developed
by the St Vincent’s team are given in Table 11.
Table 11: Eligibility criteria for hand transplantation, St Vincent's hospital committee (current as of October 2014, under review)

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bilateral loss of hands/forearm or unilateral loss with significant contralateral dysfunction, as a result of trauma/illness &gt;1 year ago;</td>
<td>• Significant uncorrected chronic comorbid disease e.g. cardiovascular, respiratory or renal, which results in undue risk from anaesthetic or immunosuppression;</td>
</tr>
<tr>
<td>• Patient aged over 18 years or older;</td>
<td>• Active chronic infection;</td>
</tr>
<tr>
<td>• Psychologically well and stable, including the ability to form a therapeutic alliance with the transplantation team*;</td>
<td>• Active malignancy or one with high 5 year likelihood of recurrence;</td>
</tr>
<tr>
<td>• Ability to understand the complexity of the procedure, as well as the risks, benefits and alternatives, and able to communicate their informed decision.</td>
<td>• Congenital abnormalities of limbs;</td>
</tr>
<tr>
<td>*Ability to form a therapeutic alliance” refers to an ability to work cooperatively with the transplantation team throughout work-up, transplantation and follow-up.</td>
<td>• High humeral amputation and/or proximal neuromuscular dysfunction;</td>
</tr>
<tr>
<td></td>
<td>• Inability to comply with long term, complex medical and rehabilitative therapy.</td>
</tr>
<tr>
<td></td>
<td>• Untreated/active psychiatric illness</td>
</tr>
<tr>
<td></td>
<td>• Active cigarette smoking</td>
</tr>
<tr>
<td></td>
<td>• Active drug or alcohol abuse/addiction</td>
</tr>
</tbody>
</table>

Note that there is currently no intention to exclude candidates on the basis of geographical location, bilateral blindness, vaccination history (though full vaccination is preferred), or prior VCA transplant. In the latter case, the reasons for the loss of the prior graft would be considered as part of the psychological evaluation and assessment of ability to comply with therapy. Self-inflicted trauma is also not a contraindication to VCA transplantation: provided candidates are deemed to be currently psychologically well and stable and meet all other criteria, then they are eligible for a transplant. Note also that there are no plans to pursue paediatric VCA, nor live donor VCA transplantation in Australia. Inclusion/exclusion criteria that require further discussion before inclusion in local protocols include whether the patient has tried and failed with prosthetics. Financing of prosthetics in Australia makes access an issue, but there would likely be value in patients at least trialling basic prosthetics to gain an understanding of what the sensation of the transplant will be like.

Candidate evaluation includes:

- Hand surgeon assessment of proximal stump for suitability for transplant based on anticipated outcome
- Immunology physician review
- Anaesthetic review
- Psychological review
- Preoperative investigation
- FBE, Coagulation profile
- ABO serology
- Donor specific antibody
- Renal function – U+ E/Cr, Creatinine clearance – GFR estimation, urinalysis
- Liver Function Tests
- Infectious disease serology – HIV antigen, HTLV I and II antibody, HIV I and II antibody, Hep C virus, Syphilis, Hepatitis B core antibody, Hep B Surface Ag
- CMV, HSV, Toxoplasmosis and VZV antibody
- Pulmonary function tests, CXR
- ECG and Echocardiogram
- Dental consult
- Sinus imaging if indicated
- EMG for proximal muscle condition
- Imaging (Xray, CT angiography, MR angiography, MRI)
- Registration with Hand Transplant Registry (handregistry.com)
- Preoperative Functional assessment:
  - DASH score
  - Michigan Hand Score
  - Jebsen assessment
The recipient consent form developed by the St Vincent’s team includes information on the transplant operation, the potential long-term effects of transplantation, and the expectations of the recipient. The current draft of this document contains the following information for potential recipients:

1. Hand transplant does not prolong life, instead benefits are measured in improved quality of life;
2. Studies so far indicate that the function of the transplanted hand is better than that of prosthetics;
3. Success of the transplant depends as much on the extensive care following the transplant as it does on the surgery itself – some of these therapies are life-long;
4. Technical success of the surgery will be apparent in 2-3 days; by 2-3 months it is expected you will be able to make a fist, but it will be at least a year before finer finger moments and sensation to the skin develops;
5. A hand transplant is not the best option for everyone, and risks include:
   a. Risks related to the operation (infection, bleeding), those related to the anaesthetic and other post-operative complications which make, rarely, result in death;
   b. Rejection, which in some cases may lead to the hand needing to be surgically removed;
   c. Potential to develop certain infections, cancers, diabetes and heart disease as a consequence of immunosuppressive medications;
6. Responsibilities of the recipient to the transplant include:
   a. Frequent blood tests (thrice weekly) during the first few months post-transplant; thereafter the frequency of blood tests will be determined on an individual basis but will be required for the life of the graft;
   b. Regular monitoring of the skin of the transplant that may require skin biopsies (the need for which is determined on a clinical and individual basis);
   c. Strict medication adherence;
   d. Hand physiotherapy;
   e. Clinic visits;
7. Considerations of the donor family – the recipient is requested to keep details of the transplant away from the media for as long as possible.

In future cases of VCA transplantation, it is recommended that the consent process incorporate a cooling off period, whereby – after the initial consent of the potential recipient is given – they consider their decision for ~4 weeks and are then asked to reconsent. This cooling off period is an important ethical safeguard in the consent process (126).

Australian recipient eligibility and donor selection criteria for face transplantation have not yet been developed. The Brigham and Women’s Hospital in Boston has performed multiple partial and full face transplants since gaining IRB approval for the procedure in 2008, and the recipient eligibility criteria specified under the protocols of this institution are listed in Table 12.

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1 Note that the document used in the case of the first hand transplant in Australia is currently under review. It is likely that the contents will be modified in the future following a consultation process.
Table 12: Eligibility criteria for face transplantation – Brigham and Women’s Hospital’s IRB Protocol 2008P000550 (127)

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Most difficult or impossible to reconstruct facial defects;</td>
<td>• Pregnancy;</td>
</tr>
<tr>
<td>• Defect comprises &gt;25% of the facial area, and/or involves loss of one of the central facial parts such as eyelids, nose or lips;</td>
<td>• Active psychiatric illnesses are considered individually;</td>
</tr>
<tr>
<td>• Outcome of an alternative reconstructive method considered unfavourable or unsatisfactory.</td>
<td>• Unable to guarantee adequate coverage of follow-up care and immunosuppression</td>
</tr>
</tbody>
</table>

Protocol for face transplant candidate evaluation at Brigham and Women’s Hospital (127,128):

- Initial evaluation: Team leader assesses the facial defect (functional and aesthetic) and potential of restoration through face transplantation, and provides information including alternative treatments.
- Plastic surgery: Entire plastic surgery team continue with above goals and reach clinical consensus regarding whether conventional reconstruction is unsatisfactory and facial transplantation will confer significant aesthetic and functional gains.
- Psychiatry: Assess understanding and expectations of procedure and alternatives, patient motivation, quality of life, emotional state, behavioural trends, support structure, cognitive ability, coping skills, issues of identity and body image, and medical compliance.
- Social work: Assess support network, substance abuse, benefits, disability, medication coverage and lodging if applicable.
- Transplant medicine: Evaluate immunological history and status and obtain information for donor matching.
- Infectious disease: Screen for a variety of infectious disease and provide immunisation and prophylaxis planning.
- CT and angiography: Evaluates the deep structures of the head and neck and visualises vascular anatomy.
- MRI*: Evaluates the soft tissues of the head and neck
- Functional MRI: Sets a baseline for post-operative evaluation of cortical plasticity.
- PT: Discuss post-transplant rehabilitation.
- Nutrition*: improve the preoperative nutritional status.
- Speech/swallow*: Assess functional problems and provide coping strategies.
- Laboratory: Obtain a wide picture of overall health status and address issues in need of attention.
- Second opinion: A study-independent psychiatrist ensures the patient’s best interest and acts as the patient’s advocate.
- Dentistry: Treats existing problems and educates on post-transplant oral hygiene
- Age-appropriate screening: Screens for underlying problems that would compromise safety.

7.2.2. Donor eligibility criteria

In terms of donor selection, the requirement for the donor hand or face to be a match both in terms of medical compatibility and aesthetic appearance (skin tone, proportion, age,
race, gender) is unique to VCA transplantation. Secondly, because VCA transplantation is performed on physically healthy but severely disabled individuals, strict criteria are necessary to prevent donor transmission of disease. Approaching the families of potential hand and face donors also requires specialized protocols that account for the sensitivity of the request/ lower willingness to consent to donation. Further, travel time must be minimal. The length of time to wait for a suitable donor may therefore be extensive – a consideration which must be factored into recipient evaluation (including the informed consent process).

Table 13: Selection criteria for hand donors, St Vincent’s hospital

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age 18-65 years*</td>
<td>• Untreated sepsis, HIV, active CMV, EBV, active tuberculosis, HBV, HCV, viral encephalitis</td>
</tr>
<tr>
<td>• Aesthetically and physically matched to recipient gender, skin tone, race, age, and size (within 15% of recipient size)</td>
<td>• Malignancy</td>
</tr>
<tr>
<td>• Compatible with donor – matched for viral status and blood type</td>
<td>• Current intravenous drug use</td>
</tr>
<tr>
<td>• The donor should not require excessive vasoressors to maintain blood pressure prior to harvest.</td>
<td>• Tattoo within past 6 months</td>
</tr>
<tr>
<td></td>
<td>• Systemic or limb-related neuropathies</td>
</tr>
<tr>
<td></td>
<td>• Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td>• Osteoarthritis</td>
</tr>
</tbody>
</table>

*this upper limit is likely to be lowered in the future.

An Australian donor consent form has also been developed, that covers important information such as the fact that after donation a prosthesis will be placed to restore body integrity.

Table 14 shows a comparison of facial allograft donor inclusion and exclusion criteria specified in the institutional protocols of the Brigham and Women’s Hospital and the Cleveland Clinic. These and other international protocols agree on the requirements for ABO compatibility, skin colour and sex match, and exclusion of donors with unresolved sepsis (129,130). The Boston and Cleveland teams, however, differ on the inclusion of potential donors with comorbidities prior to death, craniofacial abnormalities, or available mandible imaging, and on the exclusion of potential donors with connective tissue disorders, facial nerve palsy, history of craniofacial or neck trauma or history of carcinoma (129). The philosophy of the Boston team is to avoid ruling out too many potential donors, given the difficulty of finding suitable donor candidates and the uniqueness of each recipient’s defect; in contrast, the Cleveland team prefers to rule out all potential donor-related risks to the aesthetic, functional and survival outcomes for the recipient of the face transplant (129). Both DBD and DCD donors are considered suitable for face transplantation, though DBD donors are preferred as ischaemia time can more easily be controlled and blood loss minimised.

7.3. Ethics assessment in VCA

The ethical complexity of VCA is unlike any other area of transplant medicine. This explains why clinical ethicists are often members of VCA teams, assisting with the development of protocols, policies, procedures, and forms (126). The VCA clinical ethicist should also be involved in screening recipient candidates for matters of ethical relevance including but not
limited to capacity assessment and informed consent, as well as coercion and conflict of interest. VCA does not save lives, but hopes to enhance them (without any guarantees), and the expectations and outcomes of patients and surgical teams may conflict. It is critical to understand these matters, as well as the motivations and motivation level of the patient. The patient’s philosophical meaning of the hand/face/etc. must be understood, as well as the values, behaviours, and emotions that are linked to these body parts. Also, the clinical ethicist can help detect and resolve moral distress pertaining to the donation and transplant (including donor-related issues such as death and dying, fingerprints and identity, and personhood issues). Explicit details of a VCA Ethics Assessment can be obtained by contacting VCA teams directly.

Table 14: Donor selection criteria for face transplantation – comparison of Brigham and Women’s Hospital and Cleveland Clinic protocols (129)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented brain death with hemodynamic stability</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Minimal amount of medical/surgical comorbidity before death</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Acceptable craniofacial imaging to identify unknown hardware and/or vascular abnormalities</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Acceptable mandible imaging to rule out dental caries</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>ABO compatibility</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Suitable HLA typing</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Negative crossmatch</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sex match</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Skin colour match</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Age match</td>
<td>No*</td>
<td>Yes**</td>
</tr>
<tr>
<td>Location Max 4hr flight Case-by-case</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of significant craniofacial or neck trauma and/or surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of recent carcinoma (&lt;5 years)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Family is planning an open casket funeral</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Although age-matching is not requirement, an ideal donor is considered to be up to 20 years younger or 10 years older than the recipient.
**Age matched by skin texture.
7.4. Psychosocial evaluation in VCA transplantation

Given that the primary goal of VCA is to improve the psychosocial status and quality of life of the recipient, psychosocial evaluation both before and after transplantation is critical not only to establish patient suitability, identify at-risk patients and those in need of ongoing counselling, but also to assess the success of the transplant itself. Psychosocial evaluation should therefore ideally establish (i) a detailed baseline understanding of the impact of the injury on the patient and the extent to which they have adapted to their disability, (ii) the existence of any demonstrable active or untreated psychiatric or psychological impairment that would preclude VCA transplantation, (iii) patient perceptions of the goals of treatment and expectations post-transplant (also relevant to informed consent), (iii) requirements for psychosocial support pre- and post-transplantation, and (iv) post-transplant changes in quality of life and other psychosocial outcomes over the longer term. It must be further established that the potential VCA recipient will be able to tolerate the physical and psychological stress of all pre-, peri- and post-operative procedures and rehabilitation involved, while simultaneously coping with media attention, a changed physical appearance and a complex immunosuppression regimen (128).

Therefore – in addition to the standard pre-transplant evaluation of psychiatric wellbeing, social support, substance use, knowledge of transplantation and predicted compliance – VCA transplantation also requires the assessment of body image, adaptation to the trauma, cognitive preparedness, motivation, expectation of transplant outcomes, and potential for psychological regression of the transplant candidate (125). The principle concern is the potential for a recipient to psychologically reject or otherwise be unable to cope with the transplant, leading to lower quality of life and potentially to non-adherence to immunosuppression and loss of the graft (125). A list of psychosocial factors indicating likely suitability for hand transplantation is given in Table 15.

In an effort to move towards standardized psychosocial assessment of candidates for hand transplantation, the Innsbruck Psychological Screening Program for Reconstructive Transplantation (iRT-PSP) was developed in 2011 (131). This assessment method measures cognitive functioning, affective status, psychosocial adjustment, coping, quality of life and life satisfaction based on a semi-structured interview, standardized psychological screening procedures and ongoing follow-up assessment. The iRT-PSP therefore provides a tool for pre-transplant assessment, post-transplant follow-up ratings, and the identification of needs of psychological/psychiatric treatment. Key aspects of the psychosocial evaluation of potential hand transplant recipients as identified by Kumnig et all include (131):

1. Psychological aspects of transplant surgery
   • Premorbid psychiatric status, poor social support, substance abuse, psychological status and perception of self-efficacy may all affect the likelihood of adherence to post-transplant immunosuppression, likely in a dose-dependent manner.

2. Motivational aspects
   • Motivation will be different from patient to patient, dependent on whether the impairment is bi- or uni-lateral, the loss of hand/s was congenital or accidental, physical status, psychological status, and social integration.
   • Motivations are likely to involve difficulties with coping and psychological burden, or need for increased function.
   • Psychosocial evaluation must ensure that the patients have the pertinent information they need regarding benefits, risks and expected outcomes, and alternative
treatments, to weight against their motivation for transplantation, in order to give informed consent.

3. Body image and self concept
   • Potential hand transplant recipients may experience psychological distress related to body image/self-concept as a consequence of both their physical disability and physical appearance.
   • Repeat assessment of body image and self-concept is relevant to determining the success of the transplant.

With respect to psychosocial evaluation for face transplantation, given the centrality of the face to our understanding of identity the relevant psychosocial issues – particularly body image and self-concept – are likely to be magnified relative to hand transplantation, and to require long-term psychological/psychiatric support (132). The small number of face transplants performed to date worldwide, however, means that there is currently very little evidence on which to base face transplant-specific psychosocial evaluation criteria.

### Table 15: Psychological factors used as indications for hand transplantation, based on a systematic review of reports of psychosocial assessment in hand transplantation (125)

<table>
<thead>
<tr>
<th>Psychological factors</th>
<th>Psychological factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No relevant history of psychiatric pathology and/or ongoing severe psychiatric disorder</td>
<td>• Knowledge about hand transplantation, realistic appreciation of the risk-benefit ratio</td>
</tr>
<tr>
<td>• High anticipated compliance with postoperative treatment plan</td>
<td>• Adequate anxious beliefs toward hand transplantation and positive personal surgical experiences</td>
</tr>
<tr>
<td>• Strong motivation for hand transplantation, and evaluated stability of decision-making process and scope of personal choice</td>
<td>• Cognitive preparedness and good cognitive level</td>
</tr>
<tr>
<td>• Reduced quality of life pre-transplant, reduced psychological well-being and restricted daily activities (high motivation for hand transplant)</td>
<td>• Adequate affective function level</td>
</tr>
<tr>
<td>• Adequate self-image and body-image (high body image adaptation)</td>
<td>• No chemical dependence history</td>
</tr>
<tr>
<td>• Reduced or no pre-transplant phantom limb pain</td>
<td>• No history of suicide attempt</td>
</tr>
<tr>
<td>• Ability to engage in rehabilitation program</td>
<td>• Social and family support</td>
</tr>
<tr>
<td>• Adaptive coping, no traumatic reactions because of the hand loss</td>
<td>• Restricted social behaviour because of hand loss</td>
</tr>
<tr>
<td>• Realistic appreciation of the post-transplant results and anticipated level of comfort</td>
<td>• Anticipated adequate psychological development after hand transplant.</td>
</tr>
</tbody>
</table>

7.5. Allocation of VCA organs

Despite having only performed one hand transplant in Australia so far, it is conceivable that in the near future there may be multiple candidates simultaneously awaiting VCA. In this circumstance it will be necessary to have a policy for the allocation of organs that is fair and transparent. The UNOS/OPTN protocol for VCA allocation offers benchmark against which a local policy might be developed.

Under the UNOS/OPTN allocation protocol the host OPO will offer VCAs to candidates with compatible blood type willing to accept a VCA with similar physical
characteristics to the donor. The OPO will first offer VCAs to candidates that are within the OPO’s region, and second to candidates that are beyond the OPO’s region.

In addition to the absolute requirements for blood group compatibility and the absence of a cytotoxic cross-match, proposed criteria for allocation include age difference, size (especially bones), colour and texture of the skin, and soft-tissue features (123). Other factors that may enter into allocation criteria include urgency and waiting time. Given the small size of the potential donor pool, HLA matching will not be feasible. Proximity of the donor and recipient may be a factor given the importance of short ischaemia time.

7.6. International outcomes of VCA transplantation: The International Registry on Hand and Composite Tissue Transplantation

The International Registry on Hand and Composite Tissue Transplantation (IRHCTT) reports on international activities, practices and outcomes with respect to upper-extremity and face transplantation (133). The registry was established in 1998 in recognition of the need for transparency and sharing of experience in this relatively new field, which to date has involved total cases numbering approximately one hundred.

The average age of recipients of hand transplants recorded in the IRHCTT between 1998 and 2014 was 37.4 years (range: 17-65 years). Just over half of these hand transplants were performed in recipients with bilateral amputation. The average age of donors of upper limbs was 31 years (range 15 to 62). Average cold ischaemia time was 5 hours, with a maximum of 12.5 hours. Donor-recipient pairs were cross-match negative in all cases. In the first year following transplantation, 85% of recipients recorded in the IRHCTT had developed at least one episode of acute rejection. Chronic rejection was declared in 4 cases recorded in the registry:

Case 1: chronic rejection and patient decision to amputate (771 days post-transplantation)

Case 2: Chronic rejection after ongoing acute rejection episodes and non-compliance, resulting in amputation (12 years post-transplantation)

Case 3: Chronic rejection due to non-reported acute rejection episodes and self-medication (13 years post-transplantation)

Case 4: Graft vasculopathy resulting in amputation (11 years post-transplantation)

One- and five-year graft survival for hand transplant recipients recorded in the registry were 87% and 72% respectively. A total of nine hand transplants were removed in Western countries: three for reasons of chronic rejection, four because of vascular complications or sepsis in the early period following surgery, and two for other reasons:

• Simultaneous face and bilateral hand transplant: hand removed due to bacterial infection and bleeding (45 days post-transplantation)
• Simultaneous face and bilateral hand transplant: bilateral hand removal due to sepsis and necrosis (5 days post-transplant)
• Bilateral hand transplant: hand removed due to necrosis of distal phalanges (15 days post-transplantation)
• Single hand transplant: hand removed due to poor vascularisation (3 days post-transplantation)
• Single hand transplant: hand removed due to the non-compliance of the patient (29 months post-transplantation)
• Single hand transplant: hand removed due to intimal hyperplasia (275 days post-transplantation)

A total of three recipients of hand transplants recorded in the registry have died: one simultaneous face and bilateral hand transplants recipient from cerebral anoxia on day 65 post-transplant; one bilateral arm recipient from pulmonary oedema and congestive heart failure on day one; one patient from sepsis on day 101 post-transplant.

The average age of face transplant recipients recorded in the IRHCTT between 1998 and 2014 was 35 years (range 19 to 59). Cause of disfiguration was trauma in 12 cases, congenital malformation in 2 cases, tumour/malformation in 2 cases, and burns in 7 cases. Three had blindness, 14 had impaired or no swallowing function, 10 required a feeding tube or enteral tube, 18 had slurred or unintelligible speech, and 16 had a tracheostomy. Average cold ischaemia time was 2 hours (range 0 to 6). Patient survival at 1 and 5 years was 96% and 87% respectively. A total of three recipients died post-transplant: one simultaneous face and bilateral hand transplant recipient from cerebral anoxia on day 65 post-transplant (as above); one from pharyngo-laryngeal neoplasia 3 years post-transplant; and one patient from China died 2 years after transplantation (no details available).

International outcomes of hand transplantation as reported by the IRHCTT highlight two principal causes of graft loss: (i) vascular complications in the early post-transplant phase or sepsis (strong lymphocyte depletion); or (ii) non-compliance, or acute rejection that is not reported or not adequately managed. The high rate of acute rejection episodes does not appear to influence graft survival, however, if treated promptly. Again, this highlights the importance of recipient selection. Yet candidates presenting for VCA in different countries are not a homogenous group – the reasons for the original amputation in each case are widely variable – and this limits the ability to extrapolate outcomes from one setting or one case to set guidelines in another, and makes the development of international consensus guidelines on eligibility very difficult. Australia’s first hand transplant was performed in a quadramembranal amputee resulting from sepsis (meningoceoccus), however this is not a case that is broadly representative of the international experience. Poland, for example, has never seen this type of case – presumably because health system factors make death a more likely outcome of meningococcal septicaemia – instead the majority of hand transplant recipients in this context are young manual farm workers who have experienced traumatic amputation(s). Further, it may also be that strict guidelines are not appropriate, as the evidence does not yet exist in many areas to know what the appropriate guidelines should be.
REFERENCES


Review of Eligibility and Allocation Protocols in Deceased Donor Transplantation


71. Levertransplasjoner i Norge gjennom 25 år. 2014 Jul 8;1–6.


Review of Eligibility and Allocation Protocols in Deceased Donor Transplantation


Review of Eligibility and Allocation Protocols in Deceased Donor Transplantation


APPENDIX A

Review of international deceased donor kidney allocation policies

United States

In 2013, the Organ Procurement and Transplantation Network (OPTN) approved a new national Kidney Allocation System based on the kidney donor profile index (KDPI). Details of the new United States Kidney Allocation System are given in APPENDIX B.

The existing system in the United States (as of October 2014) categorises donors into six mutually exclusive groups: standard criteria donors (SCD) younger than 35 years, SCD >=35 years, donors after circulatory death (DCD) younger than 35 years, DCD >=35 years, expanded criteria donors (ECD), and ECDs who are also DCDs. Separate allocation algorithms are run for each donor category. Allocation priority is given to candidates listed for simultaneous kidney and non-kidney transplants; second, allocation priority is given to candidates with zero antigen mismatch; third, allocation follows a geographic sequence. Kidneys are offered first to local candidates (within the donor service area), then within the region, then nationally. In the case of an SCD <35 years, after allocation for simultaneous kidney and non kidney transplant, kidneys are offered to ABO blood group identical candidates according to the following sequence:

<table>
<thead>
<tr>
<th>Level</th>
<th>Location</th>
<th>Match type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Donor hospital's DSA</td>
<td>Zero ABDR mismatch and blood type identical to donor</td>
</tr>
<tr>
<td>2</td>
<td>Any OPOs owed at least 2 payback kidneys</td>
<td>Zero ABDR mismatch, 80%-100% cPRA, and blood type identical to donor</td>
</tr>
<tr>
<td>3</td>
<td>Donor hospital's region</td>
<td>Zero ABDR mismatch, 80%-100% cPRA, and blood type identical to donor</td>
</tr>
<tr>
<td>4</td>
<td>Nation</td>
<td>Zero ABDR mismatch, 80%-100% cPRA, and blood type identical to donor</td>
</tr>
<tr>
<td>5</td>
<td>Any OPO's owed at least 2 payback kidneys</td>
<td>Zero ABDR mismatch, younger than 18 years at time of match, cPRA &lt;80% and a blood type identical with the donor</td>
</tr>
<tr>
<td>6</td>
<td>Donor hospital's region</td>
<td>Zero ABDR mismatch, younger than 18 years at time of match, cPRA &lt;80% and a blood type identical with the donor</td>
</tr>
<tr>
<td>7</td>
<td>Nation</td>
<td>Zero ABDR mismatch, younger than 18 years at time of match, cPRA &lt;80% and a blood type identical with the donor</td>
</tr>
<tr>
<td>8</td>
<td>Any OPO's owed at least 2 payback kidneys</td>
<td>Zero ABDR mismatch, cPRA &gt;=20% but &lt;80%, and a blood type identical with the donor</td>
</tr>
<tr>
<td>9</td>
<td>Donor hospital's region</td>
<td>Zero ABDR mismatch, cPRA &gt;=20% but &lt;80%, and a blood type identical with the donor</td>
</tr>
<tr>
<td>10</td>
<td>Nation</td>
<td>Zero ABDR mismatch, cPRA &gt;=20% but &lt;80%, and a blood type identical with the donor</td>
</tr>
</tbody>
</table>

Zero antigen-mismatched kidneys are then allocated to ABO compatible candidates following the same sequence as above.

1 The KDPI is derived from the KDRI, and expresses the quality of a given donor kidney relative to other donors. A donor with a KDPI of 90% has a KDRI higher than 90% of donor from a given reference population (http://optn.transplant.hrsa.gov/ContentDocuments/Guide_to_Calculating_Interpreting_KDPI.pdf)
Table 16: Comparison of kidney allocation policies under the current OPTN system, and under the new Kidney Allocation System (36).

<table>
<thead>
<tr>
<th>Policy</th>
<th>Current system</th>
<th>New system</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCD allocation (defined as KDPI &lt;=0.85 under the new policy)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DCD allocation</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>ECD allocation (defined as KDPI &gt;0.85 for new policy)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Payback system</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Waiting time since listing</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Waiting time from dialysis initiation</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Waiting time points based on fractional years</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>A2/A2B blood type donor to B candidates as priority</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Classification for highest scoring cPRA</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Paediatric candidates cannot receive non-zero mismatch ECD offers</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Longevity matching (top 20th percentile survivors first offered kidneys with KDPI&lt;0.20)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Share KDPI&lt;0.35 kidneys paediatric priority (donor age &lt;35 current policy)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Priority points for cPRA&gt;19%</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Priority points for cPRA&gt;79%</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>National priority sharing for cPRA 100%, regional priority sharing for cPRA 99%, local priority for cPRA 98%</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Regional sharing for marginal kidneys (KDPI&gt;0.85)</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Source: http://optn.transplant.hrsa.gov/ContentDocuments/OPTN_Policies.pdf#nameddest=Policy_08

United Kingdom

All kidneys from brain death donors (DBD) are allocated by a computer algorithm that assigns one of 5 tiers:

A: Zero mismatched paediatric patients – highly sensitised* or HLA-DR homozygous
B: Zero mismatched paediatric patients – others
C: Zero mismatched adult patients – highly sensitised* or HLA-DR homozygous
D: Zero mismatched adult patients – others; favourably matched paediatric patients (100, 010, 110 mismatches)
E: All other eligible patients

*<sup>c</sup>PRA >=85% (based on a comparison with a pool of 10,000 donor HLA types)

Within tiers A and B, paediatric patients are prioritized according to waiting time. Within tiers C, D and E, patients are assigned points based on waiting time, HLA match combined with age, donor-recipient age difference, location of patient relative to donor, HLA-DR homozygosity, HLA-B homozygosity, blood group match.

Kidney offers continue in the order specified until 20 hours of cold ischaemia time have been accrued, at which point the centre holding the kidney can use the kidney for their patient of choice. Alternatively, the kidney will be offered back to the designated local transplant centre if not required for use at the receiving centre. When selecting a patient of their own choice, a
centre may, in exceptional circumstances, select a patient with a level 4 HLA mismatch (up to 2 HLA-DR mismatches and 2 HLA-B mismatches) or a patient who falls outside of the specified blood group matching criteria.


**Eurotransplant**

Within the Eurotransplant system, priority in kidney allocation is determined based on medical urgency, %PRA, HLA-A, B-, and DR- match, ABO blood group rules, waiting time, and donor region. Potential recipients are ranked by a point score system: the candidate with the highest score receives the first offer, with all following offers made in descending order. Simultaneous transplants of a kidney and non-kidney organ have priority over all categories of kidney-only transplants.

In addition to the general Eurotransplant Kidney Allocation Scheme (ETKAS), two alternative programs exist: the Acceptable Mismatch (AM) program, which allocates organs to recipients who are immunologically compromised because of current or historical HLA-sensitization, and the Eurotransplant Senior Program (ESP), which allocates kidneys from deceased donors >=65 years to recipients >=65 years without the use of donor HLA typing.

Eurotransplant has three separate allocation algorithms, depending on donor age:

**Donors <16 years:**
1. To AM program recipients (paediatric and adult);
2. To zero ABDR mismatch recipients (paediatric and adult): in the case of a fully homozygous donor, recipients are ranked from fully homozygous to fully heterozygous. Within each group recipients are ranked according to point score;
3. Recipients with paediatric status, ranked according to their point score;
4. All other highly sensitised, sensitised, transplantable and high urgency recipients ranked according to point score.

**Donors >=16 and <65 years:**
1. To AM program recipients;
2. To zero ABDR mismatch recipients: in the case of a fully homozygous donor, recipients are ranked from fully homozygous to fully heterozygous. Within each group recipients are ranked according to point score;
3. All other highly sensitised, sensitised, transplantable and high urgency recipients ranked according to point score.

**Donors >=65 years:**
1. To recipients aged >=65 years (without HLA matching);
2. Then according to the standard ETKAS scheme after reporting of HLA typing.

Catalonia

There are 26 organ procurement hospitals in Catalonia, and 8 organ transplant hospitals. There is only one histocompatibility lab - at Hospital Clinic - and this lab manages the regional kidney transplant waiting list for Catalonia. Organs retrieved within the 8 transplant hospitals are offered first to the waiting list of the centre at which they are retrieved, with exceptions; organs retrieved and other retrieval centres are allocated to the regional list. Transplant centres allocate deceased donor organs retrieved at their centre to recipients on their own waiting list first, and centres manage their own transplant waiting list. Currently, kidneys are allocated according to blood group compatibility, age, weight, waiting time/time on dialysis, HLA compatibility, and sensitisation. Two groups of candidates are prioritised above all – sensitised patients and paediatric patients. The current kidney allocation system age-matches donors and recipients as follows: (i) old for old - kidneys from donors aged 65 and older are allocated to recipients aged 65 and older, (ii) young for young - kidneys from donors aged less than 40 years are allocated to recipients less than 40 years, (iii) all others- kidneys from donors between 40 and 65 years are age matched to recipients within 10 years of age, however sensitised patients are matched within 30 years of age.

There are three priority categories, for which regional then national sharing occurs automatically:

1. Paediatric donor organs are offered to paediatric recipients within Catalonia first, then the rest of Spain;
2. Simultaneous kidney pancreas candidates (to compensate for the loss of good kidney donors through SPK, a payback system is in place whereby transplant centres are compensated with a young donor kidney. Difficulties with the payback system have led to the introduction of a new quota-based system, where there is a fixed number of SPK donors per annum, calculated according to the capacity to generate young donors);
3. Sensitised patients (defined as a PRA >80%).

In 2014, a new allocation policy will be introduced based on priority scoring. This new policy is intended to create uniform opportunities for transplantation for all candidates, regardless of the centre at which they are waitlisted (it is only possible to be waitlisted at one centre). Under the new system, allocation decisions will be made in the following order:

1. ABO group;
2. Regional priorities (paediatric, combined, sensitised);
3. Only one kidney is shared, the other is retained for use by the transplant center (if applicable);
4. Allocation according to candidate score, which is derived from waiting time, HLA match and age combined, donor-recipient age difference, location of patient relative to donor, HLA-DR homozygosity, HLA-B homosygosity, blood group match (score applied both regionally and within the center).

The new allocation score adopted by OCATT is based on the kidney allocation policy of the UK NHSBT. In adapting this policy, two major changes have been made: (i) double
weighting will be given to HLA match, and (ii) whereas the UK policy gives additional priority to HLA-matched candidates under 55 years, the Catalan policy gives priority to HLA-matched candidates under 65 years. In addition, the OCATT policy considers a valid difference in age between donor and recipient to be a maximum of 15 years (or 30 years if the recipient is highly sensitised). Paediatric priority is retained in the new OCATT system: organs from donors younger than 40 years are offered first to paediatric candidates.

**Table 17:** Comparison of the points based allocation system being implemented in Catalonia, and the system of the UK NHSBT.

<table>
<thead>
<tr>
<th></th>
<th>UK Model</th>
<th>Catalan Model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HLA Incompatibility and age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>$3500/(1+(age/55)^3)$</td>
<td>$7000/(1+(age/65)^3)$</td>
</tr>
<tr>
<td>Level 2</td>
<td>$2000/(1+(age/55)^3)$</td>
<td>$4000/(1+(age/65)^3)$</td>
</tr>
<tr>
<td>Level 3</td>
<td>$500/(1+(age/55)^3)$</td>
<td>$1000/(1+(age/65)^3)$</td>
</tr>
<tr>
<td>Level 4</td>
<td>$250/(1+(age/55)^3)$</td>
<td>$500/(1+(age/65)^3)$</td>
</tr>
<tr>
<td><strong>Waiting time</strong></td>
<td>1 point / 1 Dialysis day</td>
<td></td>
</tr>
<tr>
<td><strong>D-R age difference</strong></td>
<td>-1/2 (Donor age – Recipient age)^2</td>
<td></td>
</tr>
<tr>
<td><strong>Age difference Limit</strong></td>
<td>15 years non Hyper immunized R</td>
<td>30 years Hyper immunized R</td>
</tr>
<tr>
<td><strong>Antibodies Rate</strong></td>
<td>(exp(3.5 (PRA/100))-1)117,1456753</td>
<td></td>
</tr>
<tr>
<td><strong>HLA-DR Homozygote</strong></td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td><strong>HLA- B Homozygote</strong></td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td><strong>Recipients blood group B with donor blood group 0</strong></td>
<td>- 1000</td>
<td></td>
</tr>
</tbody>
</table>

Source:

**Norway**

In Norway, a single transplant centre (Oslo University Hospital) services the whole country. Waiting time is given primary emphasis in the allocation of kidneys; however, age matching is always considered on a case-by-case basis with a general rule that kidneys should not be matched beyond a 20-year age difference. Allocation decisions are made based on the following factors, in order of consideration:

1. Waiting time;
2. Age match (assessed on a case by case basis, but a general rule that kidneys should be matched within 20 years of age, particularly in the case of older donors to younger recipients);
3. HLA match;
4. BMI of the recipient (the allocation of marginal kidneys to patients with a large BMI is avoided where possible).
Norway is part of the Scandiatransplant association. By HLA compatibility, at least one kidney per deceased kidney donor must be offered to patients on the Scandiatransplant waiting list (assuming both kidneys are eligible for transplantation) according to the following rules in order of priority:

1. Highly sensitised patients (PRA >=80%) who are HLA-A, B and DR compatible with the donor.
2. Patients with STAMP-status when all donor HLA-A, A, C, DR and DQ antigens are either shared with the recipient or are among those defined as acceptable.
3. Sensitised patients (PRA>=10% but below 80%) who are HLA-A, B, DR compatible with the donor.
4. If the donor is <40 years of age, at least one kidney is offered to patients <16 years of age (counted from time of registration), if there is HLA-DR compatibility and not more than two HLA-A/B mismatches.
5. Patients who are HLA-A, B, DR compatible with the donor unless the proposed recipient is >30 years older than the donor.

International comparison of specific policies in kidney allocation

Table 18: HLA-matching policies

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>At the national level, points are awarded to a candidate based on the number of HLA mismatches with the donor in combination with peak PRA value as follows:</td>
</tr>
<tr>
<td></td>
<td>• 60,000,000 points if 0 HLA mismatches, peak PRA &gt;=50%</td>
</tr>
<tr>
<td></td>
<td>• 59,000,000 points if 1 HLA mismatch, peak PRA &gt;80%</td>
</tr>
<tr>
<td></td>
<td>• 58,000,000 points if 2 HLA mismatches, peak PRA &gt;80%</td>
</tr>
<tr>
<td></td>
<td>• 57,000,000 points if 0 HLA mismatches, peak PRA &lt;50%</td>
</tr>
<tr>
<td></td>
<td>• 56,000,000 points if 0 HLA-DR mismatches, 1 mismatch at HLA-A or HLA-B, peak PRA &lt;=80%, centre credit difference &lt;=-3</td>
</tr>
<tr>
<td></td>
<td>• 55,000,000 points if 0 HLA-DR mismatches, 2 mismatch at HLA-A or HLA-B, peak PRA &lt;=80%, centre credit difference &lt;=-6</td>
</tr>
<tr>
<td></td>
<td>• 54,000,000 points when score is null and centre credit difference &lt;=-20</td>
</tr>
<tr>
<td></td>
<td>If total score &lt;54,000,000 (including paediatric bonus, centre credit, and bonus for recipient at the same centre as the donor), then the relevant state-based algorithm applies.</td>
</tr>
<tr>
<td></td>
<td>Each of the state-based algorithms assigns a base score for a 0 HLA mismatch, from which a set number of points for each HLA-DR, -A or -B mismatch is deducted. The state-based algorithms take into account HLA match, paediatric status and waiting time, with varying emphasis on HLA match versus waiting time.</td>
</tr>
<tr>
<td></td>
<td>In Queensland and South Australia, if there is nobody on the waiting list who is well-matched with the donor then the National Organ Matching System (NOMS) ignores HLA match and produces a list of ABO compatible patients, in order of who has been on dialysis the longest. Western Australia gives considerable emphasis to waiting time, so that candidates with uncommon tissue types will receive priority above those with a better matched kidney.</td>
</tr>
<tr>
<td>United States</td>
<td>The OPTN policy assigns priority points for HLA matching based on the HLA-DR loci only. HLA-B matching historically contributed to racial disparities in access to deceased donor kidney transplants in the United States, and the allocation system was revised in 2033 to eliminate priority for HLA-B similarity.</td>
</tr>
<tr>
<td>(OPTN)</td>
<td>Points will be assigned to a candidate based on the number of mismatches between the candidate’s antigens and the donor’s antigens at the DR locus. Quality of match points is assigned as follows:</td>
</tr>
<tr>
<td></td>
<td>– 2 points if there are no DR mismatches</td>
</tr>
<tr>
<td></td>
<td>– 1 point if there is 1 DR mismatch</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Patients with HLA type that are not compatible with the donor’s HLA type are not eligible to receive that donor’s organs. Recipient antibodies reported at the HLA-A, B, C, DR and DQ loci are considered. However, the HLA match between donor and recipient is determined on the basis of the HLA-A, B and DR loci only.</td>
</tr>
<tr>
<td>(NHSBT)</td>
<td>The numbers of unique, broad level donor antigens not present in the recipient are counted to determine the HLA mismatch level upon which points are based. This is done on the basis of defaulting rare HLA specificities to more common equivalents, so that patients with rare tissue types match with more donors. The defaults are applied as part of the NHSBT allocation algorithm: should a donor with the same rare specificity become available, they will be matched with the recipient with that rare tissue type.</td>
</tr>
<tr>
<td></td>
<td>Points for allocation assigned as follows:</td>
</tr>
<tr>
<td></td>
<td>3500 points/(1+(age/55)^2) = Zero HLA mismatch (adult) or favourable mismatch (paediatric; no DR mismatch and no more than one B mismatch)</td>
</tr>
<tr>
<td></td>
<td>2000 points/(1+(age/55)^2) = no DR mismatch and no more than one B mismatch (excluding paediatric patients)</td>
</tr>
</tbody>
</table>
500 points/(1+(age/55)) = no DR mismatch and up to two B mismatches OR 1 DR mismatch and no more than 1 B mismatch

500 points allocated for HLA-DR homozygous patients (where HLA level>1)
100 points allocated for all HLA-B homozygous patients (where HLA level >1)

**Eurotransplant**

The HLA match program considers the HLA-A, B- and DR loci only. The HLA-A and –B typing of the donor and recipients is converted to a match HLA-typing by the HLA broad match phenotype reduction program. If present, split HLA-antigens are converted to their respective broad HLA antigen.

The HLA mismatch program calculates HLA-antigen mismatches for HLA-A and –B based on broad antigens only. HLA mismatches for HLA-DR are calculated based on split HLA antigens. The converted HLA-typing is only accepted by the HLA-mismatch calculation program in the presence of at least 1 HLA-antigen on each of the three HLA loci (ABDR). In the case that only 1 HLA-antigen is identified, the donor or recipient is assumed to be homozygous for that locus; if two identical broad HLA-A, B- or DR antigens are identified, the presence of only one antigen will be assumed for the calculation and only 1 mismatch can occur at that locus. Points are assigned for matching at the HLA-A, B- and DR loci as follows:

\[
\text{Points} = 400 \times \left[1 - \left(\frac{\sum \text{broad HLA-A, B- split HLA-DR mismatches}}{6}\right)\right]
\]

<table>
<thead>
<tr>
<th>Number of mismatches</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>400.00</td>
</tr>
<tr>
<td>1</td>
<td>333.33</td>
</tr>
<tr>
<td>2</td>
<td>266.67</td>
</tr>
<tr>
<td>3</td>
<td>200.00</td>
</tr>
<tr>
<td>4</td>
<td>133.33</td>
</tr>
<tr>
<td>5</td>
<td>66.67</td>
</tr>
</tbody>
</table>

The points for HLA-antigen mismatches are doubled for paediatric candidates. In the case of a fully homozygous donor, 0 ABDR mismatch candidates are ranked from fully homozygous to fully heterozygous, then according to point score. Candidates with outdated screening (>=150 days) are not selected in match-runs.

**Norway**

Waiting list seniority takes priority over HLA-match or DR-match in kidney allocation. However, among patients with the longest waiting time, within s seniority frame of 6-12 months the HLA-DR-compatible recipient (then the HLA-A/B compatible recipient) is given priority in allocation (with age and weight matching also taken into account). The following general rules apply:

- After >12 months on the waiting list, recipients are selected in relation to waiting time (and, second, by HLA match)
- Zero HLA mismatch takes priority over the previous rule (with a latency of >12 months)
- With <12 months on the waiting list, recipients are selected on the basis of HLA-match (primarily DR)
- When the donor is >60 years, a match is sought within a 20 year age range of the donor

In the case of retransplants, HLA mismaches are avoided.

For HLA-DR homozygous recipients, given that they are disadvantaged on the waiting list the following rules apply:

- If the donor has only one DR antigen, DR-compatible recipients with only one DR antigen are prioritized. But DR-compatible with PRA+ and negative cross match pairs should still go ahead;
- Among one DR mismatch recipients, priority should be given to those with only one DR antigen.
Table 19: Blood group compatibility rules

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>National blood type compatible rules are:</td>
</tr>
<tr>
<td></td>
<td>A&gt;A/AB</td>
</tr>
<tr>
<td></td>
<td>AB&gt;AB</td>
</tr>
<tr>
<td></td>
<td>B&gt;B/AB</td>
</tr>
<tr>
<td></td>
<td>O&gt;O</td>
</tr>
<tr>
<td></td>
<td>States however vary in their application of blood group compatibility rules. South Australia permits O donors to be transplanted into A, AB and B recipients, Queensland and Western Australia permit O to B transplants, and Western Australia additionally permits O to AB.</td>
</tr>
<tr>
<td>United States (OPTN)</td>
<td>Blood type O kidneys must be transplanted only into type O candidates, except in the case of zero antigen mismatched candidates. Blood type B kidneys must be transplanted only into type B candidates, except in the case of zero antigen mismatched candidates.</td>
</tr>
<tr>
<td>United Kingdom (NHSBT)</td>
<td>Candidates with blood groups incompatible with the donor are not eligible to receive that donor’s organs. Restrictions on blood group-compatible (but not identical) as follows:</td>
</tr>
<tr>
<td></td>
<td>• Donor O, recipient A/AB: zero mismatched, highly sensitised OR zero HLA-DR homozygous adult OR zero mismatched paediatric patients only;</td>
</tr>
<tr>
<td></td>
<td>• Donor B, recipient AB: zero mismatched, highly sensitised OR a zero HLA-DR homozygous match with the donor OR zero mismatched paediatric patients only;</td>
</tr>
<tr>
<td></td>
<td>• Donor A, recipient B: incompatible except that kidneys from donors of subtype A2 can be allocated to patients of blood groups B as part of a pilot scheme in London.</td>
</tr>
<tr>
<td></td>
<td>1500 points are allocated for blood group B patients when the donor is group if A (provided that their waiting time exceeds 730 days) For non-sensitised adult patients, and paediatric patients with no DR mismatch and no more than one B mismatch, 1000 points are allocated for blood group B patients when the donor group is O.</td>
</tr>
<tr>
<td>Eurotransplant</td>
<td>For the ETKAS and ESP programs, ABO-incompatible kidney transplants from deceased donors are not allowed. For the Acceptable Mismatch program, the following blood group rules apply:</td>
</tr>
<tr>
<td></td>
<td>A &gt; A/AB</td>
</tr>
<tr>
<td></td>
<td>B &gt; B/AB</td>
</tr>
<tr>
<td></td>
<td>AB &gt; AB</td>
</tr>
<tr>
<td></td>
<td>O &gt; A/B/AB/AB/O</td>
</tr>
<tr>
<td>Norway</td>
<td>ABO compatibility if required. Kidneys from donors with blood group O should be only given to recipients with blood group O or B.</td>
</tr>
</tbody>
</table>
### Table 20: Waiting time and priority for transplantation

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>The national kidney allocation algorithm assigns 1 point for every additional month of waiting time. At the national level, therefore, waiting time acts as a tie-breaker between candidates with similar peak PRA, who are a similar HLA match with a given donor. At the state level, allocation rules are that at least 30% of all kidneys are allocated according to waiting time (rather than HLA matching). This is achieved differently in different states, but essentially points are subtracted for every HLA mismatch for a given donor recipient pair, and added for every additional month of waiting time. Thus well-matched kidneys will still go to local well-matched recipients, but as waiting time increases for a given candidate they will receive an increasing number of offers, regardless of HLA match.</td>
</tr>
<tr>
<td>United States (OPTN)</td>
<td>Except for candidates &lt;18 years, waiting time begins from the time a candidate listed for an isolated kidney or simultaneous kidney pancreas transplant has a measured or estimated creatinine clearance or eGFR is &lt;=20 ml/min/1.73m², or from initiation of maintenance dialysis. For paediatric candidates (&lt;18 years), waiting time begins when the candidate is placed on the waiting list. All candidates, regardless of age, continue to accrue waiting time while registered on the waiting list as inactive. Once waiting time begins to accrue, one point will be assigned to the candidate waiting for the longest period, with fractions of points being assigned proportionately to all other candidates according to their relative waiting time. For each full year of waiting time a candidate accrues, an additional 1 point will be assigned to that candidate.</td>
</tr>
<tr>
<td>United Kingdom (NHSBT)</td>
<td>Waiting time (days accrued) is determined from the date of first active listing for a graft. Each day on the list accrues 1 point, including any days of temporary suspension from the list. Waiting time starts at 0 on the day they are made active on the waiting list, with the exception of patients whose previous graft failed within 180 days of transplantation. In this case, waiting time starts from the first day of the failed transplant. When a patient is removed from the list, their waiting time is lost.</td>
</tr>
<tr>
<td>Catalonia (OCATT)</td>
<td>1 point awarded per day on dialysis.</td>
</tr>
<tr>
<td>Eurotransplant</td>
<td>Waiting time is calculated from the commencement date of maintenance dialysis (defined as uninterrupted dialysis for &gt;=90 days), or date of reinstatement of maintenance dialysis after previous kidney transplantation. In eligible cases, waiting time includes the waiting time accumulated before transplantation of a graft that failed within 90 days of transplantation. Points = 33.3 per year of waiting time (0.091 points per day) There is no limit to the time accumulated on the waiting list, thus waiting points are accumulated without restriction. Preemptive recipients can be registered on the waiting list as an active high urgency candidate, but receive no points for waiting time.</td>
</tr>
<tr>
<td>Norway</td>
<td>Waiting time is given primary emphasis in the allocation of deceased donor kidneys.</td>
</tr>
</tbody>
</table>
### Table 21: Priority for highly sensitised patients

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>See policy for HLA-matching. The National Interstate Exchange Program gives national allocation priority to candidates with peak PRA &gt;50% (and only 0,1 or 2 HLA mismatches with the donor).</td>
</tr>
<tr>
<td>United States (OPTN)</td>
<td>Current system: Sensitised candidates (calculated PRA &gt;=80%) are assigned 4 points. New system: A new priority point scale from 0-202 will be awarded based on the cPRA. This scale is calculated based on the inverse probability of receiving a kidney offer (see APPENDIX C).</td>
</tr>
</tbody>
</table>
| United Kingdom (NHSBT)     | Highly sensitised patients defined as cPRA >=85% (based on comparison with pool of 10,000 donor HLA types on national database). Offers of kidneys are made as follows:  
- Zero HLA mismatch: All highly sensitised patients;  
- No DR and no more than two HLA-B mismatches, or one DR mismatch and no more than one HLA-B mismatch (100, 010, 110, 200 or 210 mismatches): All local centre highly sensitised patients and all other highly sensitised patients where all antibody specificities have been identified (residual sensitisation level of zero);  
- All other mismatches: No kidneys are offered for any highly sensitised patients. |
| Eurotransplant             | Highly sensitised patients defined as PRA >=85%; moderately sensitised patients defined as PRA <6% and <85%. Eurotransplant’s Acceptable Mismatch (AM) program aims to allocation organs to HLA-sensitised recipients (PRA >=85%). The program identified ABDR mismatches not resulting in a positive cross-match by checking against which ABDR antigens the recipient has not yet reacted to with allo-antibodies. Recipients selected by this program have priority over ETKAS-selected recipients (within the AM program, recipients awaiting combined kidney-non-renal transplants have priority over kidney-only candidates). All eligible AM-recipients are presented to and discussed with an ETRL immunologist prior to a kidney offer (see APPENDIX C). |
| Scandiatransplant          | Highly sensitised patients defined as PRA >=80%  
Highly sensitised patients who are HLA-A, B, and DR compatible with the donor have the highest priority.  
Patients with STAMP status (see APPENDIX C) when all HLA-A, -B, -C, -DR, -DQ antigens are either shared with the recipient or among those defined as acceptable have the second highest priority.  
Sensitised patients (PRA >=10% but <80%) who are HLA-A, B, and DR compatible with the donor also have priority under the Scandiatransplant rules of exchange. |
### Table 22: Role of age in assigning priority for transplantation

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Paediatric bonus only (see paediatric priority policy).</td>
</tr>
<tr>
<td>United States (OPTN)</td>
<td>Under the new kidney allocation system based on longevity matching, priority is assigned according to the biological effect of recipient age (in combination with time on dialysis, prior organ transplant and diabetes status). The 20% of kidneys with the longest estimated function will be allocated to the group of candidates with the longest estimated survival post-transplant. Approximately 97% of candidates aged 18-25 would fall into the top 20% of candidates for longevity. Kidneys with a KDPI &gt;85% will be allocated based on waiting time alone to patients who consent to receiving a higher-risk kidney (see APPENDIX B).</td>
</tr>
<tr>
<td>United Kingdom (NHSBT)</td>
<td>Points awarded for HLA match and donor-recipient age difference combined. Points are defined as: 3500 points/(1+(age/55)^5) for zero HLA mismatch patients and favourably matched paediatric patients (100,010, 110 mismatches). 2000 points/(1+(age/55)^5) for 0 HLA-DR and 0/1 HLA-B mismatch patients (excluding favourably matched paediatric patients) 500 points/(1+(age/55)^5) for 0 HLA-DR and 2 HLA-B or 1 HLA-DR and 0/1 HLA-B mismatch patients. In addition, points are awarded for age difference as follows: (-\frac{1}{2}(\text{donor-recipient age difference})^2)</td>
</tr>
<tr>
<td>Catalonia (OCATT)</td>
<td>Points awarded for HLA match and donor-recipient age difference combined. Points are defined as: 7000 points/(1+(age/65)^5) for zero HLA mismatch patients and favourably matched paediatric patients (100,010, 110 mismatches). 4000 points/(1+(age/65)^5) for 0 HLA-DR and 0/1 HLA-B mismatch patients (excluding favourably matched paediatric patients) 1000 points/(1+(age/65)^5) for 0 HLA-DR and 2 HLA-B or 1 HLA-DR and 0/1 HLA-B mismatch patients.</td>
</tr>
<tr>
<td>Eurotransplant</td>
<td>The Eurotransplant Senior Program allocated kidneys from deceased donors &gt;=65 years old to recipients &gt;=65 years without the use of HLA typing. Cold ischaemia time is kept as short as possible.</td>
</tr>
<tr>
<td>Norway</td>
<td>When the donor is &gt;60 years, a match is sought within a 20-year age range of the donor. As a general rule, kidneys should be matched within 20 years of age. At least one kidney per deceased donor retrieved in Scandinavian countries must be offered for transplantation of a recipient on the Scandiatransplant waiting list. Kidneys shared through Scandiatransplant are allocated according to the following rules of candidate priority: highly sensitised &gt; STAMP-status (acceptable mismatch program) &gt; sensitised &gt; paediatric &gt; HLA compatible, &lt;=30 years older than the donor. That is, for all eligible, non-sensitised, adult patients, Scandiatransplant gives priority to patients who are no more than 30 years older than the donor.</td>
</tr>
</tbody>
</table>
### Table 23: Paediatric priority

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>A paediatric bonus is awarded at the national and state level to candidates &lt;18 years of age who commenced dialysis before age 17 and have been on dialysis for &gt;1 year. However, state policies for paediatric priority vary widely (see Section 2.2.4).</td>
</tr>
<tr>
<td>United States (OPTN)</td>
<td>Kidneys from donors &lt;35 years, that are not mandatorily shared for zero HLA mismatching, renal/non-renal organ allocation, or locally for prior living organ donors, will be offered first for transplant candidates who are &lt;18 years at time of listing, regardless of the number of points assigned to that candidate relative to candidates &gt;=18 years (with the exception of highly sensitised candidates assigned 4 points for PRA &gt;=80%). When multiple paediatric candidates are eligible for organ offers under this policy, organs will be allocated in descending point sequence. To assign priority among paediatric candidates, candidates &lt;11 years are assigned an additional point. In the case of zero mismatch with DCD donor kidneys allocated regionally or nationally, candidates &lt;11 years receive 4 additional points, and candidates 11-17 years receive 3 additional points. These points are retained until the candidate reaches 18 years of age. In the new kidney allocation system, the Share 35 policy will be replaced with a Share KDPI&lt;0.35 paediatric priority policy. Paediatric candidates will in general maintain the same priority over adult candidates.</td>
</tr>
<tr>
<td>United Kingdom (NHSBT)</td>
<td>Patients aged &lt;18 years at time of active listing will not be considered for kidneys from donors over 50 years of age. Patients registered as active on the waiting list prior to their 18th birthday but still waiting for a kidney after their 18th birthday retain their paediatric status and associated priority on the waiting list. Period of suspension from the waiting list do not affect this entitlement. For zero HLA mismatches, paediatric patients (&lt;18 years) have priority; favourably matched paediatric patients (no DR mismatch and no more than one B mismatch – 100, 010 or 119 mismatches) have priority over mismatched adults. For paediatric patients &lt;18 years at time of active listing who have a waiting time longer than two years, patients are prioritised for any compatible kidney. Additional points are allocated for favourably matched or other eligible patients, to improve their chance of being allocated a kidney. For patients waiting 2-3 years, 2500 extra points are awarded; for patients waiting longer than 3 years, 5000 points are awarded.</td>
</tr>
<tr>
<td>Eurotransplant</td>
<td>A candidate is defined as paediatric if dialysis started before the 16th birthday OR registration on the waiting list was before the 16th birthday and dialysis started before the 17th birthday OR recipient is proven to be in maturation (maturation accepted based on a request including an X-ray of the left hand, to be approved by the Eurotransplant Kidney Advisory committee: maturation is granted for 1 year from date of registration on the waiting list if the patient is not on dialysis, or until successful transplant if dialysis commences within one year of registration). Each pediatric transplant candidate is assigned a pediatric bonus of 100 points, and HLA-antigen mismatch points are doubled.</td>
</tr>
<tr>
<td>Scandiatransplant</td>
<td>Priority is given for candidates &lt;16 years for offers of kidneys from donors &lt;40 years (if there is HLA DR compatibility and no more than two HLA-A or B mismatches).</td>
</tr>
</tbody>
</table>
Table 24: Priority for combined kidney and non-kidney transplants

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Policy</th>
</tr>
</thead>
</table>
| Australia                     | Current system: when kidneys are procured for the purpose of simultaneous kidney and non-renal organ transplantation, only one of the kidneys procured must be shared as a zero ABDR mismatch. If the kidney/non-renal organ transplant is not performed, the kidney retained for that transplant must be immediately offered for zero ABDR mismatch candidates. This exception does not apply to kidney-islet transplants or kidney-pancreas transplants for zero mismatched highly sensitised candidates.
|                               | An offer of a donor kidney to a highly sensitised candidate for whom there is a zero ABDR mismatch with the donor, who is also a candidate for kidney-pancreas transplant, must be accompanied by an offer of the pancreas from the donor. |
| United States (OPTN)          | Patients requiring a simultaneous kidney pancreas transplant will be prioritised after 0 mismatched sensitised, paediatric or HLA-DR homozygous kidney only candidates.
|                               | Under the National Pancreas Allocation Scheme, pancreas transplant centres are entitled to accept just the pancreas when it is offered with a kidney – the kidney is then offered to the local kidney transplant centre and may be allocated according to the centre policy. |
| United Kingdom (NHSBT)        | Combined transplantation of a kidney and a non-renal organ are given priority over all categories of kidney-only transplants (i.e. over recipients from the acceptable mismatch and Eurotransplant Senior Program and/or those with a zero ABDR mismatch). In the case of kidney-after-liver transplant (such as in the case of hepatorenal syndrome), the recipient gets 500 extra points in the kidney allocation system during the period from 90-360 days after the liver only transplant (provided that the recipient was registered on the kidney waiting list at the time of liver transplantation and the creatinine clearance is <15 ml/min). |
| Eurotransplant                | The Eurotransplant Senior Program (ESP) allocates kidneys from deceased donors >=65 years to recipients >=65 years without the use of HLA typing. The ESP aims at a cold ischaemic period (CIP) that is as short as possible. Kidneys from an ESP donor that cannot be allocated locally or regionally are allocated through the regular kidney allocation (ETKAS) after reporting HLA typing. |

Table 25: Policies for the allocation of expanded criteria kidneys

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Policy</th>
</tr>
</thead>
</table>
| United States (OPTN)          | OPTN defines expanded criteria donors (ECDs) as donors with a relative risk of graft failure (donors older than ten years) of >1.7 based on donor age >=60 years OR donor age >=50 years and at least two of the following: cerebrovascular accident as the cause of death, history of hypertension (at any time), or creatinine >1.5 mg/dL. All other donor types are referred to as standard criteria donors (SCDs).
|                               | Consent must be obtained from candidates prior to being listed for an ECD transplant. Candidates who agree to be listed to receive an ECD kidney will also be eligible to receive a standard criteria donor kidney according to standard policies for the allocation of SCD kidneys. Patients on the ECD waiting list are assigned points for waiting time in exactly the same manner as for the SCD waiting list. In the new system, the ECD classification will be replaced by KDRI >0.85. |
| Eurotransplant                | The Eurotransplant Senior Program (ESP) allocates kidneys from deceased donors >=65 years to recipients >=65 years without the use of HLA typing. The ESP aims at a cold ischaemic period (CIP) that is as short as possible. Kidneys from an ESP donor that cannot be allocated locally or regionally are allocated through the regular kidney allocation (ETKAS) after reporting HLA typing. |
Table 26: Organ sharing and return obligations

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Policy</th>
</tr>
</thead>
</table>
between Eurotransplant countries is calculated. Points assignment is calculated relative to the balance of imports and exports and assigned only to resident recipients.

National balance points = (highest import balance - recipient country balance) x 10

i.e. recipients in countries that have a lower net inflow of kidneys compared to other ET members get extra points.

| Scandiatransplant | Kidneys exchanged between Scandinavian countries must be paid back, if possible within 6 months and by a kidney of the same blood group as the one received. The organ must be of a quality acceptable to the recipient centre. |
APPENDIX B

OPTN transition to a kidney allocation system based on longevity-matching

The current United States kidney allocation system

The current United States allocation protocol for deceased donor kidneys gives priority to prior living donors, paybacks between OPOs, and paediatric candidates (who are given first priority for kidneys from donors under 35 years). A points system assigns priority according to waiting time (1 point per year), prior sensitisation (4 points for PRA >=80%), and HLA-DR match (2 points for zero HLA-DR mismatch, 1 point for a one HLA-DR mismatch). Under the current United States deceased donor kidney allocation algorithm, 70% of standard criteria donor kidneys are allocated to HLA mismatched candidates (primarily at the local level), with 8% allocated to zero ABDR mismatched kidney or SPK candidates, and 7% to candidates awaiting a non-renal organ. Of all donated kidneys ~15% are designated as ECD and are allocated based on waiting time alone to candidates who have consented to receiving an ECD kidney in the expectation of reducing their waiting time. As the average waiting time for a kidney transplant has increased to exceed 4 years, waiting time has emerged as the principal determinant of kidney allocation under the existing system.

Critiques of the current allocation algorithm have included:

- Priority weights are non-objective, e.g. one year of waiting time is assigned the same allocation priority as one HLA-DR mismatch, or 4 points for PRA 80 and zero points for PRA 79.9;
- Allocation does not match the life expectancy of the organ to the life expectancy of the recipient, thus 10,000-15,000 years of potential future recipient survival are lost due to death with a functioning graft (Wolfe AJT 2008);
- High rates of retransplantation;
- System-wide inequities in access, in particular racial/ethnic, socioeconomic and geographical inequities in transplant rates and waiting times (the 25th percentile among adult kidney transplant programs varies from 3 to 55 months);
- Uneven access for sensitised candidates – 4 points provides a different advantage depending on your DSA’s median waiting time, and no priority is given to moderately sensitised candidates;
- Does not account for medical need for transplantation;
- Existing allocation protocols are time consuming, contributed to prolonged ischaemia time and high rates of discard;
- Waiting times for individual patients are highly unpredictable, and favour younger healthier candidates;
- By emphasising waiting time, sensitisation, and HLA match, the current system does not link access to transplantation with either progression of disease or measures of benefit (in contrast to allocation algorithms for liver, heart and lung transplantation);
- The current emphasis given to waiting time in assigning allocation priority, combined with an aging kidney transplant waiting list, has resulted in a decline in the average post-transplant lifespan of kidney transplant recipients over the past two decades.
Compared to an average estimated lifespan of 14.2 years for recipients transplanted in 1995, the estimated lifespan for recipients transplanted in 2006 was 12.7 years;

- The ECD/SCD designation does not adequately assess the relative survival potential of a given donor kidney;
- Patients with very similar medical characteristics may have very different access due to the emphasis on waiting time;
- Lastly, the current allocation system does not conform to the OPTN final rule that allocation systems must seek to achieve the best use of donated organs, be designed to avoid wasting organs, set priority rankings based on objective and measurable criteria and deemphasize waiting time.

The OPTN revision process

After the adoption of the MELD system for liver allocation, the OPTN kidney Advisory Committee began to discuss whether more a biologically-based allocation system might be feasible for kidneys. In 2003 the OPTN Kidney Committee was charged with performing a 360-degree review of the existing kidney allocation algorithm. The OPTN took the decision to have consultation sessions with various experts on the theory, philosophy and ethics of organ allocation, after which the OPTN would go into closed session to develop a new allocation system. The Kidney Allocation subcommittee heard submissions on a range of topics for 12 months (2003-2004) – such as whether certain patient groups should have protected access, equity issues, how to weight medical criteria, priority for waiting time, and options for incorporating biological matching (e.g. age matching, survival matching, life years from transplantation, etc.). There were also discussions about de-emphasising waiting time and HLA matching. Patient groups responded with concern with regards to particular groups losing their allocation privilege, and the potential for loss of hope among patient groups whose access would be reduced by a change in policy. Thus the challenge was to accommodate the concerns of these groups, maintain enough of the status quo that privileged groups would not be adversely affected, and revise the allocation system sufficiently to achieve a meaningful increase in fairness in allocation across each of the domains identified in submissions to the Kidney Allocation subcommittee.

In 2004, the Kidney Committee reported to the OPTN Board of Directors three main areas of concern with respect to the performance of the existing kidney allocation system: (i) inequity, inefficiency and suboptimal utility in allocation protocols, (ii) the supply of donor organs, and (iii) the effects of geography on allocation (i.e. disparities in access/waiting time based on area of residence). The Kidney Committee was charged with addressing the first of these points: revising the kidney allocation protocol.

There was particular concern regarding potential years of life lost from the existing donor pool, as a consequence of policies that allocated kidneys with a long potential life span to recipients that do not (due to emphasis on waiting time and, to a lesser extent, zero HLA mismatch), and geography (the fact that candidates in OPOs with a surplus of very good organs would preferentially get these organs, regardless of the case mix of their waiting list). For historical reasons, the boundaries for organ recovery are the same as the boundaries for kidney allocation, however this creates these geographical inequities. In OPOs where the waiting list is
small (perhaps artificially, through low rates of wait listing) there is less pressure to retrieve organs from older or marginal donors. The new kidney allocation system does not address geographical disparities in access (this is a future project), however it is worth noting the interaction between rates of wait listing, organ retrieval, and the performance of the allocation system.

**The transition from Life Years From Transplant to Longevity matching**

The concepts of life years from transplantation (LYFT or incremental survival) and survival matching had both initially been proposed by SRTR at the beginning of the revision process. There was debate over whether there should be a single goal in allocating donor organs: adoption of incremental years of life saved would diminish other allocation priorities. The idea of allocating all SCD organs by life years from transplant, with all ECD organs allocated according to waiting time, was proposed and initially broadly accepted but faced push-back from groups that perceived they would be potential losers in such a system. An advantage of the LYFT system over longevity matching, is that LYFT privileges vulnerability (i.e. priority is given to those with the most to gain by transplantation, who would be harmed the most by remaining on dialysis), whereas candidate vulnerability is not incorporated into longevity matching (this system instead allocates the best organs to those who would be injured the least by remaining on dialysis). Allocation of organs to those who would be harmed the most (lose the most potential life years) by not receiving a timely transplant is closest to a “fair innings” approach to resource distribution. The two alternatives advantage very different groups of people.

**The new kidney allocation system**

In June 2013, the OPTN Board of Directors approved a new kidney allocation system for the United States based on maximising the utility from each donated kidney. This system will be based on the following policies:

1. Deceased donors kidneys will be assigned a kidney donor profile index (KDPI), ranking all recovered kidneys (as opposed to transplanted kidneys) on a scale from zero to one, based on expected survival in a hypothetical “modal” recipient: the lower the numeric score, the longer the expected survival. Kidneys are then allocated within 4 bands of the KPDI - <0.2, 0.2 to <0.35, 0.35 to <0.85 and >=0.85;
2. Kidneys with a KDPI<0.2 (i.e. the kidneys with the longest survival potential), will be matched with the top 20% of candidates by estimated post transplant survival (calculated based 4 variables: on patient age, time on dialysis, prior organ transplant, and diabetes status);
3. Continuous scale of allocation priority based on PRA >20%;
4. Paediatric candidates limited to kidneys with a KPDI<0.35, and prior living donors to kidneys with a KPDI <0.85;
5. Encourage blood type A2 and A2B to type B transplants;

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1 http://optn.transplant.hrsa.gov/PublicComment/pubcommentPropSub_311.pdf
6. Waiting time calculated from earliest date of first dialysis or date of waitlist registration if eGFR \( \leq 20 \text{ ml/min} \)

7. Current priority for waiting time, HLA similarity and prior living donors are maintained.

Although age-matching of the donor to recipient (within 15 years +/-) was proposed during the development of the new kidney allocation system, explicit age-matching was ultimately impermissible on the basis of age discrimination laws. Instead, priority is assigned according to the biological effect of recipient age – in combination with time on dialysis, prior organ transplant, and diabetes status. The 20% of kidneys with the longest estimated function (relative to the national case mix) will be allocated to the group of candidates with the longest estimated survival post-transplant based on these four factors (i.e. “longevity matching”). The use of the EPTS will not change how the majority of kidney candidates are assigned priority for transplant – only those expected to benefit from the transplant the longest. Approximately 97% of candidates aged 18-25 years would fall into the top 20% of candidates for longevity, 81% of 26-35 year olds, 43.8% of 36-45 year olds, 10.1% of 46-55 year olds, and 0% from age 56 onwards. Unlike the liver allocation system or the lung allocation system, the new kidney allocation system does not give priority based on risk of death while on the waiting list.

The new kidney allocation system does away with the old classification of donor kidneys as ECD or SCD – instead the quality of the organ is reflected in the KDPI, which is a more precise indicator of expected graft years. Currently, kidneys from ECD are offered first locally and candidates who elect to receive ECD kidneys are rank ordered only according to waiting time. The goal is to expedite placement of these kidneys; however, discard rates for ECD kidneys are high and also vary widely across OPOs. Generally, OPOs with longer waiting times tend to procure and transplant more ECD kidneys than OPOs with shorter waiting times. This suggests that demand drives decision making on whether to utilise these kidneys, more so than clinical utility.

In order to improve procurement and transplantation rates for kidneys with a high KPDI, the new proposed approach is to allocate kidneys with a KDPI >85% to a combined local and regional list, making available with less cold ischemic time those kidneys that would be discarded in one OPO due to shorter candidate waiting times but utilised in a neighbouring OPO with longer waiting times. In the same way that candidates formally had to consent to being waitlisted for an ECD kidney, candidates will have to consent to being waitlisted for a KDPI >85% kidney. The KDPI>85% kidneys will also still be allocated based on waiting time alone, with the difference compared to the old system that they will be allocated regionally rather than locally to prevent unnecessary discard of marginal organs.

The current system calculates waiting time from the date of waitlisting if already on dialysis or if GFR\( \leq 20 \text{ ml/min/1.73m}^2 \). The new system will also retrospectively award waiting points for dialysis time accumulated prior to registration on the transplant waiting list, thereby shifting the emphasis to time spent with ESKD as the basis for assigning priority. This policy change is particularly relevant to minority candidates, who tend to be less likely to be listed for a kidney transplant at (or before) dialysis commencement with the consequence that – by the time they are listed and receiving waiting time priority – their disease is more advanced with additional health complications. The policy change should introduce greater equality in waiting
times. Also relevant to minority candidates is the shift in policy with respect to blood type compatibility. Blood type B is more common in minority populations, however only ~12% of deceased donors have this blood type. By permitting allocation of blood type A2/A2B donor kidneys to type B candidates, this should reduce waiting times for type B (commonly minority) candidates.

The current system has been successful in expediting transplantation for paediatric candidates by prioritising kidneys from donors younger than 35 years to candidates listed prior to their 18th birthday. The new system will achieve the same level of access by prioritizing donors with KPDI scores of <0.35 to paediatric candidates (and preventing offers of kidneys with a KPDI any higher than 0.85).

On the basis that the current system of kidney paybacks was found to be administratively challenging and unfair to candidates (by affecting all candidates in an OPO even though it was one centre that was responsible for the debt), kidney paybacks will no longer be permitted under the new system.

Caveats of the new kidney allocation system

1. The top 20% of candidates based on EPTS is determined based on national case mix, and thus the access to the highest quality kidneys will vary across OPOs.

2. The application of an EPTS threshold for access to kidneys of high quality has the effect that similar candidates are not treated similarly. EPTS is calculated based on a simplified model of post transplant survival estimated at the national level, and is insensitive to the case mix of a given OPO. The firm 20% cut-off (applied at the level of the OPO) means that an individual that has access to KPDI <0.2 kidneys in one OPO could potentially not have access to these kidneys in a different OPO, depending on the candidate case mix. For example, in a DSA where the waiting list is older and sicker, these candidates will get relatively good kidneys. In a DSA with a healthier population, there will be young, good candidates that won’t be offered the best quality kidneys. This would be compounded in a DSA with generally poor access to transplantation.

3. The same threshold problem applies for donor kidneys: what constitutes a 20th percentile organ is also calculated at the national level, and thus in one OPO only 5% of organs might be in the top 20th percentile for the country, whereas in another perhaps 40% of organs might pass the threshold. The effect is that the top 20th percentile of candidates in each OPO will be competing for an organ pool of varying size, representing a potentially widely varying proportion of organs retrieved in that OPO.

4. The second issue for the thresholds applied to the KPDI and EPTS is that there is effectively no difference between the candidate in the 20th percentile for EPTS and the candidate in the 21st percentile, but these two individuals will have access to an entirely different pool of organs. Although the EPTS is good at separating the
extremes in the candidate pool, there is no difference in the survival potential of candidates at the boundary.

5. The new system is largely the same as the old, but with allocation in bands according to organ quality. Otherwise allocation is by the same points system for candidates within each band, with the (equal) emphasis on waiting time and HLA matching. Thus the ethical problems of the old system have largely been transferred to the new.

6. The decision to go with longevity matching instead of life-years from transplant means that the new KAS system allocates organs to candidates with the least need, at the expense of those with the most need (for need defined as ability to benefit from kidney transplantation).

7. Although longevity matching yields a significant gain in life years, it does not achieve the same level of utility as allocation according to life years from transplantation.

<table>
<thead>
<tr>
<th>#</th>
<th>KDPI &lt;=20%</th>
<th>KDPI &gt;20 and &lt;35%</th>
<th>KDPI &gt;=35% and &lt;=85%</th>
<th>KDPI &gt;85%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Local, PRA 100%</td>
<td>Local, PRA 100%</td>
<td>Local, PRA 100%</td>
<td>Local, PRA 100%</td>
</tr>
<tr>
<td>2</td>
<td>Regional, PRA 100%</td>
<td>Regional, PRA 100%</td>
<td>Regional, PRA 100%</td>
<td>Regional, PRA 100%</td>
</tr>
<tr>
<td>3</td>
<td>National, PRA 100%</td>
<td>National, PRA 100%</td>
<td>National, PRA 100%</td>
<td>National, PRA 100%</td>
</tr>
<tr>
<td>4</td>
<td>Local, PRA 99%</td>
<td>Local, PRA 99%</td>
<td>Local, PRA 99%</td>
<td>Local, PRA 99%</td>
</tr>
<tr>
<td>5</td>
<td>Regional, PRA 99%</td>
<td>Regional, PRA 99%</td>
<td>Regional, PRA 99%</td>
<td>Regional, PRA 99%</td>
</tr>
<tr>
<td>6</td>
<td>Local, PRA 98%</td>
<td>Local, PRA 98%</td>
<td>Local, PRA 98%</td>
<td>Local, PRA 98%</td>
</tr>
<tr>
<td>7</td>
<td>Zero mismatch, top 20% EPTS</td>
<td>Zero mismatch</td>
<td>Zero mismatch</td>
<td>Zero mismatch</td>
</tr>
<tr>
<td>8</td>
<td>Prior living donor</td>
<td>Prior living donor</td>
<td>Prior living donor</td>
<td>Local + Regional</td>
</tr>
<tr>
<td>9</td>
<td>Local, paediatric</td>
<td>Local, paediatric</td>
<td>Local</td>
<td>National</td>
</tr>
<tr>
<td>10</td>
<td>Local, top 20% EPTS</td>
<td>Local, adult</td>
<td>Regional</td>
<td>Limited to adult candidates</td>
</tr>
<tr>
<td>11</td>
<td>Zero mismatch (all)</td>
<td>Regional paediatric</td>
<td>National</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Local (all)</td>
<td>Regional, adult</td>
<td>No pediatric priority</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Regional, pediatric</td>
<td>National, paediatric</td>
<td>National</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Regional, top 20% EPTS</td>
<td>National, adult</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Regional (all)</td>
<td>No priority for top 20% EPTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>National, paediatric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>National, top 20% EPTS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>National (all)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX C

Priority for sensitised patients in kidney allocation protocols

*Eurotransplant*

The Eurotransplant Acceptable Mismatch program gives the highest priority to eligible sensitised patients as soon as a donor becomes available who is compatible with the patient’s antibody profile. HLAMatchmaker, a computer program that defines HLA antigens as a string of potential antibody epitopes, is used for the identification of potential acceptable HLA mismatches in highly sensitised patients. In the case of no or only a few epitope mismatches, the chance of positive cross-match is low. In contrast, standard HLA matching at the broad antigen level will indicate a positive cross-match even though the donor and recipient are compatible at the epitope level. All identified acceptable HLA mismatches are added to the HLA phenotype of the recipient.

To be eligible to participate in the Eurotransplant Acceptable Mismatch program, a PRA >=85% must be found in the serum of two separate blood samples, or a >=85% virtual PRA (vPRA) calculated from the unacceptable HLA antigens reported by the transplant center of the recipient (provided they mainly activate complement). Recipients should wait at least two years (from date of first dialysis) before inclusion in the Acceptable Mismatch program. For every Acceptable Mismatch potential recipient, Eurotransplant calculates the chance that a suitable donor will become available in the Eurotransplant population. Potential recipients are then divided into either low chance for a donor (2 or fewer kidney offers per year), or high chance of a donor (more than 2 offers expected per year). This calculation was introduced in recognition of the fact that approximately 40% of highly sensitised patients will not be transplanted through the Acceptable Mismatch program simply because no compatible donor will be found from within the Eurotransplant donor pool. On the basis of a given patient’s chance of finding a donor, alternatives such as desensitisisation or participation in paired donor exchange programs can be more accurately evaluated (46).

Recipients selected by the Acceptable Mismatch program have priority over recipients awaiting kidney transplantation in the standard program. Within the acceptable mismatch program, recipients awaiting a combined kidney/non-renal transplant have priority over kidney only recipients. For recipients with a high chance of an organ, minimal criteria for sharing are 1 HLA-B and 1 HLA-DR or 2 HLA-DR antigens. The acceptable mismatch program is run for every deceased kidney donor with known HLA type. All eligible acceptable mismatch recipients are presented to and discussed with a Eurotransplant immunologist prior to a kidney offer.

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Review of Eligibility and Allocation Protocols in Deceased Donor Transplantation
Scandiatransplant

The Scandiatransplant Acceptable Mismatch Program (STAMP) was introduced in April 2009 to reduce waiting times and increase the likelihood of transplantation for highly sensitised kidney transplant candidates – defined as a PRA >=80% (48).

STAMP Guidelines define criteria for success as: (a) reduced waiting time for highly sensitised patients; (b) minimal frequency with which a shipped kidney is not transplanted into the indicated STAMP patient (~<10%); and (c) survival comparable to graft survival in non-sensitised kidney transplant candidates (134).

Acceptance criteria for the STAMP program are (48,134):.

1. On waiting list >1 year (not mandatory for patients <16 years);
2. PRA >=80% in 2 consecutive samples over a period of more than 3 months (calculated from last test sample, with proven reactivity against HLA class I and/or class II antigens;
3. Last tested sample drawn less than 3 months before acceptance to the program;
4. Recipient HLA antigens must be assigned by serology or molecular typing at the split level;
5. Definition of acceptable HLA mismatches at the split level may include HLA-A, -B, -Cw, -DR, and -DQ antigens.

Patients accepted into the program must be regularly screened at least every 3 months, with PRA reactivity re-evaluated at least once a year. Once accepted, patients stay included even if their PRA drops below 80%. Potential STAMP eligible patients are also evaluated to assess the difficulty they would have in obtaining a kidney from local donors. Good candidates for STAMP are considered to be those with a reason for sensitisation (previous transplant, pregnancies, blood transfusions), both CDC and solid phase reactivity, high level reactivity in antibody testing, or a history of positive cross matches.

Patients who do not meet STAMP criteria may instead be eligible for the Local Acceptable Mismatch Program (LAMP). The patients are matched the same was as for STAMP patients, based on defined acceptable mismatches. Each centre defines the acceptance criteria themselves and there is no approval requires from the committee (134).

When a STAMP match is identified in a Scandiatransplant match-run, the donor kidney is mandatorily offered to the identified recipient. Kidneys which are shipped through the STAMP (or due to any of the 5 Scandiatransplant exchange obligations) must be paid back – where possible by a kidney of the same blood group and quality (48).

Similar to Eurotransplant, in 2011 the calculation of “transplantability” – based HLA-A, B, DR, DQ and AB0 typing against a historical pool of 1000 Nordic deceased donors – was added to the STAMP protocol (48). A high value of calculated transplantability corresponds to a higher likelihood of transplantation. This calculation is not yet used as an inclusion criterion for
the STAMP, however the potential for its future inclusion is currently under discussion. Combined with waiting time and blood group, transplantability may be a more equitable way to evaluate eligibility for STAMP. For example, a patient with PRA>=80% and blood group A is eligible for STAMP but has a higher transplantability than a patient with PRA >=50% and blood group B (135). For highly sensitised patients with low transplantability, desensitisation may be more appropriate.

Determining which HLA antibodies are clinically relevant remains a challenge, and ongoing monitoring and improvements are a feature of the STAMP program. For example, the first 30 months of STAMP yielded 8 positive cross-matches, suspected in some cases to be caused by HLA-C antibodies. The STAMP steering committee and The Nordic Tissue Typers Group therefore approved the inclusion of HLA-C in the STAMP matching algorithm in September 2012 (48). Consideration is currently also being given to the inclusion of DQA1 and DP typing and registration. A further consideration is the size of the donor pool - approximately 400 donors per year across Scandinavia. With such a small donor pool, the probability of matching with a suitable donor kidney remains relatively low.

Table 28: Comparison of antigens used in an ordinary versus STAMP match, and hypothetical example of calculated transplantability (48)

<table>
<thead>
<tr>
<th>HLA match requirements</th>
<th>Example</th>
<th>Transplantability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ordinary match: only recipients own HLA-A, B and DR type</td>
<td>A2, 25; B18, 39; DR15, 16</td>
<td>0.00% = no match found.</td>
</tr>
<tr>
<td>STAMP matching algorithm: includes both recipients own HLA-A, B, C, DR and DQ type, and all antigens identified as acceptable</td>
<td>A1, 2, 3, 11, 23, 24, 25, 26, 29, 30, 31, 32, 33, 34, 36, 66, 68, 69, 74, 80; B8, 14, 18, 35, 37, 38, 39, 41, 44, 45, 46, 53, 59, 64, 65, 72, 75, 77, 78; DQ5, 6; DR1, 103, 3, 4, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18</td>
<td>2.40% = 24 matching donors from 1000.</td>
</tr>
</tbody>
</table>

Revised OPTN policy for sensitised patients

The existing OPTN policy awards 4 points for a calculated PRA (cPRA) >=80%, with no points awarded to moderately sensitised patients. Although this system yields a small improvement in access for patients with 80-85% PRA, it is ineffective in improving access for candidates with a CPRA >=90%. The new Kidney Allocation System (KAS) incorporates a priority point scale from 0-202 starting at cPRA >=20% (reflecting time-to-offer analyses showing that candidates begin to experience access barriers starting at a cPRA score of >=20%). A sliding scale of points was determined based on a mathematical transformation of the current offer rate for sensitised patients. Increasing points are awarded up until 98% cPRA, at which point candidates are assigned immediate priority. Importantly, someone who is immediately below the threshold for priority status (e.g. 97%) is awarded a large number of points and would theoretically not be at a significant disadvantage compared to the candidate with 98% cPRA.

1 Minutes of STAMP Committee meeting, 15th September 2014: http://www.scandiatransplant.org/members/stamp/minutes
2 “calculated PRA” used by OPTN and “virtual PRA” used by Eurotransplant are equivalent.
Figure 35: Kidney offers per patient-year by cPRA under the existing OPTN allocation system (data for 2010); priority points that will be awarded to each category of cPRA under the new Kidney Allocation System. Source: personal communication, R Formica.
APPENDIX D

Pancreas allocation systems

NHSBT National Pancreas Allocation Scheme (NPAS)

Pancreases that are offered through the NPAS include those donated after brain death (DBD) and those donated after circulatory death (DCD). Pancreases that are preferentially offered and accepted for multivisceral (e.g. pancreas and small bowel) or multiple organ transplants (e.g. pancreas and liver), with the exception of combined pancreas and kidney transplants, are not offered through this scheme.

Under the NPAS, pancreas transplant candidates are prioritised based on points. Patients are awarded individual points based on a number of clinically relevant donor-, patient-, and transplant-related factors. For each patient, these points are accumulated to give an individual Total Points Score (TPS). The patient with the highest TPS is ranked first in the offering sequence. As the scoring system is based on a combination of donor, recipient and transplant factors, patient scores and rankings will differ for each given donor. The seven elements that are taken into account to calculate the TPS are:

1. Total HLA mismatch
2. Waiting time
3. Sensitisation
4. Travel time
5. Donor body mass index
6. Dialysis status
7. Donor to recipient age matching

The TPS algorithm for solid organ pancreas allocation is as follows:

<table>
<thead>
<tr>
<th>Factor</th>
<th>Points calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-A,-B,-DR mismatch</td>
<td>0 to 4 HLA mismatches = 730 points</td>
</tr>
<tr>
<td></td>
<td>5 to 6 HLA mismatches = 0 points</td>
</tr>
<tr>
<td>Waiting time</td>
<td>Waiting time (days)²/365</td>
</tr>
<tr>
<td>Sensitisation points</td>
<td>Sensitisation (%)²/1000</td>
</tr>
<tr>
<td>Travel time</td>
<td>For DBD:</td>
</tr>
<tr>
<td></td>
<td>closest 3 centres = 365 points</td>
</tr>
<tr>
<td></td>
<td>For DCD:</td>
</tr>
<tr>
<td></td>
<td>closest centre = 10,000 points;</td>
</tr>
<tr>
<td></td>
<td>closest 3 centres (excluding closest) = 5000 points</td>
</tr>
<tr>
<td>Donor BMI</td>
<td>BMI &lt;22 = 730 points</td>
</tr>
<tr>
<td></td>
<td>BMI 23-25 = 365 points</td>
</tr>
<tr>
<td></td>
<td>BMI 26-28 = 0 points</td>
</tr>
<tr>
<td></td>
<td>BMI 29-31 = -365 points</td>
</tr>
<tr>
<td></td>
<td>BMI ≥32 = -730 points</td>
</tr>
<tr>
<td>Dialysis status</td>
<td>On dialysis = 180 points</td>
</tr>
<tr>
<td></td>
<td>Not on dialysis = 0 points</td>
</tr>
<tr>
<td>Donor to recipient age match</td>
<td>Age difference (years)²/13.9</td>
</tr>
</tbody>
</table>
Two notable features of this algorithm are how points are awarded for donor BMI and for donor-recipient age match. On the basis that it is clinically desirable that pancreases from donors with a low BMI are used for solid organ pancreas transplantation, and that a higher yield of pancreas islets can be extracted from pancreases recovered from donors with a high BMI, the scoring system awards points such that a pancreas from a donor with a low BMI will be allocated for solid organ transplantation, whereas the pancreas from a high BMI donor will be allocated to islet transplantation. Secondly, age matching is included in the algorithm as a tie-breaker between patients with similar scores. This factor is the least influential in the overall scores. For example a 30 year age difference will result in a deduction of 65 points from the TPS for a given match.

Full details of the NPAS can be found at:

**Eurotransplant Preprocurement Pancreas Allocation Suitability Score (P-Pass)**

The P-PASS (Preprocurement Pancreas Allocation Suitability Score) was implemented in 2009 in order to facilitate recognition of a suitable pancreas donor. A combination of nine clinical parameters available at time of donor reporting including age, BMI, ICU stay, cardiac arrest, sodium, amylase, lipase, (nor)adrenaline and dobuta-/dopamine are calculated, providing a P-PASS score between nine and 27 for each donor. In Eurotransplant, all potential pancreas donors with a P-PASS <17 pancreas should be considered for donation and transplantation.

<table>
<thead>
<tr>
<th>Item</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) x2</td>
<td>&lt;30</td>
<td>30-40</td>
<td>&gt;=40</td>
</tr>
<tr>
<td>BMI (kg/m^2) x 2</td>
<td>&lt;20</td>
<td>20-25</td>
<td>&gt;=25</td>
</tr>
<tr>
<td>ICU-stay (days)</td>
<td>&lt;3</td>
<td>3-7</td>
<td>&gt;=7</td>
</tr>
<tr>
<td>Cardiac arrest (min)</td>
<td>No</td>
<td>Yes, &lt;5</td>
<td>Yes, &gt;=5</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>&lt;155</td>
<td>155-160</td>
<td>&gt;=160</td>
</tr>
<tr>
<td>Amylase (U/I) or Lipase (U/I)</td>
<td>&lt;130</td>
<td>130-390</td>
<td>&gt;=390</td>
</tr>
<tr>
<td></td>
<td>&lt;160</td>
<td>160-480</td>
<td>&gt;=480</td>
</tr>
<tr>
<td>(Nor)adrenaline (Y) or Dobuta-/Dopamine (Y)</td>
<td>No</td>
<td>&lt;0.05</td>
<td>&lt;10</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
<td>&gt;=0.05</td>
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<td></td>
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<td>&gt;=10</td>
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</table>