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The Transplantation Society of Australia and New Zealand

# Clinical Guidelines for Organ Transplantation from Deceased Donors

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Produced in partnership with



**Australian Government**  
Organ and Tissue Authority



This document replaces version 1.4 of the previous *Consensus Statement on Eligibility Criteria and Allocation Protocols* (April 2015). As such, the current document forms version 1.0 of the *Clinical Guidelines for Organ Transplantation from Deceased Donors* (the Clinical Guidelines).

**Version control**

Version #	Changes made	Approved by	Date

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Rapid advances in medicine may cause information contained in this document to become out-dated or subject to debate.

Readers of this document who are not medical practitioners qualified in the field should seek further professional advice before any action is taken in relation to the matters described or referred to in the document.

## Table of contents

Introduction.....	vi
Part A: General issues related to recipient eligibility and donor assessment.....	viii
<b>1 Recipient Eligibility.....</b>	<b>2</b>
1.1 Referral.....	2
1.2 Assessment for eligibility.....	2
1.3 Consent.....	3
1.4 Assessment and wait-listing.....	4
1.5 Appeals.....	4
1.6 Ongoing review.....	5
1.7 Retransplantation.....	5
<b>2 Organ donor eligibility.....</b>	<b>7</b>
2.1 Organ donation.....	7
2.2 Donor and organ suitability.....	8
2.3 Donor assessment.....	9
2.4 Donor transmitted infectious disease.....	11
2.5 Donor transmitted malignancy.....	17
2.6 Transmission of other diseases.....	21
2.7 Organ distribution and allocation.....	21
<b>3 Auditing and Monitoring.....</b>	<b>25</b>
3.1 TSANZ Advisory Committee audits.....	25
3.2 ATCA/TSANZ national organ allocation, organ rotation, urgent listing, auditing process.....	25
3.3 Data collection.....	25
3.4 Governance.....	26
Part B: Organ-specific guidelines.....	27
<b>4 Heart.....</b>	<b>28</b>
4.1 Preamble.....	28
4.2 Recipient eligibility criteria.....	28
4.3 Waiting list management.....	32
4.4 Donor assessment.....	33
4.5 Allocation.....	35
4.6 Multi-organ transplantation.....	36
4.7 Emerging issues.....	37
<b>5 Kidney.....</b>	<b>40</b>
5.1 Recipient eligibility criteria.....	40
5.2 Waiting list management.....	42
5.3 Donor assessment.....	44
5.4 Allocation: Australia.....	45
5.5 Allocation: New Zealand.....	50
5.6 Multi-organ transplantation.....	51
5.7 Emerging issues.....	52
<b>6 Liver.....</b>	<b>55</b>
6.1 Preamble.....	55
6.2 Recipient eligibility criteria.....	56
6.3 Waiting list management.....	60
6.4 Donor assessment.....	62
6.5 Allocation.....	64
6.6 Multi organ transplantation.....	66
6.7 Emerging issues.....	66

<b>7 Lung</b>	<b>69</b>
7.1 Preamble	69
7.2 Recipient eligibility criteria	69
7.3 Waiting list management	71
7.4 Donor assessment	71
7.5 Allocation	72
7.6 Multi-organ transplantation	74
<b>8 Pancreas and Islet</b>	<b>76</b>
8.1 Preamble	76
8.2 Recipient eligibility criteria	76
8.3 Waiting list management	79
8.4 Donor assessment	80
8.5 Allocation	81
<b>9 Intestine</b>	<b>84</b>
9.1 Preamble	84
9.2 Parenteral nutrition	85
9.3 Intestinal transplantation in Australia	85
9.4 Recipient eligibility	86
9.5 Donor assessment	89
9.6 Allocation	90
9.7 Multi-visceral intestinal allocation versus liver-pancreas allocation	90
<b>10 Vascularised composite allotransplantation</b>	<b>92</b>
10.1 Preamble	92
10.2 Recipient eligibility criteria: hand transplantation	92
10.3 Recipient eligibility criteria: face transplantation	94
10.4 Donor assessment	95
10.5 Allocation of VCA organs	95
10.6 Multi-organ transplantation	96
10.7 Emerging issues	96
Appendix A: TSANZ Advisory Committees & Working Groups, terms of reference	99
Appendix B: Process report	100
Appendix C: Kidney allocation algorithms	103
Appendix D: Liver donor allocation flow diagram	106
Appendix E: Guidelines for lung donor bronchoscopy & CT chest	107
Appendix F: National notification for lung transplantation	109
Appendix G: Issues for further discussion	111
Appendix H: Currently recognised transplant units	112

## Introduction

Organ transplantation is a highly effective treatment for advanced organ failure that relies on the donation of organs from living or deceased persons. The focus of this document is on the transplantation of solid organs donated from deceased persons.

Currently, the number of patients who might potentially benefit from transplantation is far greater than the number of organs donated. For this reason, organ transplantation is offered primarily to patients who have end-stage organ disease and—with the exception of kidney transplantation—who have exhausted all alternative treatment options. Furthermore, transplantation is offered only to patients who have a reasonable prospect of achieving an acceptably good quality and duration of life after transplantation. Decision-making regarding the allocation and transplantation of donated organs seeks to balance the needs of individual patients against the need to maximise the overall benefit to the community from this scarce and valuable resource.

The Transplantation Society of Australia and New Zealand (TSANZ) is the body responsible for developing eligibility criteria for organ transplantation and protocols for the allocation of deceased donor organs to wait-listed patients. Specifically, TSANZ is funded by the Australian Government's Organ and Tissue Authority to maintain:

1. Current, nationally uniform eligibility criteria to ensure that there are equitable and transparent criteria by which patients are listed for organ transplantation, and
2. Current, nationally uniform allocation protocols to ensure consistency in the criteria by which donated organs are allocated.

The TSANZ document *Organ Transplantation from Deceased Donors: Consensus Statement on Eligibility Criteria and Allocation Protocols* was released in version 1.1 in June 2011, version 1.2 in May 2012, and version 1.3 in January 2014; version 1.4 was released in April 2015. The current document (*Clinical Guidelines for Organ Transplantation from Deceased Donors*) updates and replaces version 1.4 of the previous Consensus Statement, and was developed by the TSANZ Advisory Committees with written feedback sought through a targeted consultation process (see process report in Appendix B).

Central to the eligibility criteria and allocation protocols described in this document are the following ethical principles, which are embodied in the National Health and Medical Research Council (NHMRC) publication *Ethical Guidelines for Organ Transplantation from Deceased Donors* (the Ethical Guidelines):<sup>1</sup>

1. Decision-making regarding allocation must involve explicit evaluation of the risk and benefits to the potential recipient as well as the need to ensure the appropriate use of scarce health resources.
2. There must be no unlawful or unreasonable discrimination against potential recipients on the basis of:
  - Race, religious belief, gender, marital status, sexual orientation, social or other status, disability or age
  - The need for a transplant arising from the medical consequences of past lifestyle
  - Capacity to pay for treatment
  - Location of residence (e.g. remote, rural, regional or metropolitan)
  - Previous refusal of an offer of an organ for transplantation
  - Refusal to participate in research.
3. Decisions regarding eligibility and allocation will take into account the following ethically relevant factors:
  - Relative urgency of need
  - Medical factors which affect likelihood of success (e.g. comorbidities, tissue matching)
  - Relative severity of illness and disability
  - Relative length of time on the waiting list
  - Likelihood that the recipient will be able to comply with the necessary ongoing treatment after transplantation.

To be eligible to be wait-listed for organ transplantation, patients must be referred for assessment and meet the relevant eligibility criteria as specified in this document. The transplant assessment process requires referred patients to be evaluated by a transplant unit; this evaluation process takes into consideration patients' medical

history and other relevant factors. Once listed, patients are regularly reviewed to ensure that they remain eligible to receive a transplant.

Organ allocation processes vary according to the organ that is to be transplanted. Allocation of hearts, lungs, livers, and intestines involves transplant units making a clinical judgement when an organ becomes available as to which patient on the waiting list has the greatest need of that particular organ, at that particular time, based on a range of factors. Patients who require kidney or pancreas transplantation are generally stable over a prolonged period of time, and the allocation of these organs is currently based primarily on the closeness of tissue matching and the time spent on dialysis or on the transplant waiting list.

The criteria used to decide which patients are placed on a transplant waiting list and how deceased donor organs are allocated do not determine how many patients will be transplanted, but rather which patients are eligible to receive which donor organs. It is recognised that whatever process is used, there will still be many patients who might benefit from an organ transplant but will not be able to receive one because of the limited supply of organs.

The criteria and processes outlined in this document seek to achieve an appropriate balance between the needs of individuals with end-stage organ failure and the obligation of transplant teams to exercise responsible stewardship of the community's healthcare resources, including donated organs.

## References

1. Ethical Guidelines for Organ Transplantation from Deceased Donors. Australian Government National Health and Medical Research Council, Canberra, 2016.

# Part A

**General issues related to recipient eligibility and donor assessment**

# 1 Recipient Eligibility

The relative scarcity of donor organs means that transparent eligibility criteria are required to ensure a just and equitable system for deciding which patients will have access to organ transplantation as a therapy. Determining eligibility in an environment where need exceeds availability involves balancing the potentially conflicting ethical principles of equity and utility. Equity, in its purest form, requires that every potential recipient who might benefit from an organ transplant has an equal opportunity to receive one. Utility, on the other hand, requires that the community should derive the maximum possible benefit from the limited number of organs available for transplantation. The eligibility criteria and allocation processes outlined in this document attempt to balance these ethical principles in a practical and transparent manner. It should be noted, however, that because the allocation of organs is a complex process with a range of factors informing the decision to offer a particular organ to a particular recipient, wait-listed patients will wait for variable periods of time regardless of their relative medical need.

## 1.1 Referral

Patients are referred to transplant units by their treating specialist physician for assessment of their eligibility to be entered onto a transplant waiting list. Eligibility is determined on the basis of organ-specific criteria that have been developed by the relevant Advisory Committee or Working Group of the Transplantation Society of Australia and New Zealand.

Comprehensive, multidisciplinary assessment of potential candidates for transplantation is a complex and time-consuming process. It is important that referral is timely to enable suitable patients to be listed as early as is medically appropriate. In some cases—particularly in the case of kidney transplantation where the patient is not at immediate risk of death—it would usually be appropriate to optimise the patient’s medical, social and psychological situation prior to referral and evaluation for wait-listing.

## 1.2 Assessment for eligibility

### 1.2.1 General inclusion and exclusion criteria

The assessment process typically requires that patients undergo a standard set of consultations and investigations to evaluate their suitability for organ transplantation. Some patients will require further investigations depending on their specific circumstances. Clinical assessment should involve evaluation by a multidisciplinary transplant team that includes (as a minimum) both a suitably experienced transplant surgeon and a suitably experienced transplant physician (see Section 1.4).

The transplant team should regularly review wait-listed patients to ensure that they remain suitable for transplantation. Listed patients should be removed from the transplant waiting list if their condition changes (this could be either an improvement or a deterioration) to the point that they no longer meet the eligibility criteria outlined in this document.

While there are specific recipient inclusion and exclusion criteria for each organ, there are general conditions that apply across all organs. These are:

Age: with the increasing success of transplantation, the age range considered suitable for transplantation has steadily increased. Age is not by itself an exclusion criterion for most organs. However, the presence of multiple comorbidities in patients over 70 years of age is likely to exclude the

majority of such patients from eligibility for transplantation.<sup>1,2</sup>

Comorbidities: exclusion criteria generally include conditions or combinations of conditions that would result in an unacceptably high risk of mortality or morbidity during or after transplantation (e.g. active malignancy, severe cardiac disease, or chronic infection).

Behavioural risk factors: the fact that an individual may require a transplant due to lifestyle choices they have made in the past is ethically irrelevant. However, ongoing substance abuse—including excessive alcohol consumption, cigarette smoking and illicit drug use—are generally considered contraindications to transplantation. These lifestyle factors increase the risk of poor transplant outcomes.<sup>3-7</sup>

Inability to adhere with complex medical therapy: for example chronic cognitive or neuropsychiatric deficits in the absence of a carer capable of facilitating adherence to therapy.<sup>8-12</sup>

All patients assessed for eligibility for transplantation have the right to know whether or not they have been placed on the transplant waiting list, and the reasons why they have not been listed if they are deemed ineligible.

Recognised transplant units in Australia and New Zealand are listed in Appendix H.

### 1.2.2 International patients

TSANZ supports the Declaration of Istanbul on organ trafficking and transplant tourism.<sup>13,14</sup> In view of the existing gap between the need for donor organs and their availability, TSANZ considers it inappropriate for international patients (non-citizens and non-permanent residents of Australia and New Zealand) to be assessed for transplantation except under exceptional circumstances. An example of such exceptional circumstances might be when an international visitor develops acute organ failure that would normally warrant consideration for transplantation and is too unwell to return to their home country. In this situation it needs to be established that the visitor will return to a jurisdiction where appropriate post-transplant follow-up and ongoing treatment will be provided. International patients may receive an organ transplanted from a living donor at an Australian hospital, provided the usual criteria for living donor transplantation have been met and associated financial implications have been addressed and agreed upon by the recipient and the hospital.

## 1.3 Consent

Consent is defined in the Ethical Guidelines as a person's or a group's agreement, based on adequate knowledge and understanding of relevant material.<sup>15</sup> As for all medical procedures, consent should be given before transplantation can proceed. If the individual does not have the capacity to give consent or is a minor, a representative should be involved in ongoing discussions and decision-making. Sufficient information about the procedure must be made available, including the risks, the benefits, and what will happen if the procedure does not go ahead.

The acceptability of donor organs that may pose an element of risk to the recipient should be discussed with both the potential recipient and their carer at the time of wait-listing (rather than at the time of the organ offer). The provision of adequate counselling and education is critical to the potential recipient's ability to consider their options and ultimately provide informed consent if they choose to proceed with transplantation in these circumstances.

*It is imperative that the potential recipient receives comprehensive education regarding the transplant procedure and its potential short- and long-term outcomes. All patients are not equal in terms of their capacity to understand this information, and it is the clinician's role to ensure that information is provided at a level that is comprehensible to the patient. This should be done before surgery—ideally during the assessment phase—and over a series of meetings, including consultations with clinicians and patient education sessions, with the provision of supplementary reading material and/or electronic media.*

*Provision of written consent* specific to the planned transplant must be sought. Provision of written consent

should be preceded by discussion(s) of immunological and surgical risks, plus explicit discussion of any case-specific risks related to donor quality or risk of donor-derived disease (e.g. in the case of a tumorectomised kidney and cancer risk, or a hepatitis B core antibody positive donor) without compromising donor anonymity. In the case of children, both the patient and their carers should be educated and provide consent. For those deemed not legally competent, the appointed guardian should be educated and asked to provide consent.

## 1.4 Assessment and wait-listing

The referral of individuals with organ failure to a transplant unit for assessment of transplant eligibility should be initiated and completed in a timely manner to maximise the chances of successful transplantation. The transplant eligibility assessment should include:

Patient education regarding treatment options: treatment options include transplantation versus no transplantation, or living donor versus deceased donor transplantation for those with kidney failure (and for some patients with liver failure). Patients should be educated regarding likely risks, estimated benefits, and expected outcomes of transplantation. Patients should also be educated about the range of donor characteristics and the potential risks and benefits of accepting a higher-risk organ.

Medical assessment: both physical and psychological assessment is required to identify possible issues or contraindications to transplantation, and to enable an estimation of the risks and benefits of transplantation for each individual. This assessment should include clinical review by members of the transplanting team, including (at a minimum) a suitably experienced transplant surgeon and a suitably experienced transplant physician, plus any other clinicians deemed necessary. Assessment will include screening tests designed to ensure medical suitability for transplantation, as directed by the transplant team. The time required to complete medical assessment is variable, determined largely by case complexity.

Listing for deceased donor organ transplantation: this should be done by the transplant team following completion of the assessment to their satisfaction. Criteria for listing vary from organ to organ, and are detailed in each organ-specific chapter within this document. If the transplant team believe transplantation is either contraindicated or that the patient does not meet the criteria for listing—either due to the absence of an indication for transplantation or an unfavourable projected risk-benefit scenario if transplantation were to be attempted—then the patient and their referring clinician should be informed and advised as to the reasoning behind this decision. In some cases, where additional information is required, a listing decision may be deferred until such information becomes available. Every reasonable effort should be made to obtain the necessary information within a reasonable timeframe, and the referring clinician should be kept adequately informed regarding information requirements and timelines.

## 1.5 Appeals

Patients in Australia who are either (i) not referred for transplant assessment, or (ii) assessed by a transplant unit and deemed unsuitable for listing, have a right to appeal such decisions (see the NHMRC Ethical Guidelines<sup>15</sup>). The appropriate pathway for patients in scenario (i) who disagree with their assessment is to seek a second opinion from a specialist within the field. Potential outcomes of seeking a second opinion are: (a) the specialist from whom the second opinion is sought believes that referral for transplant is not indicated, in which case this should be explained to the patient; or (b) the second opinion is that referral is indicated, and that specialist refers the patient to a transplant service for assessment. In the case of scenario (ii), where the decision not to list a patient is appealed, the local unit will first review the clinical information to determine whether there are any factors that might lead to a change in the original decision. If the unit upholds their decision that the patient is not eligible for listing but the patient, their family, or other advocate(s) still disagree with this assessment, then the appropriate pathway is to seek—via the patient's specialist, and with the impartial assistance of the local unit—referral to a second transplant unit within the patient's jurisdiction; an inter-state opinion may, if required,

be sought by negotiation between the units and with the patient's consent. In the case of heart transplantation, given the logistical challenges and costs related to patient transport, the second unit should first conduct a data review, followed by a face-to-face review only if warranted. In all cases, the local unit should assist patients and families in pursuing a second opinion by providing clinical data to the second unit so that the patient does not have to undergo repeat investigations. Potential outcomes of referral to a second transplant unit are: (a) the second transplant unit agrees that the patient is not suitable for transplant listing, and this is explained to the patient; or (b) the second unit believes that the patient should be waitlisted, which should then be performed at either the primary or the secondary unit following discussion involving all parties.

In the case of intestinal transplantation and vascularised composite allotransplantation, for which only single transplant units currently exist, there is not the option of referral to a second unit within Australia or New Zealand if a patient appeals the decision of the transplant unit. For intestinal transplantation, an understanding exists with the United Kingdom to refer cases for second opinion to the UK National Adult Intestinal Transplant forum, which convenes every two months.

New Zealand has a formalised process for appeals relating to kidney transplantation, which are referred to the National Renal Transplant Leadership Team.

## 1.6 Ongoing review

Factors affecting patient suitability for transplantation may change over time. For this reason, patients wait-listed for organ transplantation should be monitored by their local physician. In addition, patients should be reviewed by the transplant unit (i) regularly, at an interval determined by the transplant unit based on patient comorbidity profile and stability (typically annually), AND (ii) ad-hoc, when the transplant unit is alerted to a potential change in suitability by the patient's usual treating physician or other medical staff. For example, unscheduled hospitalisations, intercurrent events such as myocardial infarction, or concerns with respect to non-adherence to therapy may warrant ad-hoc review by the transplant unit. If, upon review, the patient is determined to no longer be suitable for transplantation, they should be (i) delisted, if the change in status is deemed likely to be permanent, or (ii) temporarily moved to the inactive list, if the problem identified is felt to be remediable—in this case a plan for reassessment with a view to reinstatement to the active list should be made. The patient and their referring physician should be kept informed of any changes in listing status and, subsequently, of the steps involved in determining suitability for reinstatement to the active list.

## 1.7 Retransplantation

Organ transplant recipients who develop failure of the transplanted organ (e.g. a kidney transplant recipient who develops failure of the transplanted kidney) or another organ (e.g. a patient with a functioning liver transplant who develops kidney failure) are entitled to be assessed and listed for transplantation of a subsequent organ. The assessment should determine medical eligibility and the likelihood of successful transplantation in the same way as those seeking transplantation of a first organ. The presence or absence of a previous transplant should not affect access to transplantation, except where this impacts upon medical suitability.<sup>15</sup>

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## 2 Organ donor eligibility

The majority of transplantation in Australia and New Zealand is possible because of deceased donation, including all heart, lung, pancreas, most liver, and approximately 70% of all kidney transplantation.<sup>1</sup> Deceased donation is based on altruistic decisions of individuals and/or their families to donate organs to benefit other people. In Australia and New Zealand, as in all countries, there are more people who might benefit from organ transplantation than there are donor organs available. This is largely due to the small proportion of people who die in the specific circumstances under which organ donation is currently medically feasible (approximately 1% of hospital deaths). The framework within which deceased organ donation occurs includes the laws and regulations that govern the determination of death and the use of human organs and tissues for transplantation, as well as the policies and guidelines that direct clinical practice.<sup>2-6</sup>

### 2.1 Organ donation

#### 2.1.1 Prerequisites for deceased organ donation

Before organ donation can take place:

- The donor must have been declared dead by qualified physicians using accepted guidelines that are consistent with the laws and regulations of the jurisdiction in which the donor's hospital is located, and
- Consent to organ donation must have been given and documented according to the laws and regulations of that jurisdiction.

It is the formal responsibility of a designated officer appointed by the hospital authorities, reinforced by the Donation Specialist Coordinator and all surgeons in charge of donor surgical teams, to confirm that these laws and regulations have been fully complied with and documented appropriately before proceeding to the retrieval of organs.

#### 2.1.2 Determination of death and pathways to organ donation

Criteria for declaring death in Australia and New Zealand are:<sup>2,5</sup>

- Irreversible cessation of all function of the brain of the person, or
- Irreversible cessation of the circulation of blood in the body of the person.

Death declared according to neurological criteria (brain death) is only possible when the person is maintained on a mechanical ventilator, usually whilst receiving treatment in an intensive care unit. Conditions causing sufficient brain injury to culminate in brain death include haemorrhagic or occlusive stroke, trauma, hypoxic-ischaemic brain injury following a cardiac arrest, central nervous system infections and tumours. There are strict criteria and procedures for the determination of brain death in Australia and New Zealand, which are outlined in the clinical guidelines of the Australian and New Zealand Intensive Care Society.<sup>2</sup> Donation after brain death (DBD) provides for the best conditions for organ donation, since more of the donor's organs are suitable for transplantation compared to donation after cessation of circulation. DBD also results in better transplant outcomes for some organs, and the DBD donation process is more predictable with only a small proportion of cases not proceeding to the surgical retrieval of transplantable organs. The number of DBD donors is limited by the low and decreasing incidence of stroke, brain trauma and other causes of brain death observed in many developed countries including Australia and New Zealand. This means that DBD is possible in fewer than 1% of the deaths that occur in hospital.

Death is more commonly determined using circulatory criteria and—in a limited number of such circumstances—

organ donation may be possible. Donation after circulatory death (DCD) in Australia and New Zealand can occur after a decision has been made to withdraw treatment because it is considered to be no longer in the person's best interest.<sup>4</sup> This decision is usually reached by the healthcare staff and family, although in very rare and exceptional circumstances the decision may be made by the conscious, competent patient. The majority of patients suitable for DCD are receiving mechanical ventilation and/or other cardio-respiratory supportive treatments in intensive care units. If cardiac arrest, and thus death, occurs within a short timeframe after withdrawal of cardio-respiratory supportive treatment (generally within 60 to 90 minutes), donated organs can be transplanted with successful outcomes.

Situations where DCD is considered include severe brain injury that has not and is not likely to progress to brain death, end-stage cardio-respiratory or other organ failure, high spinal cord injury, and progressive neuro-muscular conditions.

DCD gives individuals and their families the opportunity to donate organs when brain death hasn't occurred, and provides additional organs for transplantation to the community. Currently, donors following a DCD pathway comprise about 30% of organ donors in Australia and 5% of organ donors in New Zealand. There are, on average, fewer organs transplanted per donor via a DCD versus a DBD pathway, given the narrower organ suitability criteria that are applied in the situation of DCD.

Currently, approximately 30% of planned DCD does not proceed to organ retrieval because death does not occur within 60 to 90 minutes of withdrawal of cardio-respiratory support. The number of potential DCD donors is uncertain and there may be scope to further increase donation via this pathway.

### 2.1.3 Retrieval surgery

Each jurisdiction has processes in place to identify teams to undertake the surgical retrieval of abdominal or thoracic organs that have been assessed to be suitable for transplantation. Key team members who will travel to the donor hospital are associated with cardio-thoracic, liver or renal transplant units, and may include surgeons, cardiac anaesthetists and perfusion technicians. Team members from the local hospital include theatre nursing staff, operating theatre technicians, anaesthetists and, sometimes, surgical assistants. The Donation Specialist Coordinator also attends the surgical retrieval operation to assist with logistic arrangements, documentation of the process, and care of the deceased post donation.

At surgical retrieval, organs are further assessed for suitability by retrieval surgeons in consultation with transplant surgeons and physicians. This may at times require adjunctive information such as the results of biopsies, which may not be available until after organ procurement. Arrangements for the transportation of organs are made according to the organ type and whether organs are for local use or interstate use.

There must be a reasonable prospect of at least one organ being transplantable before making the decision to proceed to retrieval surgery. The rate of discard of retrieved organs is expected to be small but greater than zero, since the final assessment of organ suitability can only be made at surgical retrieval.

## 2.2 Donor and organ suitability

Organ suitability for transplantation is determined by the answers to two questions: (i) is the donor suitable to donate any organ, and (ii) is a particular organ suitable for transplantation.

Transplantation inevitably carries a small potential risk of transmission of infection or cancer from the donor to the recipient.<sup>6</sup> That risk may vary depending on the organ and is assessed by consideration of donor risk factors and by testing the donor. Donor-derived disease transmission complicates less than 1% of all transplantation procedures (excluding *Cytomegalovirus* and Epstein-Barr virus) but can result in significant morbidity and mortality.<sup>7</sup> While it is possible to quantify risks through screening and testing, the risks of transmission of infectious and other diseases cannot be completely eliminated.

The level of risk of disease transmission must be balanced against the risks for an individual recipient of not proceeding with transplantation. The medical urgency of transplantation for some patients may mean that transplantation with an organ from a donor with increased risk of disease transmission is considered. Particularly where transplantation is life saving, an increased risk of disease transmission may be regarded as acceptable to the recipient. Conversely where transplantation is not immediately life saving but instead aims to improve the quality of the recipient's life, a greater margin of safety is appropriate. Nonetheless, transmission of infectious or other disease to recipients always remains a possibility, as there are limitations on diagnostic capabilities and limited time frames for donor assessment. It is also important that the recipient has an informed view of accepting an organ of poorer quality and/or increased risk of disease transmission, which takes into account the prospect of benefit (in terms of survival and/or quality of life) from transplantation with the organ on offer, the likelihood of subsequent organ offers, and the risk of deterioration of their health status whilst waiting for an alternative offer.

Suitability of a particular organ for transplantation is influenced by a range of factors including age, size, medical history (including co-morbidities), lifestyle choices and specific organ pathology. The donation process will also influence organ suitability; that is, suitability will be affected by whether the donation is via a DCD or DBD pathway, the cold ischaemic time, the warm ischaemic time in case of DCD, the surgical retrieval process, organ perfusion and storage, and logistics.

Therefore, it is increasingly possible to grade the quality of donated organs in order to provide a more accurate prediction of the medium and long-term functional outcomes of that organ post-transplantation. It is also possible to grade the risk of transmissible disease associated with a given organ. This grading of organ quality and risk of disease transmission allows acceptance decisions to be tailored to individual recipients' needs. That is, the potential benefit that is offered by a given organ may be insufficient for the needs of certain individuals (for example patients who are stable on medical therapy), however the same organ may increase the quality of life and survival prospects of other wait listed individuals (for example patients who are deteriorating on the waiting list or who are older).

## **2.3 Donor assessment**

Obtaining a thorough medical and lifestyle history of the donor, performing a careful clinical examination and undertaking suitable investigations, is a critically important part of transplant risk assessment. In Australia, an electronic donor record (EDR) is completed for all donors and captures information about the donor's medical history, examination and investigations, with the relevant information components provided to transplant units when organs are offered for transplantation.

There are specific requirements for determining the suitability of each individual organ being considered for transplantation, and these are identified in each organ-specific chapter. The general evaluation of the donor must ensure that all available information is provided to allow for accurate assessment of organ quality and its suitability for transplantation.

### **2.3.1 Medical history**

Assessment of donor suitability includes obtaining detailed information about the donor's past medical and social history, paying particular attention to:

- Diseases and surgeries, especially those that may affect organ function
- Diabetes, hypertension and/or other cardiovascular disease
- Smoking, alcohol intake, and/or recreational drug use
- Tumours or cancer—including stage, pathology details, treatment and current status
- Risk factors within the past 12 months for the transmission of HIV, hepatitis B and hepatitis C, including non-medical injecting drug use, sex with a person at increased risk of these infections, a young child of a mother at increased risk of these infections, or time in prison

- Risk factors for the transmission of Creutzfeldt-Jakob disease, including family history of early dementia, use of pituitary hormone extract, notification of treatment with pituitary hormone extract
- Travel history, especially recent travel (past six months).

Information required regarding the donor's current medical status and recent medical history includes:

- Illness course and cause of death
- Vital signs and cardio-respiratory status, including mechanical and pharmacological supports
- Organ function of potentially transplantable organs, including pathology and microbiological tests and imaging results
- Surgery or other procedures
- Medications
- Administration of intravenous fluids and blood products (noting especially that haemodilution from large volume intravenous fluid may result in false negative serological test results).

### 2.3.2 Examination

Physical examination provides information relevant to possible disease transmission risks. This should include examination for skin lesions, scars indicating prior surgery (including those suggestive of removal of skin lesions and breast lumps), lumps and masses (including any of the lymph nodes and the breasts), and needle track marks suggesting intravenous drug use.

An additional physical examination by an experienced surgeon(s) at the time of retrieval is also important, as this may reveal unexpected clinically occult lesions such as bowel cancers or renal or liver tumours.

### 2.3.3 Investigations

Mandatory investigations:

- Blood group for ABO and Rhesus
- HIV type 1 antibody
- HIV type 2 antibody
- Hepatitis B surface antibody (HBsAb)
- Hepatitis B surface antigen (HBsAg)
- Hepatitis B core antibody (HBcAb)
- Hepatitis C antibody (HCVAb)

Recommended investigations:

- *Cytomegalovirus* (CMV) IgG antibody
- Epstein-Barr virus (EBV) capsid IgG antibody
- Nucleic acid testing (NAT) for hepatitis B, hepatitis C and HIV using polymerase chain reaction (PCR) assays, in donors with increased risk of these infections (see Table 2.1)
- Syphilis serology
- human T-cell-lymphotrophic virus (HTLV) I/II antibody, especially for donors from population groups with a high prevalence of infection
- Samples for microbiological testing if infection suspected
- Beta human chronic gonadotrophin hormone in females of child-bearing age dying from unexplained intracerebral haemorrhage to detect metastatic choriocarcinoma
- Post mortem examination—whilst routine post mortem examination has become an uncommon procedure in clinical medicine, it is important to detect potentially transmittable disease and therefore it is desirable for recipient safety.

## 2.4 Donor transmitted infectious disease

Infection transmission through organ transplantation may include viruses (e.g. CMV, EBV, HIV, hepatitis B, hepatitis C), bacteria, fungi and other transmittable agents. It is possible to screen for a limited number of organisms and, while some infections can be treated in the donor and/or recipient, transmitted infections—particularly when unexpected—can result in significant recipient morbidity and mortality.

### 2.4.1 Viral infection

#### Viral hepatitis and HIV

Viral hepatitis and HIV have been transmitted through organ transplantation.<sup>8,9</sup> Transplantation of organs from donors known to have viral hepatitis may deliberately proceed in, for example, the case of a hepatitis C viraemic recipient. Similarly, recipients who are adequately immunised against or given prophylactic treatment for hepatitis B may be transplanted with organs from donors with the potential to transmit hepatitis B (see Sections 2.4.2 and 2.4.3). Although donors with HIV are absolutely contraindicated for non-HIV-positive recipients, there are potential benefits of transplanting organs from HIV-positive donors into HIV-positive recipients, however this has not yet occurred in Australia or New Zealand.

#### Donor risk classification for viral hepatitis and HIV transmission

The risk of unexpected viral hepatitis or HIV transmission can be reduced but not eliminated by obtaining a thorough patient history and performing serological testing. Information about behavioural risk factors obtained from the next of kin may be limited or inaccurate, and the rapid turnaround times needed for donor testing and associated logistical and technical limitations—balanced against the risks of death while awaiting transplantation—make the screening of organ donors different from the screening of blood or tissue donors.

**Table 2.1:** Criteria for identifying organ donors at increased risk for HIV, hepatitis B, and hepatitis C infection. MSM= men who have sex with men. Derived from Seem.<sup>8</sup>

People who have had sex with a person known or suspected to have HIV, HBV, or HCV infection in the preceding 12 months
MSM in the preceding 12 months
Women who have had sex with a man with a history of MSM in the preceding 12 months
People who have had sex in exchange for money or drugs in the preceding 12 months
People who have had sex with a person who had sex in exchange for money or drugs in the preceding 12 months
People who have had sex with a person who injected drugs by IV, intramuscular, or subcutaneous route for nonmedical reasons in the preceding 12 months
A child who is 18 months old and born to a mother known to be infected with, or at increased risk for, HIV, hepatitis B or hepatitis C infection
A child who has been breastfed within the preceding 12 months, and the mother is known to be infected with, or at increased risk for, HIV infection
People who have injected drugs by IV, intramuscular, or subcutaneous route for nonmedical reasons in the preceding 12 months
People who have been in lockup, jail, prison, or a juvenile correctional facility for more than 72 consecutive hours in the preceding 12 months
People who have been newly diagnosed with, or have been treated for, syphilis, gonorrhoea, chlamydia, or genital ulcers in the preceding 12 months
People who have been on haemodialysis in the preceding 12 months (increased hepatitis C risk only)
When a deceased potential organ donor's medical/behavioural history cannot be obtained or risk factors cannot be determined
When a deceased potential organ donor's blood specimen is haemodiluted so that testing for HIV, HBV, and HCV infection is less reliable

Donors can be considered either to have “standard risk” or “increased risk” for HIV and viral hepatitis transmission. The US Public Health Service has determined criteria for donors at increased risk of HIV, hepatitis B, and hepatitis C infection, as outlined in Table 2.1. These risk criteria were developed for use in the United States and may apply differently in the Australian population; however, no similar data exist on which to base the assessment of risk of HIV, hepatitis B and hepatitis C transmission through organ transplantation in the Australian context.

The risk of HIV and viral hepatitis transmission can be reduced by serology and nucleic acid testing (NAT) of donor blood. Testing should be undertaken using blood samples obtained from the donor prior to significant haemodilution, and should be processed by laboratories with the appropriate accreditation (as per NATA—National Association of Testing Authorities and RCPA—Royal College of Pathologists of Australia). Serological testing for HIV, hepatitis B and hepatitis C is performed as part of the evaluation of all donors, with results obtained prior to proceeding with organ transplantation. The window periods for detecting infection can be reduced by the addition of NAT (see Table 2.2). Viral hepatitis risk minimisation is explained in Section 2.4.2 and Section 2.4.3 below.

**Table 2.2:** Window periods\* for pathogen testing. Modified from Humar.<sup>10</sup>

Pathogen	Standard serology	Nucleic acid testing
HIV	17 – 22 days	5 – 6 days
HCV	~70 days	3 – 5 days
HBV	35 – 44 days	20 – 22 days

\*Window period = the interval from infection to ability to detect that infection by a given testing method.

Infection transmission may still occur despite negative serology and NAT, with the degree of residual risk influenced by the nature of the risk behaviour(s) and how recently the risky behaviour(s) occurred in relation to the time of the donor’s death (see Table 2.3).<sup>11</sup>

**Table 2.3:** Residual risk\* of undiagnosed HIV and hepatitis C infection per 10 000 donors at increased risk of infection. Modified from Ison, derived from studies of the United States population.<sup>11</sup>

Risk Factor	HIV		HCV	
	Serology alone	Serology + NAT	Serology alone	Serology + NAT
Men who have sex with men	8.3	3.4	36.0	3.8
Nonmedical intravenous, intramuscular, or subcutaneous drug use	12.9	5.3	350.0	37.8
Haemophilia	0.05	0.02	0.46	0.05
Persons who have had sex in exchange for money or drugs	2.9	1.2	107.8	11.5
Partners with any of the above risk factors	2.7	1.1	126.2	13.5
Individuals who have been exposed to blood or blood products from someone with HIV or HCV	1.3	0.5	22.0	2.3
Incarceration	1.5	0.6	68.6	7.3

\*Residual risk is the rate of undetected infection depending on risk factor and testing strategy.

While routine NAT of potential organ donors might seem an appropriate means of minimising the residual risk of infection transmission, the change of false-positive results and time delays associated with testing can lead to unnecessary loss of uninfected, transplantable organs, and thus to adverse consequences for potential recipients of those organs. In 2009, the United States and Canada held a consensus conference to review the risks and benefits of NAT and to develop recommendations for its use in donor screening. The resulting consensus

statement recommends against NAT in donors with no identifiable risk factors for HIV, hepatitis B or hepatitis C infection, arguing that the false-positive rate in this low-risk group outweighs the likelihood of identifying true-positive infections. The use of NAT was recommended for groups at increased risk of infection to reduce the risk of HIV and viral hepatitis transmission, and to potentially increase organ utilisation from NAT-negative, increased-risk donors.<sup>10</sup>

### General considerations when transplanting from increased-risk donors

When the transplantation of solid organs is being considered from a donor identified as being at increased risk of viral hepatitis transmission, either on the basis of the clinical information or serological testing, standard measures should be taken, including:

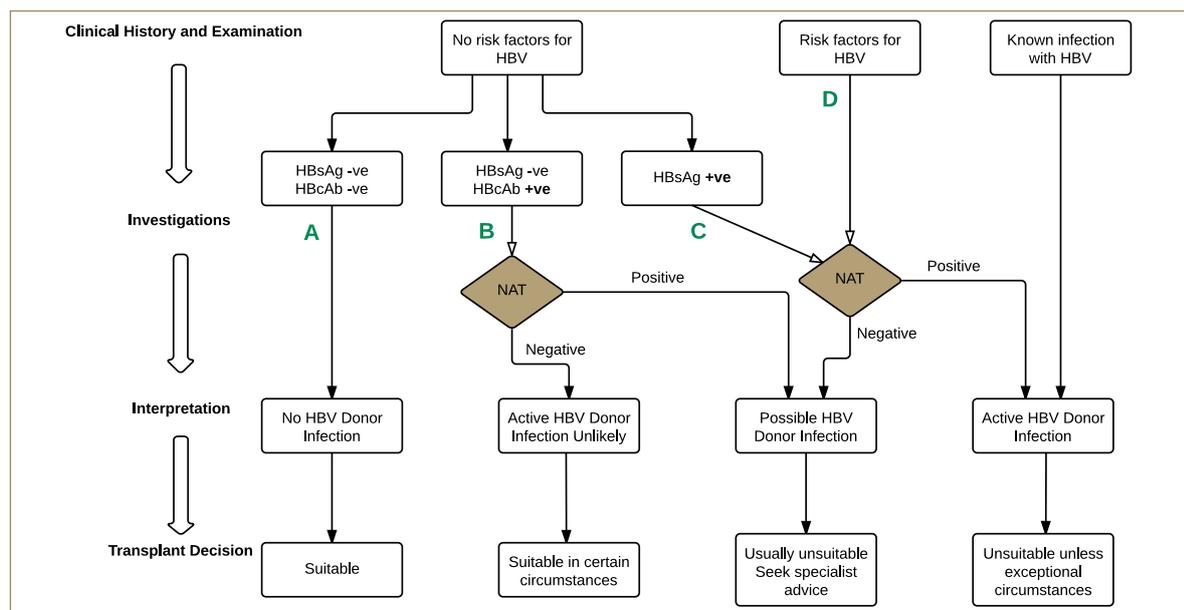
- A prospective NAT
- Discussion with hepatitis specialist with transplantation expertise (e.g. hepatologist or infectious diseases specialist)
- Consideration of recipient status—transplantation is more likely to be appropriate in recipients who are either immune (for hepatitis B), at risk of reactivation, or with active infection
- Specific informed consent must be obtained from the recipient prior to transplantation
- Post transplant prophylaxis, where applicable (i.e. hepatitis B), should be considered in consultation with a hepatitis specialist
- Post transplant screening for transmission of disease using NAT should occur within 30 days.

### 2.4.2 Hepatitis B testing and use of hepatitis B-positive donor organs

For donors with no identified risk factors, mandatory serological testing for hepatitis B comprises:

- Hepatitis B surface antigen (HBsAg)
- Hepatitis B core antibody (HBcAb)
- Hepatitis B surface antibody (HBsAb).

Hepatitis B NAT is not a mandatory test for all donors. It should not be performed routinely in low-risk donors due to the possibility of false-positive results. Furthermore, NAT may cause time delays due to a turnaround time of several hours.



**Figure 2.1:** Decision flow-chart for hepatitis B testing and utilisation of hepatitis B-positive donors

\*Note that this assumes prospective qualitative NAT is available prior to transplantation. Where this is not possible, the spectrum of risk must be considered, in the context of other risk factors.

A. Naïve and hepatitis B-vaccinated donors may be used for all recipients without need for further special measures.

B. Donors who are HBsAg-negative but HBcAb-positive can be considered, though with caution. Possible interpretations include:

- Past infection (HBsAb typically positive, but may be lost in the case of longstanding past infection)
- Persistent infection (within hepatocytes, without detectable HBsAg in the bloodstream, HBsAb typically negative)
- Acute phase infection (after disappearance of HBsAg, before appearance of HBsAb)
- False-positive test result.

Many factors influence the risk of hepatitis B transmission. Transmission rates are much higher in liver transplantation (34 – 86% without prophylaxis<sup>12,13</sup>) than in transplantation of other solid organs (0 – 5%<sup>14</sup>). Prophylaxis for recipients with oral antivirals +/- hepatitis B immune globulin (HBIG) has been shown to be effective, although rare events of infection transmission despite treatment have been reported.<sup>15-17</sup> For non-liver organ recipients who are immune prior to transplantation, there is a negligible risk of transmission;<sup>17</sup> for non-immune recipients, the transmission risk is believed to be related to donor hepatitis B virus DNA titre.<sup>12</sup> The transmission rate is not well characterised in non-vascularised tissues.<sup>18,19</sup>

Use of these donors should be considered on a case-by-case basis in consultation with a transplant hepatologist or infectious disease specialist with transplantation expertise.

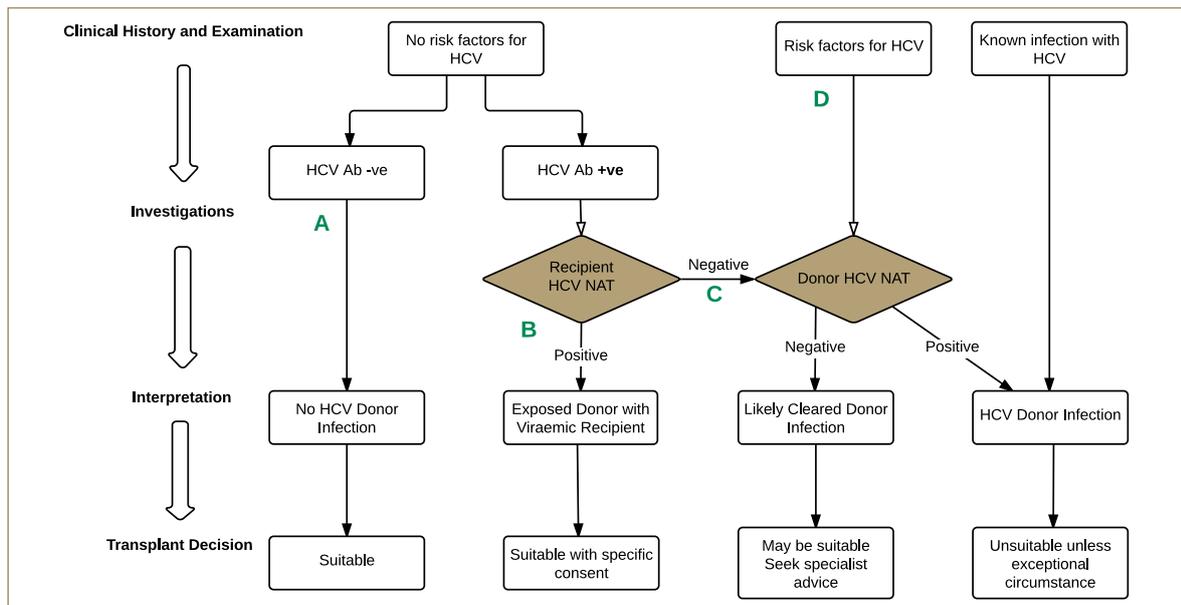
C. Donors who are HBsAg-positive are likely have active hepatitis B infection, and pose a high transmission risk.<sup>20,21</sup> Transplantation with HBsAg-positive donors should only be considered after consultation with a transplant hepatologist or infectious disease specialist with transplantation expertise.

The risk of hepatitis B transmission by transplantation of livers from donors who are HBsAg positive is very high, although this risk is attenuated with use of prophylaxis and in vaccinated patients.<sup>20-22</sup> Similarly, for non-liver solid organs, transplantation into naïve recipients will usually result in chronic hepatitis B infection, whereas for vaccinated recipients the use of HBIG and antivirals post-transplant results in good outcomes, particularly where NAT is negative.<sup>12</sup> There is evidence that HBsAg-positive recipients, where they are eligible for transplantation, show no detriment from receiving an HBsAg-positive organ.<sup>23</sup> Although transmission rates are lower in non-vascularised tissue, given the non-urgent nature of these transplants the use of HBsAg-positive donors should usually be avoided.

D. Donors with risk factors for hepatitis B—see Section 2.4.1 for general considerations when transplanting from donors at increased risk of hepatitis B infection.

### 2.4.3 Hepatitis C testing and use of hepatitis C positive donor organs

Exposure to hepatitis C results in life-long anti-hepatitis C antibodies. Positive NAT indicates ongoing infection. However, presence of antibodies in the absence of viral detection (NAT negative) most likely indicates a cleared infection.



**Figure 2.2:** Decision flow-chart for hepatitis C testing and utilisation of hepatitis C-positive donors.

A. Naïve donors may be used for all recipients without need for further special measures.

B. Hepatitis C-positive recipients and antibody-positive donors—HCVAb-positive donors should be considered for recipients who are hepatitis C NAT positive—with specific informed consent—for both liver and non-liver transplants.

Data suggest that hepatitis C-infected recipients of hepatitis C-positive livers do not have a worse outcome than hepatitis C-infected recipients of hepatitis C-negative livers.<sup>24-26</sup> There is evidence that hepatitis C-infected recipients of kidney, pancreas or heart transplants have significantly worse long-term outcomes following transplantation (regardless of donor HCV status) than non-infected recipients.<sup>27,28</sup> Data on the natural history of hepatitis C infection after lung transplantation are limited.<sup>29</sup> Despite having worse post-transplant outcomes than non-infected recipients, HCVAb-positive kidney transplant recipients have better outcomes than their counterparts who remain on dialysis.<sup>30,31</sup> A Hepatitis C-Positive Register exists to allow transparent and equitable allocation of kidneys from HCVAb-positive donors to hepatitis C NAT-positive recipients who have agreed to be considered for such kidneys (see Chapter 5, Section 5.4.4).

C. Non-infected recipients and antibody-positive donors—it is largely hepatitis C NAT-positive donors who have been documented to transmit infection<sup>10,32</sup> and up to 100% of these donors transmit hepatitis C infection to their recipient.<sup>33</sup> Not all HCVAb positive subjects are currently infected: it has been estimated that approximately 50% of HCVAb-positive donors are NAT negative.<sup>33</sup> The risk of transmission from NAT-negative HCVAb-positive donors remains to be established.<sup>34</sup> In particular, where there are multiple documented negative NAT results for a donor, this is most likely to represent cleared infection—although this does not absolutely exclude infectivity.<sup>35</sup>

Presence of hepatitis C infection in HCVAb-positive potential donors should be ascertained on the basis of hepatitis C RNA NAT testing. Given that hepatitis C has no reservoir and a negative NAT for >6 months in the absence of risk factors represents probable clearance of the virus, use of hepatitis C NAT-negative donors could be considered in some circumstances. However, hepatitis C NAT-positive donors have active hepatitis C and should not be used other than in hepatitis C infected recipients as this is associated with almost universal transmission<sup>36</sup> and poorer recipient outcomes.<sup>35-38</sup>

Where a non-infected recipient is transplanted with an increased-risk donor, the recipient should be tested for hepatitis C transmission with NAT within 30 days of their transplant.<sup>11</sup>

With the advent of new hepatitis C agents that may enable effective post-transplant prophylaxis or the eradication of infection, protocols in this area are likely to significantly change in coming years.

D. Donors with risk factors for hepatitis C—see Section 2.4.1 for general considerations when transplanting from donors at increased risk of hepatitis C infection.

#### 2.4.4 Other chronic viral infections

Other chronic viral infections that are transmissible via organ transplantation include those that are highly prevalent such as CMV, EBV, BK/polyomavirus, herpes simplex virus, and varicella, and those that occur in a minority such as HTLV I and II. Viral infections may be associated with acute life-threatening disease, chronic damage to the transplanted organ or other organs, increased risk of opportunistic bacterial and fungal infections, or malignancy.<sup>39</sup>

HTLV-1 is endemic in various areas of the world, including among Indigenous populations in central and northern Australia. Transmission occurs predominately from breast-feeding, sexual intercourse or blood transfusion. Fewer than 5% of carriers develop adult T-cell leukemia/lymphoma or myelopathic spastic paraparesis.<sup>40</sup> There have been a very small number of reports of infection transmission via organ transplantation that have led to the development of these diseases in recipients.<sup>41,42</sup> HTLV-1 screening of deceased donors is no longer required in the United States due to low prevalence, organ wastage due to false-positive results, and poor availability of the test.<sup>43</sup> While there may be value in screening donors from populations known to have a higher prevalence of HTLV-1 infection, what approach should be taken in the event of a positive result is unclear, particularly given the high false-positive rate of the test. If a donor is confirmed to be infected with HTLV-1 and organs are transplanted, monitoring of recipients for both infection and disease development is recommended.<sup>43</sup> It is important to note that HTLV-1/2 screening assays do not distinguish between HTLV-1 and HTLV-2 infection. HTLV-2 has not been convincingly associated with human disease.

#### 2.4.5 Bacterial infections

Bacterial transmission through organ transplantation is probably common, as transient fever or infection with common organisms in recipients may not be recognised as donor-derived. An estimated 5% of organ donors have unrecognised bacteraemia at the time of donation, and abdominal contents are commonly contaminated during retrieval. Recipient outcomes are not adversely affected when the organisms are common, sensitive pathogens and appropriate prophylactic antibiotics are administered.<sup>44</sup> When significant infection that is proven to be donor-derived does occur, it is more likely to be with resistant bacteria not covered by routine antibiotic prophylaxis or treatment in the donor and/or recipient (e.g. methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and multidrug resistant gram negative bacilli).<sup>45</sup> These infections are more problematic given the limited antimicrobial options, and they are likely to result in worse recipient outcomes.

Syphilis has been transmitted through organ transplantation.<sup>46,47</sup> Donor screening may reveal initial positive results that require confirmatory testing due to a 40% false-positive rate of the rapid plasma reagin (RPR) test.<sup>48</sup> If syphilis is confirmed, treatment of the recipient using a regimen similar to that which is used to treat late latent syphilis has been recommended.

#### 2.4.6 Central nervous system infection

Most CNS infection is bacterial or viral meningitis and/or encephalitis. Individuals with meningitis and/or encephalitis sometimes deteriorate to the point of brain death as a result of these infections, at which time they might be considered for organ donation.

Cases of donor-transmitted CNS infection reported in the international literature have also involved more unusual infectious agents, including mycobacterium tuberculosis, lymphocytic choriomeningitis virus, rabies, cryptococcus, coccidioides immitis, aspergillus, and balamuthia, with significant morbidity and mortality in recipients.<sup>49</sup> In some cases of donor-derived transmission, CNS infection was not suspected due other pathology such as trauma, stroke and hypoxic-ischaemic brain injury. Suspicion of any of the above agents as the cause of CNS infection in a potential donor should preclude donation.

By comparison, donors with microbiologically proven bacterial meningitis (e.g. *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Escherichia coli*, or group B streptococcus) are acceptable if the donor has been receiving appropriate antibiotic therapy (ideally for 48 hours) and pathogen-directed prophylaxis

is provided to the recipient. Donors infected with highly virulent organisms such as *Listeria* species should be rejected.

Patients with viral encephalitis should be excluded as donors, given the risk of transmission of herpes simplex virus, Murray Valley encephalitis, lymphocytic choriomeningitis virus, and bat-related lyssavirus.<sup>49</sup>

Given that in some reports of donor-derived disease transmission CNS infection was not suspected, the following should raise the suspicion of possible CNS infection:<sup>49</sup>

- Stroke in a patient without risk factors (e.g. young or paediatric) or clear mechanism
- Fever early in presentation, or other features of CNS infection such as altered mental status or seizures (note that fever after hospitalisation is common in critically ill patients)
- Travel or contact history posing a risk of CNS infection (e.g. travel to endemic regions for mosquito borne CNS infection or bat contact)
- Donor is immunosuppressed either through medication or disease (e.g. autoimmune disease, cirrhosis or previous transplant)
- Cerebrospinal fluid pleocytosis with decreased glucose and increased protein.

If suspicious of the presence or uncertain of the cause of CNS infection, a lumbar puncture should be performed followed by cerebrospinal fluid polymerase chain reaction (PCR) and other rapid diagnostic techniques.

## 2.5 Donor transmitted malignancy

### 2.5.1 Solid malignancy not involving the central nervous system

Active malignancy is generally a contraindication to organ donation, with some specific exceptions. However, transmission of malignancy may nonetheless occur as a result of occult malignancy in the donor, or as a result of past or active malignancy that was judged to have a low chance of transmission at the time of donor evaluation.

Data on the occurrence of malignancy transmission through organ transplantation is captured by tumour registries, such as the Israel Penn International Transplant Tumor Registry (IPITTR), and databases such as the United Kingdom Transplant Registry and the United States United Network for Organ Sharing (UNOS) Registry. These data sources are limited in that registries, such as IPITTR, rely on voluntary event-based reporting and lack routine follow-up data on all recipients so tend to over-estimate risk. Conversely, databases may incompletely track recipients and thus under-report the development of cancer, resulting in under-estimation of risk.

A number of guidelines and publications exist that provide support for decision-making when potential donors have cancer or a history of cancer. Publications are available from the UK,<sup>50</sup> Europe,<sup>51</sup> and the USA.<sup>52</sup> There are also a number of useful on-line resources that provide information relevant to donor-derived malignancy, including estimates of transmission rates and treatment options for transmitted cancers (Table 2.4).

**Table 2.4:** Online resources relevant to cancer transmission through organ transplantation. From Hutchinson.<sup>53</sup>

<https://ipittr.uc.edu/>  
<http://optn.transplant.hrsa.gov/converge/members/committeesDetail.asp?ID=95>  
<http://www.srtr.org/>  
<http://seer.cancer.gov/about/overview.html>  
<http://surveillance.cancer.gov/software/>  
<http://www.cdc.gov/cancer/npcr/about.htm>  
<http://www.efretos.org/>  
<http://www.sohovs.org/soho/mod/resource/view.php?id=36>  
<http://www.eurocet.org/>  
[http://www.who.int/transplantation/tra\\_notify/en/](http://www.who.int/transplantation/tra_notify/en/)  
<http://www.notifylibrary.org/>

There is a consensus that donation is absolutely contraindicated when the donor has active metastatic cancer or active haematological malignancy.

Malignancies considered to have a high risk of transmission where donation is usually contraindicated—even if there has been a long cancer-free interval—include choriocarcinoma and malignant melanoma. The IPITTR reports transmission rates for choriocarcinoma and malignant melanoma of 93% and 74% respectively. In contrast, a UNOS database report of 140 transplants involving donors with a history of melanoma found a single case of transmission to a lung recipient from a donor with a 32-year cancer-free interval (melanoma stage not stated).<sup>54</sup> Generally, a history of melanoma is considered a contraindication for donation except possibly for superficial spreading type with curative surgery or in situ melanoma.<sup>50,52</sup>

Other cancers with a high risk (>10%) of transmission include renal cell carcinoma (if tumour size > 7cm or stages 2 – 4), lung, breast, and colon cancer, other than the exceptions outlined below.<sup>50,52</sup>

In the case of a solitary, well-differentiated renal cell carcinoma the risk of transmission is minimal (<0.1%) if  $\leq 1.0$  cm in size, or low (0.1 – 2.0%) if >1.0 cm and  $\leq 2.5$  cm in size, even permitting transplantation of the affected kidney following tumour resection.<sup>50,52,55</sup>

Based on an exceedingly low risk of nodal or metastatic disease associated with T1 colon cancers in the general population, a 2003 US consensus conference endorsed the use of donors with T1 colon cancers in certain circumstances.<sup>56</sup> Similarly, although a history of breast cancer is generally a contraindication to organ donation, the risk of malignancy transmission is minimal in those with in situ cancers (ductal carcinoma in situ and lobular carcinoma) and the use of such donors has been endorsed.<sup>57</sup> More recent reports offer somewhat conflicting risk estimates, stating intermediate risk (1 to 10%) for both colonic and breast carcinoma in situ<sup>52</sup> and low risk (0.1 to 2%) for stage 1, hormone receptor negative breast cancer, or adenocarcinoma of the colon, provided there has been curative surgery and a cancer-free period of > 5 years.<sup>50</sup>

Prostate cancer confined to the prostate also has a low risk of transmission and is likely to be present in many male donors without consequence for recipients. An autopsy series of “healthy” organ donors found that 35% of those aged 60 – 69 years had undiagnosed prostate cancer.<sup>58</sup>

Non-melanoma skin cancer (basal cell and squamous cell) is the most common malignancy encountered in donors and is not considered a contraindication to donation. A UNOS database report included 776 recipients of organs from such donors with no incidence of disease transmission.<sup>54</sup>

In situ cervical cancer, small thyroid carcinomas (< 0.5cm) and superficial bladder carcinomas are also considered to pose minimal transmission risk (<0.1%).<sup>50,52</sup>

In summary, the risk of cancer transmission varies depending on the type of cancer and stage and/or cancer-free interval; the risk of disease transmission must be evaluated according to these factors as well as weighed against recipient factors including medical need. Advice from an oncologist with suitable expertise should be obtained, the patient thoroughly informed about the risk, and—if the transplant proceeds—appropriate follow-up should be provided.

### 2.5.2 Central nervous system tumours

Patients with CNS tumours may progress to a clinical state where organ donation can be considered (via either a DBD or DCD pathway). CNS tumours are the second most common tumour in organ donors (behind skin cancer) and are usually present at the time, and related to the cause, of the donor's death. Extraneural spread of brain tumours is rare, though there are reports of malignancy transmission to the recipients of organs from such donors.

The World Health Organisation has a grading of primary brain tumours from Grade 1 to Grade 4 (including glioblastoma multiforme), which is based on biological behaviour and prognosis.<sup>59</sup> Grade 4 tumours are cytologically malignant and generally fatal, and this has been interpreted as representing the highest risk of donor-to-recipient transmission.

Cerebral lymphoma and secondary malignancy are absolute contraindications to donation. There is a risk of donors with brain metastases being misdiagnosed as having a primary brain tumour or intracerebral haemorrhage. Underlying metastases should therefore be considered for any patient with a history of cancer presenting with a non-traumatic cerebral haemorrhage and, if suspected, donation should not proceed.

Data providing insight into the risk of transmission is available from registries and databases that, as described above, have limitations related to reporting bias and completeness. The IPITTR, in a review of transplants performed from 1965 to 2003 with a potential for donor-transmitted malignancy, reported a transmission rate for CNS tumours of 23%.<sup>57</sup> A number of large databases report much lower rates of transmission. A report of the registry of Australian and New Zealand found no transmission events from 46 donors, 9 with high-grade tumours, with organs transplanted into 153 recipients.<sup>60</sup> A UNOS database report that included 642 recipients of organs from donors with CNS tumours, including 175 recipients of organs from donors with high grade tumours, identified a single donor with glioblastoma multiforme who transmitted disease to three recipients.<sup>54</sup> A report of the UK Registry found no malignancy transmission from 177 donors, 32 with high-grade tumours, with organs transplanted into 526 recipients.<sup>61</sup> A Czech report of 42 donors, 11 with high-grade tumours, found no transmission among 88 recipients.<sup>62</sup>

Factors considered to be positively associated with transmission of CNS malignancy include a higher-grade of tumour (grade IV, or both III and IV) and interventions such as brain irradiation, chemotherapy, previous craniotomy and ventriculo-peritoneal shunt, possible through breaching the blood brain barrier and so facilitating tumour spread. There is debate about the role and significance of such interventions and it is difficult to differentiate between causality and coincidence—it may be that some interventions are more commonly employed in tumours that are more likely to spread.

There are case reports of tumour deposits identified around the peritoneal end of a V-P shunt,<sup>63</sup> though the pattern of metastases is similar in those with and without shunts. It has been suggested that the presence of a shunt should not contraindicate donation, provided that there is meticulous examination of the shunt tract at the time of retrieval surgery.<sup>64</sup> Similarly, prior craniotomy or biopsy should not contraindicate donation, however at the time of the retrieval procedure there should be a close examination of the craniotomy site and cervical nodes.<sup>64</sup>

There are a number of published guidelines that give advice on organ donation and CNS tumours. The European Committee on Organ Transplantation recommends the following: WHO Grade I and II tumours—organ donation not contraindicated; WHO Grade III tumours—organ donation not contraindicated, except if any of the other risk factors are present (shunt, craniotomy, radiotherapy, chemotherapy); WHO Grade IV tumours—organ donation contraindicated, regardless of the presence or absence of the aforementioned risk factors, except for vital urgencies after individually assessing each case and having previously informed the potential recipient.<sup>51</sup>

The 2014 guidelines of the United Kingdom Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) take an approach that balances the risks of non-transplantation against the risks of transplantation.<sup>50</sup> Only cerebral lymphoma and secondary tumours are considered absolute contraindications. The overall risk of cancer transmission from deceased donors with a CNS tumour is estimated to be 1.5%. The presence of a cerebro-spinal fluid shunt increases the risk of extra-neural metastasis but this additional risk is estimated at less than 1%. There is an emphasis on informed consent of the recipient, with the (derived) risk estimates shown in Table 2.5 provided to inform the recipient's decision.

In summary, primary CNS tumours do not contraindicate organ donation. Cerebral lymphoma and secondary malignancy absolutely contraindicate donation. In each case, the risk to the potential recipient of not receiving the organ on offer should be weighed against the risk of transmission of donor malignancy. Based on reported data, the risk of transmission is likely to be low, even with high-grade malignancy. Informed consent is required from the recipient and an estimate of the risk of transmission can be based on the SaBTO Guidelines (table below). Craniotomy or other breach of the blood brain barrier does not contraindicate donation, though a ventriculo-systemic shunt may increase the risk of transmission slightly.<sup>50</sup> During the evaluation of a donor with a cerebral tumour, the following should occur during the donor procedure: a thorough thoracic and abdominal exploration with visualisation and palpation of organs and nodes and direct inspection of the cervical lymph nodes and craniotomy site (if present).<sup>64</sup>

**Table 2.5:** Recommendations on the use of organs from donors with CNS tumours. Derived from SaBTO and the 2007 WHO classification of tumours of the central nervous system.<sup>50,59</sup>

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**High-risk intracranial tumours—Absolutely contra-indicated**

- Primary cerebral lymphoma
  - All secondary intracranial tumours
- 

**Organ donation not contraindicated**

WHO Grade I and II tumours:

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>• Pilocytic/ Subependymal giant cell/ Pilomyxoid/ Diffuse astrocytoma</li> <li>• Pleomorphic xanthoastrocytoma</li> <li>• Oligodendroglioma</li> <li>• Oligoastrocytoma</li> <li>• Subependymoma/ Myxopapillary ependymoma</li> <li>• Choroid plexus/ Atypical choroid plexus papilloma</li> <li>• Angiocentric glioma</li> <li>• Chordoid glioma of the third ventricle</li> <li>• Gangliocytoma</li> <li>• Ganglioglioma</li> <li>• Desmoplastic infantile astrocytoma and ganglioglioma</li> <li>• Dysembryoplastic neuroepithelial tumour</li> <li>• Central/ Extraventricular neurocytoma</li> <li>• Cerebellar liponeurocytoma</li> </ul> | <ul style="list-style-type: none"> <li>• Paraganglioma of the spinal cord</li> <li>• Papillary glioneuronal tumour</li> <li>• Rosette-forming glioneuronal tumour of the fourth ventricle</li> <li>• Pineocytoma</li> <li>• Schwannoma</li> <li>• Neurofibroma</li> <li>• Meningioma/ Atypical meningioma</li> <li>• Haemangiopericytoma</li> <li>• Haemangioblastoma</li> <li>• Craniopharyngioma</li> <li>• Granular cell tumour of the neurohypophysis</li> <li>• Pituicytoma</li> <li>• Spindle cell oncocytoma of the adenohypophysis</li> </ul> |
|--|---|
- 

**Low-risk intracranial tumours—risk of transmission <2%**

WHO Grade 3 and equivalents:

- |   |   |
|---|---|
| <ul style="list-style-type: none"> <li>• Anaplastic astrocytoma</li> <li>• Anaplastic oligodendroglioma</li> <li>• Anaplastic oligoastrocytoma</li> <li>• Ependymoma</li> <li>• Choroid plexus carcinoma</li> <li>• Anaplastic gangliomyoma</li> <li>• Pineal parenchymal tumour of intermediate differentiation</li> </ul> | <ul style="list-style-type: none"> <li>• Papillary tumour of the pineal region</li> <li>• Malignant peripheral sheath tumour</li> <li>• Anaplastic/malignant meningioma</li> <li>• Papillary meningioma</li> <li>• Rhabdoid meningioma</li> <li>• Haemangiopericytoma.</li> </ul> |
|---|---|
- 

**Intermediate-risk intracranial tumours—risk of transmission 2.2% with an upper 95% CI of 6.4%**

WHO grade 4 tumours and equivalents:

- |   |   |
|---|---|
| <ul style="list-style-type: none"> <li>• Glioblastoma</li> <li>• Giant cell glioblastoma</li> <li>• Gliosarcoma</li> <li>• Pineoblastoma</li> <li>• Medulloblastoma</li> <li>• CNS primitive neuroectodermal tumour</li> <li>• Medulloepithelioma</li> <li>• Ependymblastoma</li> </ul> | <ul style="list-style-type: none"> <li>• Atypical teratoid/rhabdoid tumour</li> <li>• Malignant peripheral nerve sheath tumour</li> <li>• Germinoma</li> <li>• Immature teratoma</li> <li>• Teratoma with malignant transformation</li> <li>• Yolk sac tumour</li> <li>• Embryonal carcinoma</li> <li>• Choriocarcinoma.</li> </ul> |
|---|---|
- 

**Ventriculoperitoneal shunt - increase risk by <1%**

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### 2.5.3 Haematological malignancy

Current haematologic malignancy is an absolute contraindication to donation.

Low-grade haematological malignancies and other clonal haematological disorders need careful, individual risk consideration. These include monoclonal gammopathy of uncertain significance (MGUS), polycythaemia vera (PV), essential thrombocythaemia (ET) and monoclonal B cell lymphocytosis (MBCL). Median survival is approximately 20 years with PV and ET and 13 years with MGUS and MBCL.<sup>65,66</sup> Thus the risk of transmission of these donor-derived diseases with long natural median patient survival must be considered in the context of an individual recipient's need for transplantation. Discussion with an expert haematologist—preferably the donor's treating physician—is advised.

## 2.6 Transmission of other diseases

There are other types of diseases that are transmittable through organ donation. These may be a result of unrecognised disease in the donor, such as has occurred in liver transplantation with ornithine transcarbamylase (OTC) deficiency, which leads to hyper-ammonaemia and metabolic decompensation that may not be recognised as the cause of death of the donor and may lead to hepatic insufficiency in the recipient of such a liver, but would leave the recipients of other organs unaffected.

There are clonal immune conditions that may temporarily be transmitted to the recipient, such as when plasma cells producing anti-blood group antibody are transplanted and result in autoimmune haemolytic anaemia. There is also a group of haematological diseases that may be thought of as subclinical malignancies, such as PV and MGUS, for which there are no firm guidelines on donor acceptability.

## 2.7 Organ distribution and allocation

The allocation of organs is a complex process, influenced by a number of factors including medical need, medical urgency, recipient capacity to benefit, donor/recipient matching, and logistical factors.

The allocation process and specific allocation criteria vary depending on the type of organ to be transplanted, as outlined in Chapters 4 to 10 of this document. Whereas the allocation of kidneys largely depends on how long somebody has waited and on the degree of their match with the donor, the allocation of other organs involves many other factors. Clinical decisions about organ allocation can be very difficult due to the number and variability of factors that must be taken into account. Medical need and recipient capacity to benefit must be at the forefront of every decision, and it is for this reason that every attempt should be made to uphold the principles of allocation embodied in the Ethical Guidelines.<sup>67</sup>

Transplant units should use donated organs in a way that balances medical need with the likelihood of successful transplantation, taking into account the following general criteria when considering potential recipients for organs:

- Length of time waiting for a transplant, taken from the time that the illness progressed to a point that a transplant would be of immediate benefit
- Important medical factors, such as the closeness of tissue-matching and matching of organ quality to estimated recipient survival
- The urgency of the transplant given the likely deterioration of the patient's health without transplantation, especially if patient survival is immediately threatened by that deterioration
- Medical need, in terms of how sick the patient is without transplantation, and the prospects for transplantation to improve the patient's outcome (both in terms of survival and quality of life)
- Logistical considerations in making the transplant available to the recipient within an appropriate timeframe (see below)
- Anthropomorphic measurements for some organs, especially hearts and lungs.

For most organs, organ allocation is organised according to both location and need. The time between removal of the organ from the donor and its implantation into the recipient (the ischaemic time) is critical to post-transplantation outcomes. The majority of donated organs are allocated within their home state, which assists in minimising this ischaemic time.

Organs donated in New Zealand may be offered to Australian units, and vice versa, if there is no suitable recipient in the donor country or as required by an urgent listing.

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# 3 Auditing and Monitoring

The distribution and allocation of organs for transplantation in Australia is supported by the national Standard Operating Procedure (SOP): *Organ Allocation, Organ Rotation, Urgent Listing, Auditing Process, Version 2* (SOP001/2015). The national SOP was developed by the Australasian Transplant Coordinators Association (ATCA), the Transplantation Society of Australia and New Zealand (TSANZ) and the Organ and Tissue Authority (OTA).

## 3.1 TSANZ Advisory Committee audits

TSANZ has a number of Advisory Committees that act as peak bodies for their organ-specific special interest groups, advising in the areas of recipient eligibility, donor organ retrieval, allocation and utilisation of organs for transplantation. TSANZ Advisory Committees undertake regular scheduled auditing of organ-specific allocation and transplantation activity at local, state and national levels. Activities and outcomes that are audited include organ utilisation, inter-jurisdictional organ sharing, and the reasons why potential donors do not proceed to transplantation. Audit outcomes are reviewed at Advisory Committee meetings twice yearly and discussed at meetings of the OTA's Transplant Liaison Reference Group which are held three times per year.

## 3.2 ATCA/TSANZ national organ allocation, organ rotation, urgent listing, auditing process

The ATCA/TSANZ national organ allocation audit is retrospectively conducted on a monthly basis to ensure strict adherence to the national SOP for organ allocation, rotation of inter-jurisdictional organ offers and listing for urgent transplantation. Data are collected on the number and characteristics of organs retrieved, utilisation outcomes, the number of offers made in each jurisdiction, and detailed reasons for declined offers. Deviations from the standard allocation rotation are documented and accompanied by a detailed explanation of clinical reasons supporting the decision. Urgent listings and their impact on the national rotation are also monitored and audited. Quarterly progress reports and an annual summary report are produced by ATCA for final approval by TSANZ and OTA before broader distribution.

## 3.3 Data collection

Data related to organ donation and transplantation activity are required for the purposes of monitoring, to demonstrate adherence to the national SOP, and to enable the identification of opportunities to improve the care of donors, the donation and transplantation process, and recipient outcomes. The Australia and New Zealand Organ Donation (ANZOD) Registry, together with the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), the Australia and New Zealand Liver Transplant Registry (ANZLTR), the Australian and New Zealand Cardiothoracic Organ Transplant Registry (ANZCOTR) and the Australia and New Zealand Islet and Pancreas Transplant Registry (ANZIPTR), record and report on organ donation and transplantation activities and outcomes within Australia and New Zealand.

Through these registries,<sup>1-3</sup> information is made publicly available on:

- The number of organs donated by deceased donors, including a comparison with international donation rates
- Organ donation pathways (e.g. whether donation occurred after brain death or circulatory death,

whether donation proceeded and, if not, reasons why)

- The number of people awaiting transplantation for each organ type
- The number of organs transplanted, including reasons why donated organs were not transplanted
- Outcomes of organ transplantation.

The data collected on donation and transplantation are used by specialist advisory committees at the federal, state, and professional level to review, audit and monitor organ donation and transplantation practices. Registry reports do not include information that would allow identification of donors or recipients. However, in the event of a medical necessity the capacity exists to link donor data to the recipient(s) via transfer of medical (but not identifying) information about the donor to the transplant teams. An example of a reason for this to occur would be in the situation of an infection in a transplant recipient that might have been transmitted through the donated organ.

### **3.4 Governance**

TSANZ is an incorporated, professional membership society and is governed by a constitution. TSANZ Advisory Committees operate under the governance of the TSANZ Council, elected from the broader TSANZ membership. The organ-specific Advisory Committees have individual terms of reference (see Appendix A), and Advisory Committee Chairs meet annually with the Chair of the TSANZ Advisory Committees and Working Groups who is a member of, and reports to, TSANZ Council.

ATCA promotes communication and collaboration amongst organ and tissue donor coordinators and transplant coordinators in Australia and New Zealand. ATCA collaborates with regional and international associations or societies interested in transplant coordination and related subjects. The ATCA President (or delegate) is a member of the TSANZ Council, and ATCA is represented on all TSANZ Advisory Committees and Working Groups.

The OTA is a statutory authority within the Australian Government Health portfolio and works with Australian states and territories, clinicians, and the community sector to implement the Australian Government's national reform programme to increase organ and tissue donation for transplantation.

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# Part B

## **Organ-specific guidelines**

# 4 Heart

## 4.1 Preamble

Heart transplantation is a highly effective treatment for patients with advanced heart disease. Heart transplant recipients in Australia and New Zealand have a one-year post-transplant survival of 87%; half of all recipients will survive for 14 years or longer after transplantation, and one-third of all heart transplant recipients survive longer than 20 years.<sup>1</sup> This compares with an average survival of less than two years for eligible patients who do not receive a heart transplant.<sup>2</sup>

Current Australian estimates are that 30 000 patients are diagnosed with incident heart failure annually and 300 000 people are living with long-standing chronic heart failure (CHF).<sup>3</sup> Between 2006 and 2011, deaths from CHF in Australia rose by 20%.<sup>4</sup> The prognosis for CHF remains poorer than for common forms of cancer.<sup>4</sup> Importantly, CHF is 1.7 times more common and occurs at a younger age among Aboriginal and Torres Strait Islander peoples than among other Australians. Death rates and hospitalisation for CHF are also significantly higher in these groups.<sup>5</sup>

## 4.2 Recipient eligibility criteria

There are five adult heart transplant centres in Australia and New Zealand (four in Australia, one in New Zealand), and one paediatric centre in Melbourne. In 2014, 95 heart transplants were performed across Australia and New Zealand.<sup>1</sup> So, even though heart transplantation is restricted to patients with evidence of end-stage heart disease, the ratio of potential recipients who might benefit from heart transplantation to donors is more than 25-to-1. For this reason, heart transplantation is offered only to patients who have:<sup>6,7</sup>

- End-stage heart disease
- Exhausted all alternative treatment options, and
- An expected survival of at least 10 years post-transplantation, with a reasonable prospect of returning to an active lifestyle.

### 4.2.1 Assessment and acceptance

The great majority of patients referred for heart transplantation have advanced CHF. This represents about 5-10% of all CHF patients.<sup>8</sup> In about 90% of referred cases, CHF is secondary to ischaemic heart disease or some form of dilated cardiomyopathy with severe systolic heart failure (Heart Failure with reduced Ejection Fraction, HFrEF).<sup>1,8</sup> Less common forms of heart disease such as restrictive cardiomyopathy, congenital, or valvular heart disease account for most of the remaining 10% of referred cases. Heart transplantation for patients with Heart Failure and preserved Ejection Fraction (HFpEF) is very uncommon.

When a patient with advanced CHF is referred to a transplant centre, the initial evaluation requires an assessment of the severity of CHF, the identification of any potentially reversible factors, and an assessment of the adequacy of current medical therapy. For patients with CHF this typically includes metabolic exercise testing ( $VO_2$  max) and assessment of prognosis using well-validated scoring systems such as the Heart Failure Survival Score or the Seattle Heart Failure Model.

### Chronic heart failure

Most patients referred for heart transplantation have CHF. Before referral for heart transplantation, patients should be established on optimal medical and device therapy including maximally tolerated doses of angiotensin-

converting enzyme inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and diuretics. Patients who demonstrate poor tolerability of these drugs (usually manifested as symptomatic hypotension, renal impairment, or worsening heart failure) have a particularly poor prognosis and, in the absence of contraindications, should be referred for heart transplant assessment.

Device therapy with an automatic implanted cardioverter defibrillator (AICD), either alone or in combination with cardiac resynchronisation therapy (CRT or biventricular pacing), has become a key component of standard care for advanced CHF. AICDs may be used either as primary or secondary prevention against sudden cardiac death.<sup>9</sup> A substantial proportion of patients with an AICD, particularly those with New York Heart Association (NYHA) Class III or IV symptoms and a broad QRS complex on ECG will also be candidates for CRT.<sup>9</sup> Patients who fail to respond to CRT or who deteriorate after a period of improvement may become candidates for heart transplantation. In addition, some patients with an AICD suffer frequent discharges from their devices due to malignant ventricular arrhythmias. Transplantation may be a consideration for these patients if no alternative therapy can be found to control repeated firing of the defibrillator.

Patients who require repeated hospitalisation for decompensated CHF and who need repeated or chronic administration of intravenous diuretic or inotropic therapy to achieve fluid control and haemodynamic stabilisation have a particularly poor prognosis.<sup>10</sup> These patients should be referred for heart transplant assessment if otherwise suitable.

In summary, patients with advanced systolic CHF are deemed potential candidates for heart transplantation if they have:<sup>8</sup>

- Advanced CHF symptoms (NYHA 3 or 4) refractory to optimal treatment
- Severe left ventricular systolic dysfunction
- $VO_2 \text{ max} \leq 12 \text{ mg/kg/min}$
- Heart Failure Survival Score of medium- to high-risk, or Seattle Heart Failure Model one-year estimated survival <80%
- No contraindication to heart transplantation (see below).

Some patients with progressive or worsening CHF will require permanent mechanical circulatory support with a Ventricular Assist Device (VAD) as a 'bridge' to transplant. Currently in Australia and New Zealand, approximately 40% of heart transplants are performed in patients who are supported with a VAD.<sup>1</sup> This figure has been steadily increasing over recent years, reflecting the chronic shortage of donors and increasing waiting times to heart transplantation.

### **Acute heart failure**

Although the majority of patients who undergo heart transplantation have CHF, approximately 5% present acutely with cardiogenic shock complicating acute myocardial infarction, cardiac surgery (postcardiotomy syndrome), or myocarditis.<sup>1</sup> While some patients with cardiogenic shock will recover after a period of mechanical circulatory support, in others the heart may show no sign of recovery, in which case heart transplantation becomes the only treatment option offering any hope of long-term survival.<sup>11</sup>

### **Other criteria for referral**

A small proportion of referred patients present with disabling angina due to coronary heart disease that is not amenable to any form of revascularisation. This may be due to diffuse distal disease or failed previous revascularisation procedures.

#### **4.2.2 Inclusion criteria**

The essential indication for heart transplantation is the presence of end-stage heart disease for which no alternative therapy is available. End-stage heart disease may be manifested as:

- Irreversible cardiogenic shock (e.g. complicating acute myocardial infarction)
- Intractable symptomatic heart failure (NYHA Class III-IV) despite maximally tolerated evidence-based

medical therapy

- The need for permanent mechanical cardiac support, i.e. ventricular assist device (VAD) or total artificial heart (TAH)
- Frequent discharges from an AICD or recurrent ventricular arrhythmias
- Intractable angina despite optimal medical, interventional and surgical treatment.

All patients listed for heart transplantation have severely impaired quality of life and most have an estimated survival of less than two years without transplantation.

When heart transplantation recommenced in Australia in 1984, the acceptable age range for referral was set arbitrarily between 5 and 50 years of age. However, the success of heart transplantation over the past three decades has resulted in the age range for recipient eligibility being widened. At the time of writing, the youngest patient to undergo heart transplantation in Australia and New Zealand was 16 days old, while the oldest patient was 71 years of age.<sup>1</sup> International experience with the transplantation of patients over 70 years of age demonstrates poorer post-transplant survival in this group compared with younger recipients.<sup>12</sup> The presence of multiple comorbidities and/or advanced frailty in patients over 70 years of age would be expected to exclude the majority of such patients from consideration for heart transplantation.<sup>6,7</sup>

### 4.2.3 Exclusion criteria

Exclusion criteria include any condition or combination of conditions that would result in an unacceptably high mortality risk from heart transplant surgery, significantly and adversely affect predicted five-year post-transplant survival, or preclude active rehabilitation after transplantation.<sup>6,7,13</sup>

Major exclusion criteria for heart transplantation are as follows:

Active malignancy:<sup>6,14</sup> active malignancies other than non-melanoma skin cancers remain an absolute contraindication to heart transplantation, however patients in permanent remission—as evidenced by prolonged disease-free survival—may be suitable for transplantation. With the availability of new cancer treatments this is an area undergoing rapid change. Best practice as to whether cancer treatment is required at all is also evolving; for example low-risk, clinically localised prostate cancer may not need to be treated and ‘cured’ prior to the patient being considered eligible for heart transplantation. The decision as to whether or not to refer a patient with a history of malignancy for heart transplant assessment needs to be made on a case-by-case basis, and generally should only be made in consultation with the oncologist caring for the patient. In general, patients with a history of malignancy should only be considered for heart transplantation if their prior malignancy does not adversely impact their predicted post-transplant survival.

Complicated diabetes:<sup>15</sup> patients with diabetes mellitus and established significant microvascular complications, poor glycaemic control (HbA1c >59 mmol/mol or 7.5%), or diffuse peripheral vascular disease are generally considered unsuitable for heart transplantation.<sup>6,15</sup> On the other hand, patients with diabetes without secondary end-organ disease (proliferative retinopathy, nephropathy or neuropathy) have undergone heart transplantation with excellent long-term outcomes.<sup>15</sup>

Body Weight: several studies have identified obesity (body mass index  $\geq 30$  kg/m<sup>2</sup> or  $\geq 140\%$  of ideal body weight) as an independent risk factor for mortality in heart transplant recipients,<sup>16-18</sup> with one study reporting a doubling of mortality at five years post-transplant for patients with a BMI > 30 kg/m<sup>2</sup>.<sup>16</sup> In light of these published findings, morbidly obese patients should be required to reduce their weight below a BMI of 30 kg/m<sup>2</sup> before being considered for heart transplantation. While cachexia (BMI < 18.5 kg/m<sup>2</sup>) is not an exclusion criterion, is also an important risk factor for poor clinical outcomes after heart transplantation.<sup>18</sup>

Infection:

*HIV*—improved survival of HIV-infected patients has shifted the profile of HIV infection from a rapidly fatal condition to that of a life-long chronic disease, with cardiovascular diseases now representing the leading cause of non-HIV-related death in this population.<sup>19</sup> As yet, no heart transplants have been

performed in patients with HIV infection in Australia or New Zealand, but small case series with limited follow-up from international centres indicate that excellent survival can be achieved in carefully selected patients.<sup>20,21</sup> At this stage, the ideal HIV-positive heart transplant candidate remains speculative due to the limitations of the data published so far. Most of the available data have come from liver and kidney transplantation in this group. Potentially, HIV patients with no detectable viral load, well-maintained CD4+ T-cell counts, a stable anti-retroviral regimen, and no history of opportunistic or other concurrent infection may be considered for heart transplantation after careful discussion with an HIV specialist. Medical regimens, however, may be extremely complex due to multiple drug interactions. Rejection rates appear to be higher in liver and kidney transplant recipients with HIV.<sup>20</sup>

*Hepatitis B and C*—patients with chronic hepatitis B or C infection may also be suitable for heart transplantation, depending on the presence and severity of chronic liver disease.<sup>22,23</sup>

*Other infections*—patients colonised with multi-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococcus (VRE) have undergone successful heart transplantation, however active systemic infection with these organisms would still be regarded as an absolute contraindication to heart transplantation. The decision regarding whether or not to refer patients with a history of chronic infection for heart transplant assessment needs to be individualised and generally should only be made in consultation with an infectious disease specialist and any other specialists caring for the patient. The exception to this would be a patient with an infected VAD where removal of the device at the time of transplantation may be potentially curative.

Inability to comply with complex medical therapy:<sup>24-27</sup> this includes chronic cognitive or neuropsychiatric deficits in the absence of a carer capable of taking on this role. Noncompliance with medical therapy after heart transplantation is a powerful predictor of increased morbidity and mortality.<sup>26</sup>

Active substance abuse:<sup>27,28</sup> this includes smoking, excessive alcohol consumption, and illicit drug use. Recommencing smoking after heart transplantation has been identified as a risk factor for accelerated coronary artery disease, malignancy, kidney failure, and poor post-transplant survival.<sup>28</sup> For individuals with a history of substance abuse, a period of 6 months abstinence is mandated (with confirmatory blood testing if considered appropriate) before active listing is considered.<sup>29</sup>

Irreversible degeneration/damage of other organ systems:<sup>6,7</sup> this refers to any degeneration or damage that precludes rehabilitation after heart transplantation (e.g. advanced neurodegenerative disease, advanced rheumatoid arthritis, or severe peripheral vascular disease not amenable to revascularisation). In cases where there is irreversible failure of multiple transplantable organs, combined organ transplantation may be considered (discussed in Section 4.6).<sup>1,30-32</sup>

Acute medical conditions: a number of acute medical conditions may render a person temporarily unsuitable for heart transplantation. These include active peptic ulcer disease, acute pulmonary embolism, and active systemic bacterial or fungal infection. Patients can be reconsidered for transplantation once these diseases have been resolved with appropriate medical therapy.

Relative contraindications to heart transplantation include uraemia with calculated (or measured) glomerular filtration rate (GFR) <40 mL/min,<sup>12,13</sup> hyperbilirubinaemia >50 mol/L,<sup>12</sup> intractable ascites with hypoalbuminaemia,<sup>33</sup> and fixed pulmonary hypertension with transpulmonary gradient (TPG) >15 mmHg or pulmonary vascular resistance (PVR) >4 Woods Units after pulmonary vasodilator challenge.<sup>12</sup> These clinical characteristics identify individuals with a marked increase in post-transplant mortality regardless of whether there is evidence of intrinsic kidney, liver or lung disease.<sup>12,13,33</sup> Patients with evidence of renal and/or hepatic decompensation who otherwise meet eligibility criteria for heart transplantation should be considered for mechanical circulatory support—so called ‘bridge to decision’.<sup>34,35</sup> Similarly, patients with fixed pulmonary hypertension should be considered for heterotopic heart transplantation (see below) or long-term mechanical circulatory support, which has been shown to reverse pulmonary hypertension over a three- to six-month period in a large proportion of patients.<sup>35,36</sup>

## 4.2.4 Special circumstances and considerations

### Heterotopic (piggy-back) heart transplantation

Historically, the vast majority of heart transplants have been performed orthotopically (i.e. the donor heart is implanted in the normal anatomical site of the recipient heart following its removal). Heterotopic or 'piggy-back' heart transplantation refers to the circumstance where the recipient heart is not removed and the donor heart is implanted in the chest and connected 'in parallel' with the recipient's, so that the recipient now has two hearts pumping together. This may be considered in two clinical settings:

Fixed pulmonary hypertension: patients who meet the above eligibility criteria for heart transplantation and who have fixed pulmonary hypertension as evidenced by a TPG >15mmHg after vasodilator challenge.<sup>36</sup> Suitable agents for assessing acute pulmonary vascular reactivity include intravenous glyceryl trinitrate, intravenous prostacyclin and inhaled nitric oxide. Paediatric patients with a high pulmonary vascular resistance may be considered for orthotopic transplantation based on the presence of acute reactivity, expected regression post-transplantation, the magnitude of the perioperative risk, and the availability of other treatment options.

Higher-risk donors: where donor heart function is judged to be suboptimal for orthotopic transplantation (but the heart is still potentially recoverable), donors may be considered for heterotopic heart transplantation subject to informed consent of the potential recipient.<sup>37</sup>

## 4.2.5 Retransplantation

Heart retransplantation has rarely been performed in Australia and New Zealand and constitutes only 1% of all heart transplants performed annually. Internationally, retransplantation constitutes approximately 2-3% of all heart transplantation.<sup>1,12</sup> The results of heart retransplantation for acute rejection and early graft failure are extremely poor.<sup>12,38</sup> These patients should generally not be considered for retransplantation. On the other hand, recent data from the registry of the International Society for Heart and Lung Transplantation indicate that selected patients undergoing heart retransplantation for late graft failure secondary to cardiac allograft vasculopathy can achieve excellent short and long-term survival.<sup>12</sup> These patients may be considered for heart retransplantation provided they meet standard eligibility criteria.

## 4.3 Waiting list management

### 4.3.1 Urgent patients

Under some circumstances—for example when transplant candidates are unsuitable for mechanical support or develop life-threatening complications while on support, and the patient's survival is estimated to be days or weeks if they do not receive a transplant—the patient may be placed on an urgent list.

Urgent listing for heart transplantation is at the discretion of the Transplant Unit Director. It will be the responsibility of the Transplant Unit Director (or their nominee) to notify all other cardiothoracic transplant units in Australia and New Zealand and to notify the Donation Specialist Coordinators in all jurisdictions when a patient is placed on (and removed from) the urgent waiting list.

It is expected that the majority of individuals placed on the urgent waiting list will either die or be transplanted within two weeks of notification. *In the event that a person remains urgently listed beyond two weeks, re-notification of all cardiothoracic transplant units and Donation Specialist Coordinators is required at two-weekly intervals.*

In the event that there are simultaneously listed urgent patients, the following rules will apply:

- If a compatible donor becomes available in the same state as one of the urgently listed patient, the heart will be referred to the local transplant unit in that state
- If a compatible donor becomes available outside the state of the urgently listed patients, the heart will be offered to the patient who was first listed as urgent.

The operation of the urgent waiting list will be subject to annual audit and review by the Cardiac Advisory Committee of TSANZ.

## 4.4 Donor assessment

### 4.4.1 Donor-related risk

The majority of hearts donated for transplantation in Australia and New Zealand are obtained from donation after brain death (DBD) donors. The quality of donor hearts varies enormously, and historically less than 30% of hearts from DBD donors have been considered suitable for transplantation. In 2014/2015, a series of successful heart transplants was reported using hearts retrieved from donation after circulatory death (DCD) donors that were located in hospitals distant from the transplant unit.<sup>39</sup> It is expected that DCD donors will increasingly become a source of hearts for transplantation. With improvements in heart preservation, including the use of ex vivo perfusion, it is expected that the proportion of transplantable hearts retrieved from both DBD and DCD donors will increase.<sup>40</sup>

A number of donor-related and procedural variables are known to affect the quality of the donor heart. These include donor age, the presence of cardiovascular risk factors (e.g. hypertension, smoking), known heart disease in the donor prior to death, or injury to the heart after death. The risk of death after heart transplantation increases progressively with donor age greater than 30 years. A donor age of 50 years is associated with a 30% increase in the relative risk of death at one year post-transplantation compared with a donor age of 30 years (an increase in the absolute risk of death at one year post-transplant from 15% to 19%). The relative risk of death at one year post-transplant rises to 50% for a donor age of 60 versus 30 years (absolute risk of 23% versus 15%).<sup>41</sup>

There are limited data available on heart transplant outcomes associated with donors over the age of 60 years. The most recent publication from the International Society for Heart and Lung Transplantation reported a one-year mortality rate of 32% for recipients of hearts from donors greater than 60 years of age.<sup>41</sup> Caution is recommended in accepting hearts from donors older than 60 years due to the high risk of pre-existing coronary artery disease.

In the DBD donor, an intense sympathetic discharge that occurs during ‘coning’ of the brain stem can result in severe (although usually reversible) myocardial dysfunction, as evidenced by a reduced left ventricular ejection fraction (LVEF) on echocardiography, or a requirement for high doses of inotropic agents to maintain haemodynamic stability. In the DCD donor, warm ischaemic injury is an unavoidable consequence of withdrawal of life support. The duration of warm ischaemia is difficult to predict, however when this exceeds 30 minutes (from cessation of ventilation to administration of cardiac preservation solution) ischaemic damage to the heart is likely to be severe and not fully reversible.

The major procedural variable that affects donor organ quality is the ischaemic time—the interval between cross-clamp of the aorta in the donor and release of the aortic cross clamp in the recipient. The risk of death after heart transplantation increases progressively with ischaemic time exceeding 200 minutes. An ischaemic time of 360 minutes is associated with an 83% increase in the relative risk of death at one year post-transplantation (an increase in the absolute risk of death at one year post-transplant from 15% to 27%).<sup>41</sup> There is a strong interaction between donor age and ischaemia time in their effect on transplant outcomes, and both variables need to be considered when deciding whether to accept a donor heart—particularly from an interstate or distant hospital when a prolonged transport time is anticipated.

As with other organs transplanted from deceased donors, there is a risk of transmission of infectious diseases from donor to recipient (e.g. HIV, hepatitis B or C). Donor screening for these and other transmissible diseases

is discussed in Chapter 2, however screening may be falsely negative in donors with high-risk behaviours.<sup>42</sup> The decision to use such donors should only be undertaken after careful consideration of the risks and benefits to the recipient and with the informed consent of the recipient (or senior next of kin in the event the recipient is unable to provide consent).

It is expected that all heart transplant units in Australia and New Zealand will make use of all viable donor hearts. The acceptability of various donor types to potential heart transplant recipients should be discussed with both the patient and the patient's carer at the time of waitlisting (rather than at the point of the heart offer). Informed consent should also be confirmed on the day of transplantation when there is a potential risk of transmission of donor infection (e.g. if the donor is positive for hepatitis B or C).

#### 4.4.2 Donor information and testing

**Table 4.1:** Donor information required for heart allocation

1	Comprehensive medical history including donor age, gender, height and weight, coronary risk factors and history of any pre-existing cardiac disease.
2	History of the presenting illness leading to death including any history of chest trauma (in the event of traumatic brain injury), cardiac arrest and duration of resuscitation prior to return of spontaneous circulation.
3	Vital signs including central venous pressure (if available) and doses of vasopressor/inotropic agents
4	Blood group
5	Laboratory tests General organ donor criteria for viral studies (see Chapter 2): HIV, HBsAg, HBsAb, HBcAb, HCVAb, CMV, EBV serology
6	Investigations Current chest x-ray Electrocardiogram (ECG) done after cessation of brain function Echocardiogram Coronary angiography (selected cases)

Donor coronary angiography has been associated with significantly better heart transplant outcomes compared to no angiography in donors at high risk of coronary artery disease.<sup>43</sup> Moreover, the cost of donor coronary angiography is more than offset by the retrieval costs avoided when a donor is found to have extensive coronary disease precluding heart transplantation.<sup>44</sup>

Coronary angiography should only be performed at the request of the heart transplant physician or surgeon and not solely upon the request of a transplant coordinator. This may necessitate direct communication between the heart transplant physician and the cardiologist/intensivist on duty for the donor hospital. Communication between the transplant physician and donor hospital will be facilitated by the transplant coordinator and the Donation Specialist Coordinator.

If a coronary angiogram is requested by the transplant physician/surgeon, this request should be made with a provisional acceptance of the heart pending an acceptable coronary angiogram result. If the heart is subsequently declined on the angiography result, national rotational offers should continue as per ATCA-TSANZ National Standard Operating Procedures - Organ Allocation Rotation Urgent Listing [ATCA TSANZ SOP 001/2015 V1.2].

#### 4.4.3 Donor coronary angiography

Right and left coronary angiogram is performed with minimal contrast.

Investigations that should not be performed unless specifically requested are:

- Left ventricular angiogram
- Aortogram.

Coronary angiography should not be performed if:

- The donor is unstable
- There is a credible risk to the abdominal organs.

**Table 4.2:** Indications for coronary angiography

Indications	Including but not limited to
History of suspected CAD	Myocardial infarct, angina
LV dysfunction on ECHO	Wall motion abnormalities, EF<45%
Risk factors	Age >50 years, BMI>30 kg/m <sup>2</sup> , hypercholesterolemia, diabetes, smoking, cocaine use and significant family history of CAD.

## 4.5 Allocation

### 4.5.1 General allocation principles

The Donation Specialist Coordinator of the relevant state Donatelife agency is responsible for identifying potential cardiothoracic organ donors and notifying the transplant coordinator for the corresponding heart transplant unit.

A heart is offered to the designated heart transplant unit first, unless there is an urgent listing. Urgent listings should be checked before any offer is made, and the ATCA/TSANZ Heart Allocation Rotation is bypassed for a patient on the urgent list. In the event that a heart is not accepted for any urgently listed patients, the heart is offered back to the home state. Heart transplant units have 30 minutes to respond to the offer.

Donor hospitals have designated heart transplant units and these are listed below:

Jurisdiction of donor hospital	Location of heart transplant unit
NSW, ACT	NSW
VIC, TAS	VIC (adult and paediatric)
QLD	QLD
WA	WA
NZ	NZ

If the designated heart transplant unit declines the offer, the donation offer is made on rotation to non-home state recognised heart transplant units, with a 30-minute response time. For Victoria, both the adult and the paediatric heart transplant units must receive the offer before moving to the next state on the rotation.

Donor heart offers from South Australia and the Northern Territory are offered on the same rotation as for non-home state offers. Patients in South Australia or the Northern Territory who require heart transplantation are referred to interstate heart transplant units, usually the Victorian or New South Wales units. Donor heart offers from New Zealand that are declined by the New Zealand heart transplant unit may be offered by New Zealand to heart transplant units in the eastern states of Australia. In the event that a heart is declined by all Australian heart transplant units, the heart may be offered to New Zealand.

### 4.5.2 Allocation algorithm

Donor hearts are allocated according to the criteria shown in Table 4.3. Decisions about each individual offer and waiting list management are the responsibility of the local heart transplant unit.

**Table 4.3:** Matching criteria for heart donation

1. ABO compatibility*	Except paediatric patients aged <12 months <sup>45</sup>
2. Size and weight compatibility*	Recipient within plus or minus 20% of donor body weight Greater variability in the donor:recipient weight ratio may be acceptable depending on the ages of the donor and recipient, especially in paediatric cases <sup>46</sup>
3. Negative lymphocytotoxic cross-match*	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.
4. Urgent status**	See Section 1.3.1
5. ABO identity	
6. Recipient waiting time	
7. Logistical considerations**	

Notes:

\* Items 1–2 are absolute requirements for adult patients.

\*\* Logistical considerations include coordination with other donor retrieval teams, transport of surgical teams and donor organs, type of heart transplant operation (orthotopic, heterotopic, or domino) and number of transplants to be performed (usually heart and lung transplants are performed simultaneously in separate operating theatres) and the availability of intensive care unit beds.

Where possible, patients waiting for heart transplantation are managed at home (which is where the majority of patients prefer to be if they are well enough), however, if it is determined that a patient's residence is too remote to allow them to be transferred to the transplant unit on the day that a donor heart becomes available then arrangements will be made for the recipient to be accommodated close to the hospital.

### 4.5.3 Domino heart allocation

Domino hearts are hearts donated by recipients of heart-lung transplants. For most heart-lung transplant recipients, both the heart and lungs are severely dysfunctional and require replacement; however, some heart-lung transplant recipients have severely impaired lung function but normal heart function. In these cases, the excised heart may be suitable for transplantation into a patient who requires heart transplantation. Domino heart transplants are unique among heart transplants as they are the only circumstance where the heart donor is a living donor. However, with the advent of bilateral lung transplantation, domino heart transplantation has become a rare occurrence.

Domino hearts donated by a heart-lung transplant recipient should be donated according to the relevant jurisdiction's laws on living donation and allocated to a medically appropriate recipient on the waiting list of the donor state heart/lung transplant unit. In the event that there is no suitable heart recipient within the donor state heart/lung transplant unit, the domino heart should be offered to the non-home state heart transplant units using the same rotation as for deceased donor hearts.

## 4.6 Multi-organ transplantation

Combined organ transplantation can be carried out in carefully selected individuals with the expectation of similarly low perioperative mortality and reasonable life expectancy as for heart-alone transplantation.<sup>30-32</sup> Patients being considered for combined heart/other organ transplantation need to meet all standard eligibility criteria for heart transplantation, as well as meet the following criteria:

- Have evidence of advanced irreversible dysfunction of the other organ and meet standard eligibility criteria for transplantation of that organ (e.g. Eisenmenger Syndrome secondary to complex congenital heart disease in the case of heart-lung transplantation, or end-stage kidney failure in the case of heart-kidney transplantation), and
- Have evidence that heart transplantation alone will result in a poor life expectancy unless the other organ is also transplanted (e.g. combined heart-liver transplantation for end-stage ischaemic heart disease in association with homozygous hypercholesterolaemia or cardiac amyloidosis in association with familial amyloidosis).

Evaluation of patients for combined organ transplantation requires detailed assessment and agreement by both organ transplant teams that the patient meets all eligibility criteria.

## **4.7 Emerging issues**

### **Hepatitis B and C-positive recipients**

Patients with chronic hepatitis B or hepatitis C infection may be suitable for heart transplantation depending on the presence and severity of chronic liver disease<sup>23,47-49</sup> While hepatitis C antiviral treatment has improved dramatically over the last 10 years, immunosuppression post heart transplant may accelerate the course of the infection. Conversely, hepatitis C may accelerate coronary allograft vasculopathy, a leading cause of post-transplant mortality. Whether this is due to the virus itself or immunosuppression is unclear. Only few studies have assessed the outcome of heart transplantation in hepatitis C-positive recipients and—based on recent data—survival is reduced in this population.<sup>50,51</sup>

Treatment of hepatitis C pre-transplant should be undertaken with careful evaluation of the patient's heart failure. Interferon may exacerbate heart failure or arrhythmias, and ribavirin-induced anemia may precipitate coronary ischemia.

Whilst newer antiviral treatments in the treatment of hepatitis B and hepatitis C infection before and after transplantation appear promising, their long-term effect in heart transplant recipients is yet to be established.

### **Hepatitis C-positive donors**

The advent of potentially curative anti-viral therapies for hepatitis C raises the possibility of transplantation of donor organs from hepatitis C positive recipients into a hepatitis C-naïve recipient with subsequent treatment of the recipient with hepatitis C anti-viral therapy. While the risks of this approach in the context of heart transplantation are currently unknown, transplantation of other organs (e.g. liver, kidney) from hepatitis C infected donors combined with treatment of the recipient with interferon-free anti-viral therapy in coming years will provide further information and guidance regarding potential risks to heart transplant recipients. In the meantime, the use of donor hearts from hepatitis C positive donors should only be considered for urgently listed patients or hepatitis C positive patients with their informed consent.

### **Advances in donor heart preservation and the anticipated impact on the donor pool**

The traditional approach to donor heart preservation involves flushing the donor heart with a cold preservation solution and subsequent transport with the donor organ packed in ice. Several groups have been exploring alternative methods of donor heart preservation, including hypothermic and normothermic ex vivo perfusion.<sup>52,53</sup> The essential principle underlying both approaches is the restoration of oxygen to the donor heart during transport to allow resumption of aerobic metabolism. Normothermic ex vivo perfusion (NEVP) requires perfusion with blood (usually obtained from the donor) and allows for the assessment of cardiac viability prior to implantation into the recipient. Viability can be assessed by the measurement of myocardial metabolism and/or function during ex vivo perfusion. The Transmedics Organ Care System provides NEVP and has been approved for clinical use in Australia and internationally. Randomised controlled trials suggest that NEVP does not provide any better protection than cold storage for traditional low-risk donor hearts,<sup>54</sup> however uncontrolled studies in higher-risk DBD donors and in DCD donors suggest that this technology will allow for the safe utilisation of these higher-risk donor hearts.<sup>39,40</sup> As these donors cannot currently be utilised with simple static cold storage, ex vivo perfusion of donor hearts is expected to increase the rate of recovery of donor hearts from the existing donor pool.

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# 5 Kidney

Most patients with end-stage kidney disease would live longer, feel healthier, and have a better quality of life with a kidney transplant compared to staying on dialysis.<sup>1-4</sup> The lifestyle and quality of life benefits of kidney transplantation versus dialysis mean that some patients who would be unlikely to increase their life expectancy with a transplant might still wish to receive a kidney if there were enough organs available.

For approximately 30 years, the Renal Transplant Advisory Committee (RTAC) and state transplant advisory committees have continually developed, reviewed, and updated kidney transplantation and allocation protocols. This process takes account of changes in tissue typing technology, donor numbers, transplant outcomes, and improved allocation practices.

At the forefront of Australia's kidney allocation protocols is the National Interstate Exchange (or the National Allocation Algorithm) which is designed primarily to facilitate allocation to recipients that are very well HLA-matched with the donor—particularly highly sensitised patients (those with many HLA-antibodies) who find it much harder to obtain an immunologically compatible donor. All kidney donors are therefore first considered against the full waiting list in Australia. Where appropriate—according to the criteria for national allocation (see Section 5.4.2)—kidneys are transported to the recipient's transplant unit. If there are no candidates on the waiting list who are suitable to receive a particular kidney through the National Interstate Exchange, then this kidney is allocated within the state in which the kidney was donated according to that state's own allocation algorithm.

In New Zealand, the National Kidney Allocation Scheme (NKAS) is managed by the National Renal Transplant Leadership Team (NRTLTL). NKAS allocates deceased donor kidneys nationally, based predominantly on waiting time on dialysis and HLA matching.

## 5.1 Recipient eligibility criteria

Unfortunately, the number of deceased donor kidneys available for transplantation is far lower than the number of patients who might benefit from a kidney transplant.<sup>5,6</sup> In Australia generally only patients who have commenced dialysis are eligible to be listed to receive a deceased donor kidney transplant. In New Zealand, patients with progressive chronic kidney disease an estimated GFR of less than 15 ml/min/1.73m<sup>2</sup> are eligible for inclusion on the kidney transplant waiting list (regardless of whether they have commenced dialysis). At 31 December 2014, the number of patients receiving maintenance dialysis in Australia was 12 091, with 2610 new patients commencing renal replacement therapy in that year.<sup>7,8</sup> Compared to 1071 actively wait-listed patients at 31 December 2013, there were 637 recipients of deceased donor kidney transplants in 2014.<sup>9,10</sup> In New Zealand there were 2678 patients on maintenance dialysis at 31 December 2014, with 547 new patients commencing renal replacement therapy in that year.<sup>7,8</sup> There were only 66 recipients of kidney transplants from deceased donors in New Zealand in 2014.<sup>11</sup>

This shortage of kidneys means that not everybody who might benefit from or who might want a kidney transplant can get one. Because of this, preference is given to patients who have a good prospect of successful transplantation and reasonable life-expectancy post-transplantation.

Currently, kidney transplant units in Australia and New Zealand require that patients have an anticipated 80% likelihood of survival at five years post-transplantation to be eligible to be wait-listed for kidney transplantation. This results in some patients who might benefit from a kidney transplant being deemed ineligible for listing. Some of these patients may still be eligible for transplantation with a kidney from a living donor. There are calculation tools being used in some centres around the world that try to predict an individual's post-transplant survival based on various factors.<sup>12,13</sup> These tools are being used to inform the decision-making process regarding eligibility for deceased donor kidney transplantation. One such tool has recently been adopted in New Zealand.<sup>12</sup>

A uniform threshold of an anticipated 80% likelihood of survival five years post-transplant means that all renal

transplant units are able to use the same benchmark to assess patients. It also allows for the audit of results and the ability to modify the assessment process in the future if circumstances with respect to the supply of donor organs were to significantly change—for example a significant increase in the supply of kidneys allowing more people to be transplanted. In Australia and New Zealand, unadjusted one-year patient and graft survival for primary deceased donor grafts has been stable at around 96% for the past ten years. Kidney transplant recipients have a five-year survival rate of close to 90%.<sup>11</sup>

To make the best use of kidneys from deceased donors, it is important to try to maximise the benefit to the whole community from this scarce and valuable resource.<sup>14,15</sup> In several international programmes, kidneys with greater estimated survival are directed preferentially towards recipients predicted to have a longer life-expectancy and kidneys with shorter estimated survival are directed preferentially to recipients predicted to have a shorter life expectancy. At the present time, Australia and New Zealand have not adopted this approach to kidney allocation, however similar allocation strategies are currently being developed for implementation in the near future. The goal of so called “survival matching” will be to maximise patient and graft survival while giving a wide range of people on dialysis the opportunity to benefit from transplantation.

### 5.1.1 Inclusion criteria

Inclusion criteria for being listed for deceased donor kidney transplantation are:

End-stage kidney disease requiring dialysis (Australia) or progressive chronic kidney disease and a GFR <15 ml/min/1.73m<sup>2</sup> (New Zealand);

Low anticipated likelihood of perioperative mortality; and

A reasonable estimated postoperative graft survival, defined as an 80% likelihood of the transplant working for at least five years after transplantation. Factors that may influence this include risk of recurrent disease, and concerns regarding non-adherence with immunosuppression.

### 5.1.2 Exclusion criteria

Exclusion criteria for being listed for deceased donor kidney transplantation are detailed below.

Lower than 80% likelihood of surviving at least five years following transplantation: comorbidities that might have a significant impact on the life expectancy of a kidney transplant recipient include cardiac disease, vascular disease, diabetes mellitus and malignancies.<sup>16-21</sup>

Cardiovascular disease: severe, non-correctable cardiovascular disease would be an absolute exclusion criterion. Lesser degrees of disease would also potentially contribute to a lower anticipated five year survival, and hence would be a relative consideration.<sup>22,23</sup>

Diabetes mellitus: uncomplicated diabetes mellitus is not a contraindication to transplantation. Patients with diabetes should undergo a detailed assessment for any vascular complications that may affect their anticipated five-year survival; such vascular complications would be a relative consideration.<sup>24,25</sup>

Infection: uncontrolled infection is a contraindication to transplantation. Patients may be listed and transplanted once the infection has been treated to within acceptable limits.

Malignancy: active malignancies—other than non-melanoma skin cancers—are an absolute contraindication to kidney transplantation. However, patients with a history of malignancy that is now in permanent remission—as evidenced by prolonged disease-free survival—may be suitable for transplantation. The decision whether to refer a patient with a history of malignancy for kidney transplant assessment needs to be made on a case-by-case basis, and generally should only be made in consultation with an oncologist.

Inability to comply with complex medical therapy: the ability to correctly follow a treatment plan—particularly with respect to anti-rejection medications—is an important factor in successful outcomes

following kidney transplantation, and as such is a requirement for listing. Every effort should be made to assist patients and their carers to optimise adherence to therapy.

Other medical conditions: patients with end-stage kidney disease can have any number of comorbid medical conditions that may affect their chances of a successful transplant outcome. These include cardiac disease, chronic lung disease, cirrhosis of the liver, peripheral vascular disease, and cerebrovascular disease. Whether the existence of any such conditions is an absolute or relative contraindication to kidney transplantation needs to be considered on a case-by-case basis.

Age: although advanced age in the absence of significant medical comorbidity is not a contraindication to kidney transplantation, fewer than 5% of the dialysis patients in Australia aged over 65 were on the waiting list for kidney transplantation at 31 December 2013 due to the high rates of comorbidities in this population.<sup>7</sup> A small number of patients over the age of 70 with limited comorbidities have been transplanted successfully.

### 5.1.3 Assessment and acceptance

Patients referred for kidney transplantation (from renal/dialysis units) should be initially assessed at the transplanting hospital. The transplanting hospital should also regularly review patients after listing. Initial and subsequent patient assessments and decisions regarding acceptance onto the waiting list and continued eligibility for listing should involve a transplant physician and surgeon. Only the Director of a transplant unit (or their delegate) has the authority to have patients added or removed from the active kidney transplant waiting list.

### 5.1.4 Retransplantation

Patients who are being considered for a second or subsequent kidney transplant should be assessed according to the same criteria as candidates who are being assessed for their first kidney transplant. The vast majority of kidney transplant procedures are performed in first-time recipients. In Australia and New Zealand over the past decade approximately 10% of kidney transplant recipients went on to receive a second kidney transplant. Only 1 – 2% of recipients receive a third or subsequent kidney transplant.

## 5.2 Waiting list management

The waiting list is comprised of patients currently on dialysis who have been assessed by a transplant physician and surgeon and determined to be suitable to undergo kidney transplantation. It is not a chronological list: organs are offered to waitlisted candidates according to the national and state allocation protocols (see Sections 5.4 and 5.5) which take into account recipient sensitisation, donor-recipient HLA-match and waiting time. There are certain circumstances in which a patient may be given priority or deemed urgent (e.g. patients under 18 years of age; see Section 5.2.4). Once a patient is accepted onto the waiting list their serum is sent to the tissue-typing laboratory, and once tissue-typing is complete they are made 'active' on the waiting list. The total time from referral to activation on the waiting list can vary considerably depending on each individual's underlying medical and surgical concerns, the investigations required, the need for opinions from other specialists and many other factors. For referred patients who are relatively healthy with few comorbidities, activation on the waiting list should ideally occur within the first 6-12 months of commencing renal replacement therapy.

### 5.2.1 Calculation of waiting time

In Australia, waiting time is calculated from the date that long-term dialysis was commenced (not from the date of acceptance onto the waiting list). This is because delays in active listing may arise due to medical issues or delays in completing the necessary investigations that are outside the control of the patient. It is critical that all patients are adequately tested and prepared for transplantation, and therefore it is more important for work-up

to be done thoroughly than quickly. When calculating waiting time, periods of acute or temporary dialysis prior to the date that long-term dialysis was commenced would not normally count.

In New Zealand, waiting time is calculated from the date of first activation on the waiting list. Periods of suspension of active listing are still counted towards waiting time.

For a second or subsequent transplant, waiting time is calculated from the date that dialysis was recommenced (Australia) or the date of reactivation on the kidney transplant waiting list (New Zealand) after the failure of the previous transplant. Rarely, a kidney transplant will fail very early or never work at all. When a transplant fails very early, as a result of technical issues or the poor quality of the organ, it may be possible for the patient to retain their original waiting time credit. Usually this would only apply to graft loss for technical reasons or due to organ quality, and would not apply in the case of graft loss due to early rejection or disease recurrence. In New Zealand, the accepted timeframe from transplant to graft failure within which the recipient is able to retain the original waiting time credit is one week. In Australia this timeframe can be up to three months, however individual cases need to be reviewed and approved by the state transplant advisory committee.

### 5.2.2 Ongoing review

To remain active on the waiting list, patients must continue to be medically, psychologically and surgically suitable to receive a kidney transplant, and should undergo regular reassessment by the transplant unit. Reassessment of patients on the waiting list should occur at least annually; usually this would be an in-person assessment. It is expected that to remain on the waiting list a patient should continue to fulfil the same inclusion criteria as for their initial listing. Transplant units should have a process to formally ensure that ongoing patient reassessment occurs and that actively listed patients are suitable to receive a kidney transplant.

Sometimes an event occurs requiring a patient to be made inactive on the waiting list. Inactive status may be permanent or temporary (interim). For example, the development of uncorrectable substantial cardiac disease would require a person to be made permanently inactive; a treatable infection such as peritonitis may require a patient to be made inactive for a period of time, however—provided no other changes occur that affect eligibility—the patient can be re-activated once the infection has been cleared. Patients should be kept informed of their status on the waiting list.

### 5.2.3 Urgent patients

In rare circumstances (applicable in Australia but not in New Zealand) a patient who is active on the transplant waiting list may be deemed 'urgent'—for example if they have very limited or failing dialysis access without which their survival is threatened. The decision to give a patient urgent status is state-based, and is reviewed by each state's transplant advisory committee. It is expected that—unless there is a compelling reason—the first suitable kidney offer should be accepted for patients deemed as urgent.

### 5.2.4 Paediatric priority

Paediatric end-stage kidney disease patients are few in number (<2% of the prevalent end-stage kidney disease population in Australian and New Zealand in 2013), and have special needs with respect to physical and psychological development that are best met by transplantation.<sup>26,27</sup> In Australia, patients who are under the age of 18 years and who commenced dialysis before age 17 are eligible for paediatric prioritisation under the National Interstate Exchange protocols after 12 months on dialysis. This prioritisation will generally make them eligible for the next available kidney from a donor of the same blood group. In New Zealand, patients under the age of 15 at the time of allocation receive paediatric prioritisation.

### 5.2.5 Australian Paired Kidney Exchange (AKX) Priority

If the intended recipient of a kidney from a living donor matched through the Australia Paired Kidney Exchange (AKX)<sup>28</sup> is unable to receive that kidney but their co-registered living donor has already donated, the "orphan

recipient” will be eligible to receive NOMS priority listing for a suitable kidney from the national deceased donor organ pool. Pre-emptive recipients (i.e. patients not on dialysis) are not listed in NOMS, however in cases of pre-dialysis orphaned AKX recipients an exception will be made after notification and approval by RTAC.<sup>29</sup>

This ability to priority-list AKX recipients in case of unforeseen circumstances safeguards the live donors and recipients participating in the AKX programme. As of January 2016, following more than 150 successful transplants through the AKX programme, the need for this priority listing has not yet arisen.<sup>30</sup>

## 5.3 Donor assessment

Various medical factors have been found to influence long term kidney graft function, in particular donor age and history of diabetes, hypertension or vascular disease.<sup>31,32</sup> Internationally, transplant centres are increasingly using donor characteristics in allocation decisions in an effort to optimise the transplant outcomes from each donated kidney.<sup>33,34</sup> This is not current practice in Australia and New Zealand, however a similar approach to allocation is being developed for implementation in the near future. Given the broad variation in the characteristics of kidneys that are available for transplantation, it is intended that such an approach will increase utilisation rates and lead to improved kidney transplant outcomes overall.

### 5.3.1 Donor information and testing

As described in Chapter 2, all donors undergo a detailed general assessment. In addition, kidney function is assessed through the patient’s past and current medical history and through various medical investigations. In some cases a biopsy of the donor kidney is performed, which can be useful in assessing the likely risks to post-transplant kidney function particularly in the case of donors who are older or have a history of diabetes, hypertension and vascular disease.<sup>35</sup>

Small kidneys from donors younger than five years are associated with a higher risk of complications due to arterial or venous thrombosis. For this reason, a decision is sometimes made in the case of small kidneys to transplant both kidneys together using the larger donor vessels to improve success.<sup>36,37</sup>

Given an increasing number of older donors often with significant cardiovascular disease, some donated kidneys are thought to not be able to provide adequate function after transplantation. In a proportion of these cases, both of the kidneys from the one donor are offered to a single recipient. This is to ensure that at least one patient can be transplanted with a successful outcome.<sup>35</sup>

### 5.3.2 Donor-related risk

The quality of kidneys retrieved from deceased donors can vary significantly. Donor age may be anywhere from approximately 2 to 75 years or above. In 2014, the mean age of deceased donors was 47.8 years in Australia and 45.6 years in New Zealand.<sup>38</sup> Donors aged over 65 years accounted for 15% and 14% of all deceased donors in Australia and New Zealand respectively. Kidney function can also vary depending on the existence of any underlying disease processes in the donor (e.g. hypertension, diabetes or vascular disease). In the United States, the concept of a “Kidney Donor Risk Index” (or KDRI) has been developed in order to rank the quality of each donor kidney.<sup>39</sup> Kidneys with a low KDRI are expected to have longer post-transplant survival than those at the other end of the spectrum. Factors included in the calculation of this index include donor age, donor kidney function, presence of diabetes or hypertension, cause of death, and donation pathway (brain death or circulatory death).

Studies support the utility of transplanting kidneys from donors who are older or have diabetes, hypertension or vascular disease, as this increases the total number of kidneys available and gives more people the opportunity to be transplanted. However, long-term recipient outcomes with these kidneys are poorer.<sup>31,32</sup>

It is important to note that it is not possible to account for all potential donor-related risk factors, and there

is always the possibility that some unknown factor may affect the transplant outcome. All transplantation procedures carry some risk and recipients should be made aware of these general risks before being listed for transplantation. Units are expected to have a thorough patient education process that discusses these issues in detail prior to patients being listed and then transplanted. Some units are now using a consent form that is discussed with the patient and must be signed prior to listing, in order to better communicate the various risks and expectations of the transplant process. Queensland has been using a state-based form for several years, and one has been developed in Victoria for state-wide use commencing in 2016.

In some cases there may be important additional factors that need to be discussed with the recipient before they consent to proceed with a specific transplant. This is important if there appears to be some additional risk related to the donor, or if other factors have been identified that may influence the transplant outcome. Examples include:

- The likelihood the kidney will have delayed function requiring dialysis for a period of time after the transplant surgery—approximately one-third of kidneys transplanted do not function immediately
- The possibility that the kidney will have poor function
- The risk of infection or cancer being transmitted if there are factors in the donor history that significantly increases their risk, even though tests may be negative
- Anatomical problems that may have been identified in the donor kidney
- Greater than usual immunological compatibility problems between the donor and recipient, such as the identification of donor-specific HLA-antibodies in the recipient—these may lead to an increased risk of rejection and/or the need for additional treatment such as plasma exchange.

## 5.4 Allocation: Australia

Kidney allocation processes are based on certain principles (see Section 5.4.1), which have been refined over time and are under frequent review to ensure that allocation outcomes remain consistent with these stated principles. Allocation algorithms (see Sections 5.4.2 and 5.4.3) refer to the practical application of these principles and are dynamic because they need to respond to changes in medical knowledge and to shifts in donor and recipient characteristics over the longer term. To ensure that kidneys are not wasted, allocation algorithms also need to be sufficiently flexible to accommodate sudden changes in the medical status of recipients and/or donors that necessitate deviation from the usual allocation pathway.

Similar to many practices in medicine, no allocation process can always be rigidly applied, and clinical discretion may sometimes be necessary to overcome unexpected impediments to normal allocation. In these rare circumstances, all cases that deviate from normal allocation practice are audited by experienced transplant clinicians through RTAC and the respective state transplant advisory committees to ensure that the deviation was acceptable and justified. Where deviations occur, the over-riding principle remains to ensure that all kidneys that can be used are effectively and fairly allocated to a wait-listed patient. In addition to unplanned allocation deviations, certain authorised deviations from usual allocation rules are also recognised. These occur in the case of urgent listings, paediatric recipients, the Australian Paired Kidney Exchange, hepatitis C positive donors, and donor with a rare blood type (see Section 5.4.4).

Matching the quality of the donor kidney to the likely longer-term survival of the recipient is now seen as an important principle in allocation policy (as described in Section 5.3.2).<sup>14,40,41</sup> In basic terms, kidneys with a longer predicted life span are best allocated to recipients with a longer predicted life expectancy and *vice versa*. In this way, optimal recipient outcomes are achieved from the available donor pool. Several countries have adopted some version of this approach to allocation. Adding this principle of “survival matching” to the Australian allocation process is currently regarded as a very high priority (see Section 5.7).

### 5.4.1 Principles

The principle intention of allocation processes is to ensure all deceased donor kidneys are allocated to a recipient by a process that is transparent, equitable and standardised. The current criteria that are used by NOMS to

allocate kidneys are as follows:

- Blood group compatible (e.g. A to A) and blood group acceptable (e.g. O to B)
- Waiting time (calculated from the time a patient commences dialysis for the first time, or returns to dialysis after a failed transplant—see Section 5.2.1)
- HLA matching (tissue typing to determine the level of immunological compatibility between a donor and recipient)
- HLA-antibodies (whether pre-existing antibodies preclude or restrict access to certain donors)
- Certain priority allocations (e.g. paediatric recipients defined as age <18 years, combined organ recipients such as kidney-pancreas, highly sensitised recipients)
- The requirement to maintain an equal balance between states receiving and donating kidneys.

#### 5.4.2 Australian allocation algorithms

The specific algorithms for national and state-based allocation protocols are available to all potential recipients (see Appendix C). An overview of the allocation process is shown in Figure 5.1, including references to planned and unplanned deviations or exceptions (detailed in Section 5.4.4).

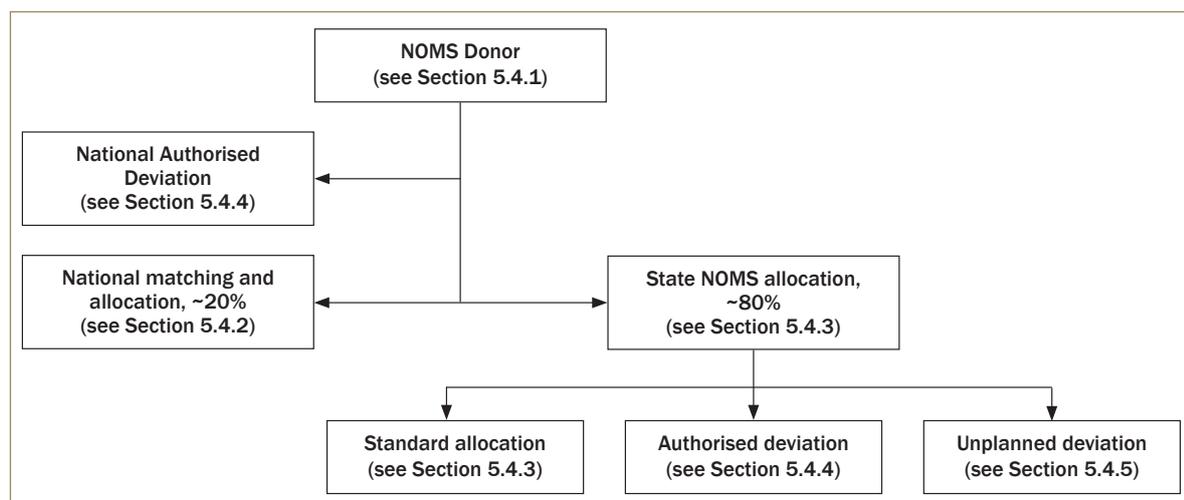
All donated kidneys go through a two-level allocation process coordinated through the national organ matching system (NOMS): first, it is determined whether any of the criteria for national allocation are met; if not allocated nationally then the kidney(s) will be allocated according to the allocation algorithm of the state in which they were donated. The first step of the allocation process is the tissue-typing of all donor kidneys in order to establish whether there is an Australian recipient who would receive a particular advantage or benefit from a specific kidney, based on a combination of their HLA-matching and HLA-antibody status. This step is primarily designed to overcome the significant immunological penalty experienced by certain patients who have many HLA-antibodies and would, without allocation priority, potentially wait for a very long time to find a suitable donor. Transplanting patients with a well-matched kidney also confers a significant advantage in terms of long-term graft survival, irrespective of the patient's HLA-antibody status. For these reasons a proportion of kidneys are allocated nationally based on immunological match. In these situations, the kidney(s) will be allocated according to the national allocation algorithm and may therefore be transported interstate (an allocation meeting the national criteria obviously may also occur within the same state as the donor). The national and state allocation algorithms are complex and are continuously monitored and reviewed. Details of the existing algorithms are provided in Appendix C. On average, about 20% of deceased donor kidneys are transported interstate through national allocation. The remaining 80% of kidneys remain in their donor state and are allocated according to state algorithms.

#### 5.4.3 State-based allocation using the state allocation algorithms

National allocation is designed to promote allocation to someone with a good immunological match (equivalent to an HLA match of  $\geq 4$  out of 6) regardless of their geographical location. Most of the time this is not possible as there is no one on the Australian waiting list who is immunologically matched at this very high level. Therefore, the majority of kidneys (about 80%) are allocated within the state in which they were donated as there is no great advantage to be gained by transporting the kidneys interstate. At the state level, approximately two-thirds of these kidneys are allocated primarily based on waiting time and the immunological match will typically be poor (equivalent to an HLA match of <2 out of 6). It is important to note that the majority of recipients will not receive a highly immunologically-matched kidney as this is usually not possible. However, excellent graft and patient outcomes are achieved despite poor immunological matching. For younger recipients who have longer life expectancy and thus may need more than one transplant in their lifetime, a good immunological match (if it is available) is considered more important as this will help to minimise the formation of HLA antibodies that would make it harder to find a compatible donor if another transplant is required in the future. For older patients and those with multiple co-morbidities, the longer-term benefit of good immunological matching is less crucial as there is a lower likelihood of requiring a subsequent transplant. These factors need to be taken into account by the transplanting unit when a kidney is offered for a given recipient.

Each state has developed its own allocation pathway and uses a slightly different algorithm, however the principles underlying allocation remain very similar across each state. The key factors determining allocation at the state level are generally waiting time and, to some degree, immunological matching. Appendix C shows each algorithm and how waiting time and immunological matching influence allocation decisions within each state. Different states have different rates of organ donation and different numbers of patient's waitlisted for transplantation. Consequently, waiting times differ between states, and thus the emphasis on waiting time in state-based allocation will have different implications in different jurisdictions.

From a practical viewpoint, state-based allocation helps to minimise ischaemia time and allows for a more efficient use of local donation, laboratory, and retrieval team resources. There is good evidence that lower ischaemia time improves transplant outcomes, especially for kidneys of lower quality (e.g. if the donor is >65 years old or had high blood pressure). An additional advantage of state-based allocation is that it allows for state-based transplant advisory committees to continually review and improve the local allocation algorithm in order to reduce inequities and imbalances within their state. It also allows states to streamline their processes for allocating kidneys that are of lower quality or pose certain additional risks (e.g. possible infection or malignancy or anatomical difficulties). These kidneys are often very difficult to successfully allocate and efficient local systems help achieve the best use of these organs by minimising ischaemia times and directing the kidney(s) to specific recipients that may be more willing to accept additional risks. The state transplant advisory committees review, audit and guide the principles applied in achieving successful allocation in these less typical cases. This helps to maximise the successful use of donated kidneys, even when the organs are not acceptable for many patients because of some perceived risk, or when the allocation algorithms may not have initially identified an appropriate recipient.<sup>17,42</sup> Some of these state-based scenarios are described below in Section 5.4.4 (dual organ allocation) and Section 5.4.5.



**Figure 5.1:** Flow diagram representing an overview of the pathway by which kidney allocation proceeds after initial matching within NOMS. Approximately 20% of kidneys are allocated at the national level, which involves transporting the kidney(s) interstate. The remaining 80% of allocations occur at a state level.

#### 5.4.4 Authorised deviations in allocation

Kidney allocation using NOMS allows for certain exceptions or authorised allocation deviations using the rules defined below.

Simultaneous pancreas and kidney (SPK) transplantation: SPK offers the best clinical outcomes for certain patients with type 1 diabetes mellitus and end-stage kidney disease.<sup>43</sup> When a suitable pancreas is donated for SPK transplant, one of the donor kidneys is also allocated to the same recipient. The second kidney is then available to be allocated using NOMS to a kidney-alone recipient. If, however, there are two highly-sensitised, kidney-alone recipients who have a very good immunological match (Level 1, 2 or 3 on the National Matching Score—see Appendix C) the allocation to the SPK patient will not occur (i.e. it will

be vetoed) and the kidneys will be allocated to the two kidney-alone patients. Patients who are matched at Levels 1, 2, or 3 have high levels of antibodies and require a well-immunologically matched kidney to ensure a successful transplant outcome.

Children (paediatric recipients <18 years): because of the special needs of children with end-stage kidney disease, mechanisms for priority allocation exist for paediatric recipients in each jurisdiction to promote timely transplantation. Details of state-specific policies are provided in Appendix C.

National Hepatitis C-Positive Register on NOMS: hepatitis C is a viral infection associated with increased risk of liver cirrhosis. About 2% of Australian organ donors carry hepatitis C.<sup>38</sup> It is not considered acceptable to transplant a hepatitis C infected donor organ into a recipient who is not infected with hepatitis C because of the risk of serious liver complications. However, transplanting a hepatitis C infected kidney into a patient who has been previously exposed to hepatitis C is considered acceptable, and allows hepatitis C infected kidneys to be usefully allocated to those recipients who are most likely to benefit. For this reason, a Hepatitis C-Positive Register exists to allow transparent and equitable allocation of kidneys from hepatitis C-positive donors to hepatitis C RNA-positive recipients who would like to be considered for these kidneys.<sup>44</sup>

In recent years, a variety of highly effective antiviral drugs able to treat hepatitis C have been developed. Because of this, in the future it may be possible to reconsider how we allocate kidneys that may carry a known or theoretical risk of transmitting hepatitis C.

Dual organ allocation through NOMS (two kidneys to one recipient): occasionally, a deceased donor may have kidneys that are considered unsuitable to be used individually (when separated) but could still provide benefit to a single individual when transplanted together—so-called dual allocation. This usually occurs when the donor is elderly and has diseases such as diabetes or hypertension, as a result of which the kidneys are partially damaged. The decision to offer both kidneys to one individual is made by the retrieving surgical and medical team after consultation and review of the donor and potential recipient's characteristics. The recipient would need to be fully informed of the risks and benefits of dual allocation.

Exceptional circumstances arising in the Australian Paired Kidney Exchange (AKX):

(For more information on the AKX, see the following link: <http://www.donatelife.gov.au/about-us/kidney-exchange-programme>)

There are two potential situations in which authorised allocation deviations may occur in relation to donors and recipients participating in the AKX:

- Orphaned kidney—this is a situation where a kidney removed from a living donor participating in a kidney exchange cannot be transplanted into the matched recipient because the recipient has an acute deterioration at the time of anaesthetic. Under these circumstances, the “orphaned kidney” may be reallocated to a patient on the deceased donor list.
- Orphaned recipient—this is a situation where a living donor kidney allocated to a recipient in the AKX programme is surgically removed but is unusable, damaged, lost, or unable to be implanted into the intended paired recipient, even though the named living donor for that recipient has already successfully donated to the other recipient in the paired exchange. In this case the recipient is defined as an “orphaned recipient”. The orphaned recipient will receive NOMS priority listing (at a ranking below Level 3 priority for national allocation) for a suitable kidney from the national deceased donor organ pool.

Neither of these circumstances has yet arisen within the AKX programme but this compensation clause exists in order to provide reassurance to donor pairs that should this occur, a system for compensation exists.<sup>45</sup> This agreement has been made with the approval of the Organ and Tissue Authority and RTAC endorsement.

Multiple organ transplantation (other than SPK transplantation): in some carefully selected patients, a combination of a kidney and another solid organ (usually a heart or liver) is requested in order to achieve a satisfactory patient outcome. In general these multi-organ transplants have good outcomes, but because other organs have much shorter acceptable cold ischaemic times compared to kidneys, the allocation

of the combined organs requires immediate acceptance without reference to HLA-matching. Requests for multiple organ retrieval are made via each state's transplant advisory committee and are nationally approved. The organs in these cases are usually allocated within the donor state (see also Section 5.6).

#### 5.4.5 Unplanned (exceptional) NOMS allocation

In clinical medicine, circumstances often arise that require immediate decision-making, and it is not possible to predict all potential deviations from the usual allocation process. In every case, the overriding principle is to ensure every donated kidney is allocated to a suitable recipient and not wasted. These exceptional cases are audited and reviewed by RTAC and state-based transplant advisory committees, to ensure the principles of allocation were followed as far as possible and, where they were not, that the reasons for deviations were acceptable. Exceptions to usual allocation procedures often occur for the sake of patient safety, or to minimise the risk of discard of an organ. Examples of such circumstances are listed below.

Prolonged ischaemia time: if there is prolonged ischaemia time, it may be particularly important to transplant the kidney as quickly as possible and therefore it may not be possible to transport the kidney interstate, as it would be deemed unusable on arrival. In these cases, the kidney would need to be allocated in the state in which it was donated, using the state-based allocation algorithm.

Technical issues: where there are technical issues that make it safer for the local surgical team who removed the deceased kidney to be involved in transplanting the organ. Examples include:

- Kidneys removed from living patients as a treatment for renal cancer. A small cancer is removed, the kidney repaired, and the kidney transplanted into a recipient who often has borderline eligibility for listing, and who understands the additional risks of possible cancer transmission and surgical complications.<sup>46</sup>
- Kidneys that have significant anatomical abnormalities of the blood vessels (e.g. an aneurysm), ureter or parenchyma (e.g. large cysts, possible tumours that require biopsy). These kidneys may also pose an increased risk to the recipient and will generally be acceptable only to some patients on the waiting list.

Intended interstate recipient is medically unfit: where the intended recipient is found to be medically unfit to undergo transplantation after the organ is shipped. For example a kidney from Sydney may be on its way to Perth, however the intended recipient in Perth is found to be medically unsuitable due to a previously unrecognised problem. In order to prevent discard of this kidney, it may be necessary to reallocate the kidney to another patient located in Perth, rather than attempting to ship the kidney interstate a second time.

No compatible recipient: where the donor has a rare blood group (usually AB or B) and there is no one on the waiting list that is blood group and HLA-compatible. In order to avoid discarding these organs, the kidney can be allocated to: (i) someone on dialysis that is not currently active on the waiting list but is deemed suitable to receive the organ (this is usually someone about to be made active on the waiting list who has met all the requirements for listing); (ii) someone of an incompatible blood group who may be able to receive the organ with additional treatment (such as plasma exchange); or, (iii) someone who is close to needing dialysis but has not yet commenced.

#### 5.4.6 Allocation of living donor kidneys using NOMS to patients waitlisted for a deceased donor kidney

In rare cases, kidneys may be removed from an otherwise healthy individual with a kidney-specific disorder who indicates that they wish to donate their kidney to someone awaiting kidney transplantation. Examples include kidneys with small tumours, cysts, scarred or blocked ureters, and occasionally kidneys with vascular aneurysms. Once removed, such kidneys can be repaired and—instead of returning the kidney to the patient, who has consented to its removal and donation—they can be offered to patients on the deceased donor waiting list using NOMS. Allocation in this circumstance is state-based. Patients who are offered this type of kidney should

be informed, counselled, and consent to the risks and benefits of receiving this organ before transplantation proceeds.

Non-directed altruistic donors are living donors who come forward wishing to donate a kidney to a person in need. These donors are fully assessed medically, surgically and psychologically, and if they are deemed suitable their donated kidney will be allocated with the oversight of the state transplant advisory committee. Generally these kidneys are allocated through the AKX programme, or alternatively through NOMS to someone on the deceased donor transplant waiting list. If allocated through the AKX programme, a chain of transplants will be performed with one kidney remaining at the end of the chain. This kidney will then be allocated through NOMS to someone on the deceased donor transplant waiting list.

## **5.5 Allocation: New Zealand**

### **5.5.1 Principles**

All deceased donor kidneys are allocated on a New Zealand-wide basis.

For DCD donors it is agreed that, where possible, kidneys will be allocated to two separate transplant centres to minimize cold ischaemia time. One kidney will be allocated to the nearest regional transplant centre, and the second kidney will be allocated to a recipient from a second transplant centre.

Donors are classified as extended criteria donors (ECD) if they are older than 55 years age, have a history of hypertension, diabetes, or kidney disease. For ECDs, or where there are other medical concerns that warrant a biopsy in the view of the transplant nephrologist, a wedge retrieval biopsy is taken from each kidney. These are processed at the histopathology laboratory at the Auckland District Health Board and reviewed by the on-call pathologist. Scores are as described by Remuzzi (with the modification that “0” is scored for up to 5% presence of any of the indices).<sup>47</sup> Kidneys with scores of 0 to 3 are offered as single-kidney transplants. Kidneys with scores of 4 to 6 are offered as dual-kidney transplants. Kidneys with scores 7 or over and/or vascular scores of greater than 2 are not used.

Waiting time points are accrued from the date of listing for recipients who are already on dialysis. Pre-emptive listing for deceased donor transplantation is allowed, but recipients accrue waiting time points only from the date of dialysis commencement. Where a transplanted kidney has primary non-function or where graft loss occurs less than one week post-transplant, following discussion and agreement at NRTL the recipient will retain their original listing date.

Kidneys must be offered to recipients according to the rules specified under the allocation algorithm (below). The left kidney is offered to the top ranked recipient unless there are specific reasons otherwise—the final decision to accept a given kidney is at the discretion of the top-ranked recipient’s transplant unit. In the circumstance that a deceased donor kidney is not transplanted into a recipient, a reason must be supplied for audit purposes.

Kidneys will only be offered to recipients where there is a suitable cross-match with no significant donor specific anti-HLA antibodies, as determined by the Medical Director of the National Kidney Allocation Scheme (NKAS).

There is no facility for urgent listing.

### **5.5.2 New Zealand allocation algorithm**

Deceased donor kidneys are allocated to recipients in the following order of priority:

1. Where another life-preserving organ (heart, liver, lungs) is to be offered to a recipient, a kidney will be allocated to that recipient on the request of the appropriate transplant team.
2. Simultaneous kidney-pancreas transplants (a maximum of 4 SPK transplants per year are permitted, with

some ability to roll this quota over from year to year). Kidney-pancreas allocation is based on the following criteria:

- Blood group—only blood group identical transplants are permitted (with the exception of A to AB)
  - Date of listing.
3. **Rank 1 match:** the purpose of this rank is to allocate kidneys to recipients with a low number of HLA mismatches. Rank 1 matches must be blood group identical (except A to AB), except if there is a 0/1 HLA mismatch, in which case the recipient must be blood group compatible. Rank 1 matches are prioritised according to the following points system:
- All are awarded 6000 points.
  - HLA mismatches are calculated first, then points modified according to the following rules:
    - Minus 2200 points for each HLA-DR mismatch
    - Minus 900 points for each HLA-B mismatch
    - Minus 800 points for each HLA-A mismatch
  - 100 points are awarded if the recipient is younger than 15 years
  - 1 point is awarded per month on the waiting list
  - If the final score is less than 4000 points (e.g. 1 HLA-DR mismatch) the recipient is excluded from rank 1.
  - Ties are separated by random number generation.
4. **Rank 2 match:** The purpose of this rank is to allocate kidneys to the recipient with the longest waiting time with an acceptable degree of mismatch. Rank 2 matches must be blood group identical (except A to AB recipients when there are more than 3 AB patients on waiting list). Rank 2 matches are prioritised according to the following points system:
- All are awarded 2000 points.
  - HLA mismatches are calculated, then points are modified according to the following rules:
    - Plus 300 points if 0 HLA-DR mismatches
    - Plus 200 points if 1 HLA-DR mismatch
  - 100 points are awarded if the recipient is younger than 15 years
  - 3 points are awarded per month on the waiting list
  - Ties are separated by random number generation.

## 5.6 Multi-organ transplantation

Uncommonly, a patient may require a multi-organ transplant, for example a liver and a kidney or a heart and a kidney at the same time. If, after detailed assessment by the treating specialists, a patient is deemed suitable, a request for consideration of a multi-organ transplant is jointly submitted to the local/state advisory committees. Each request is considered on a case-by-case basis. This decision is then relayed to RTAC, as the donor may be local or interstate.

In some cases, recipient eligibility for a multi-organ transplant may fall outside of the usual criteria for a kidney-alone transplant (i.e. the usual eligibility threshold of 80% likelihood of survival at 5 years post-transplant). Additionally, some patients may be considered for multi-organ transplantation prior to reaching end-stage kidney disease based on the degree of kidney function impairment and/or structural abnormalities.

The allocation of kidneys in the context of multi-organ transplantation follows different rules to standard allocation. For example, in the case of a patient deemed suitable for combined liver-kidney transplantation, when a liver is allocated to this patient the kidney from the same donor will be simultaneously offered. Thus the kidney is allocated outside the standard protocol.

In New Zealand, if the non-kidney transplant team consider that their patient also needs a kidney transplant, then a request is made and assessed by a kidney transplant physician at Auckland Transplant Centre. If the Auckland transplant group agrees to the multi-organ transplant, then the patient will be listed for multi-organ transplantation including a kidney.

## 5.7 Emerging issues

There are three major issues currently being critically reviewed by RTAC that will likely lead to changes in Australian kidney allocation protocols in the near future.

### **The measurement of patient sensitisation**

Some patients develop antibodies against other peoples' tissue type (HLA-antibodies). This is often referred to as being sensitised. If patients have a lot of these antibodies it can be very difficult to find a suitable kidney for them (i.e. one that they do not have antibodies against). These patients require preferential access to a well-immunologically matched kidney if one becomes available. The ability to measure a patient's level of sensitisation has improved since the current allocation algorithms were developed. RTAC is working on ways to better measure sensitisation so that the allocation algorithm can best meet the needs of patients with high levels of sensitisation.

### **Matching the prognosis of the donor kidney to the estimated survival of the recipient (also known as survival-matching)**

The wide range of donor characteristics means that the prognosis for donated kidneys post-transplantation also varies widely. Kidneys from elderly donors with significant cardiovascular disease are not likely to function for as long after transplantation as kidneys from younger, disease-free donors. If kidneys with a long survival prognosis are transplanted into patients with a shorter estimated survival, years of utility from that kidney may be lost.<sup>14,15</sup> If kidneys with a short estimated survival are transplanted into a healthy recipient with an excellent prognosis, the recipient may require premature retransplantation. Both situations are potentially inefficient and wasteful. Some level of matching of the prognosis of the donor kidney and the recipient (referred to as "survival matching") can improve the efficiency of kidney transplantation overall and maximise the benefit that is derived from the limited number of deceased donor kidneys available. In Australia, protocols for survival-matching of organs to recipients are being currently developed, and this principle will almost certainly be incorporated into future kidney allocation algorithms.

### **Facilitating greater HLA (tissue) matching for younger, healthier patients who are likely to require re-transplantation in their lifetime**

Exposure to a kidney transplant is one way that patients can become sensitised—that is, develop antibodies against other tissue types (HLA molecules). This can limit the patient's ability to find a suitable second (or subsequent) kidney if they require retransplantation in the future. Younger, healthier patients are most likely to need a second or subsequent transplant because in many cases they outlive their original graft. If better immunological matching can be achieved for these patients, it may improve their chances of successful retransplant in the future.

Potential changes to the Australia allocation algorithms in an effort to improve immunological matching for younger recipients are currently being explored by RTAC. NOMS was built in 1999, and as such is not fully equipped to meet many of these new challenges. RTAC recognises that it may be impossible to incorporate very complex changes to the allocation algorithm into NOMS in its current state. RTAC is therefore considering making some initial short-term changes to try to achieve as much improvement as possible within current technical limitations. Work towards a more sophisticated long-term solution will also proceed, in parallel with scoping work that has already commenced towards the modernisation of the NOMS computer system.

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# 6 Liver

## 6.1 Preamble

Liver transplantation is a highly successful treatment for advanced liver disease, both in terms of extending and improving quality of life. The demand for liver transplantation and the shortfall in the number of donor organs available means that it is not currently possible to transplant every patient who might individually derive benefit from the procedure. This imbalance means that if every patient who stood to benefit from liver transplantation—even if only marginally—was placed on the waiting list then the list, and therefore waiting times, would become so long that most patients would die before ever being offered a transplant. In this scenario, many patients receiving a liver transplant would have their lives extended only marginally, while others—for whom liver transplantation might extend their lives by decades—would die on the waiting list. Therefore liver transplantation is offered only to patients whose liver disease is of such a severity that their risk of dying within two years without a transplant exceeds 50%.

At the same time, it is necessary to strike a balance between maximising access to liver transplantation for those who would die without it and achieving the best possible outcome from each transplant. This balance is the single most difficult issue in liver transplantation because there is no “maintenance” treatment equivalent to renal dialysis, and thus there is only a finite time that patients can wait for a liver transplant. For the past 20 years, it has been agreed by the liver transplant units in Australia and New Zealand that eligibility for entry to the liver transplant waiting list should be set at an expectation that a patient has a greater than 50% likelihood of surviving at least five years after liver transplantation; this aligns with international benchmarks. In 2013, five-year survival among liver transplant recipients in Australia and New Zealand was over 80%, while waiting list mortality was approximately 10%.<sup>1</sup>

There are arguments for and against setting such minimal listing criteria or “survivorship thresholds”; this difficult area—of balancing utility versus individual equity—is informed by the Ethical Guidelines.<sup>2</sup> It should also be appreciated that there are some patients with liver disease who would not benefit from liver transplantation. Liver transplantation is a massive surgical procedure, and the associated risks can outweigh the risks associated with the natural history of the underlying liver disease. Therefore minimal listing criteria are needed in order to prevent patients with less severe liver disease from being offered a liver transplant that would be riskier than continuing to live with their liver disease.

Additional complexity arises because the manifestations of liver disease are varied. There is no single indicator of liver dysfunction (unlike, by comparison, serum creatinine level in chronic kidney disease) that allows transplant units to track the decline of patients with liver disease, or to compare the severity of liver disease between patients (although the MELD score comes closer than many other systems; see below). Furthermore, not all patients in need of a liver transplant will die from liver failure without one. A common example is patients with Hepatocellular Cancer (HCC)—these patients have underlying chronic liver disease but their survival is usually determined by the progression of the cancer rather than the failure of liver function. The particular relationship between HCC and eligibility for liver transplantation is covered in Section 6.2.3. Thus it is difficult to “rank” the urgency of the need for liver transplant for patients on the waiting list. This is discussed in more detail in Section 6.3.

In the case of liver allocation, unlike other forms of solid organ transplantation, tissue matching beyond simple ABO blood group compatibility has little impact on transplant outcomes. However, there are other factors that are very important considerations in liver allocation, from technical factors such as size (a liver retrieved from a very large donor may not fit in a small transplant recipient and conversely a small liver may not provide adequate function in a large recipient), to how well the graft is likely to work initially (very sick recipients do not tolerate donor livers that have impaired function immediately after transplant), to complex logistical issues related to organ transportation (long preservation times resulting from transporting a donor liver over a great distance can

have serious negative effects on the transplant outcome). The general principle is that a donor liver is allocated to the sickest patient for whom the liver is suitable: if the liver is of an incompatible blood type or there is a size mismatch then it would not be helpful to transplant it into the sickest patient on the waiting list—in this case it would be offered to the next sickest patient for whom there would be an acceptable chance of successful transplantation with that organ. In this way, allocation decisions are made to enable the best outcome from every transplant.

Most deceased donor livers are allocated to patients with chronic liver disease on a state-based allocation system. However, there are situations where the liver can suddenly fail without warning, such as in acute Hepatitis B infection or paracetamol poisoning, and in these situations patients can present to hospital and die within days. Additionally, children with a rare form of liver cancer called hepatoblastoma need access to liver transplantation in a time-sensitive manner (liver transplantation needs to occur rapidly after chemotherapy treatment is completed to secure the best chance of cure). The circumstances of urgent liver transplantation are very different from the circumstances under which patients with chronic liver disease are transplanted, and therefore waiting list management for acute and urgent patients is discussed separately in Section 6.3.3.

## Organisation of liver transplantation in Australia and New Zealand

Each state in Australia has a single liver transplant unit. There is a single unit in Auckland that serves New Zealand. The New Zealand unit is broadly aligned with the units in Australia and participates in the sharing of donor livers between the jurisdictions as described in Section 6.5. The liver transplant units and their corresponding donor jurisdictions are as follows:

Jurisdiction of donor hospital	Location of liver transplant unit
WA, SA, NT	WA, SA
QLD and northern NSW (state border to Coffs Harbour)	QLD
NSW, ACT	NSW
VIC, TAS	VIC
NZ	NZ

Each of the liver transplant units also undertakes multi-organ donor retrieval procedures as a service for the organ donation agencies that exist in each jurisdiction. Although the population of Australia and New Zealand is small compared to many European countries, the geography is very different – each liver transplant unit in Australia covers an area bigger than Western Europe and this is one of the reasons why organ allocation is organised on a jurisdictional, rather than national, basis.

## 6.2 Recipient eligibility criteria

### 6.2.1 Inclusion criteria

As a general principle, eligibility is restricted to patients for whom quality and quantity of life is expected to be enhanced by liver transplantation. Given the availability of donor organs and the risks to the patient of liver transplant surgery, patients will only be listed for liver transplantation once their liver disease poses an imminent threat to their survival or their quality of life has become intolerably poor.

Liver disease has many different manifestations and, in contrast to renal disease, it is difficult to describe the severity of an individual's liver disease with a single metric. In the United States in the late 1990s it was recognised that access to and timing of liver transplantation varied greatly around the country—some patients whose health was barely impacted by their liver disease were receiving transplants whilst many others died before receiving a lifesaving transplant. This stimulated the development of a scoring system, the Model for End-Stage Liver Disease (MELD) score, which correlates with how long a patient is likely to survive without a liver transplant (Table 6.1).

MELD score is a measure of the severity of an individual's liver failure, calculated using a mathematical formula based on blood tests: the higher the score, the greater the severity of liver failure. The Paediatric End-Stage Liver Disease (PELD) score is an equivalent system adjusted for children. The score has a reasonable, but not perfect, ability to predict the risk of dying from liver failure in the near future (3 months). It has allowed jurisdictions in the United States to allocate livers based on need alone. This is particularly important where many centres 'compete' for donor livers, and the MELD score-based allocation system has been implemented to reduce 'gaming' of the system by individual centres for their own, and their patient's benefit. It must be recognised, however, that it is quite common to have severe liver disease, posing an imminent threat to life, where the MELD score is still relatively low. In Australia and New Zealand, where all livers go to a single centre (i.e. there is no competition) the liver can be allocated to the individual with the truly greatest need even if they do not have the highest MELD score. In Australia and New Zealand, the patients are ranked within each transplant centre according to clinical need, which takes into account their MELD scores but also other less easily measured factors.

There are some patients who, although their survival is not immediately threatened, have an intolerably poor quality of life as a result of their liver disease. The best example would be patients with polycystic liver and kidney disease, for whom liver function may not be impaired but the liver can reach such a size that it completely fills their abdominal cavity and results in starvation because the patient becomes physically unable to eat.

Typical indications for liver transplantation in patients with chronic liver disease are:

- MELD score of >15 in an adult or a PELD score of >17 in a child (see Table 6.1)<sup>3</sup>
- Hepatocellular carcinoma (HCC) that fulfils the University of California, San Francisco (UCSF) criteria<sup>4</sup>
- Liver disease that would result in a two-year mortality risk of >50% without liver transplantation
- Diuretic-resistant ascites
- Recurrent hepatic encephalopathy
- Recurrent spontaneous bacterial peritonitis
- Recurrent or persistent gastrointestinal haemorrhage
- Intractable cholangitis (in primary or secondary sclerosing cholangitis patients)
- Hepatopulmonary syndrome<sup>5</sup>
- Portopulmonary hypertension<sup>5</sup>
- Metabolic syndromes (with severe or life-threatening symptoms) that are curable with liver transplantation (e.g. familial amyloidosis, urea cycle disorders, oxalosis etc.)
- Polycystic liver disease with severe or life-threatening symptoms
- Intractable itch secondary to cholestatic liver disease
- Hepatoblastoma in children.

**Table 6.1:** Calculation of MELD, PELD and HCC MELD scores<sup>a</sup>

<b>MELD score</b>	$= 0.957 \times \text{Log}_e(\text{creatinine mg/dL}) + 0.378 \times \text{Log}_e(\text{bilirubin mg/dL}) + 1.120 \times \text{Log}_e(\text{INR}) + 0.643$ Multiply the score by 10 and round to the nearest whole number
Notes: Laboratory values of <1.0 are set to 1.0 for the purposes of the MELD calculation; the maximum serum creatinine is 4.0 mg/dL, this includes those patients on dialysis.	
<b>PELD score</b>	$= 0.480 \times \text{Log}_e(\text{bilirubin mg/dL}) + 1.857 \times \text{Log}_e(\text{INR}) - 0.687 \times \text{Log}_e(\text{albumin g/dL}) + 0.436$ if patient is <1 year old + 0.667 if the patient has growth failure (<2 standard deviations below the mean) Multiply the score by 10 and round to the nearest whole number
Notes: Laboratory values of <1.0 are set to 1.0 for the purposes of the PELD calculation	
<b>HCC MELD</b>	If the maximum tumour diameter is >2cm but total tumour burden is within UCSF criteria (i.e. solitary tumour not >6.5 cm in diameter, or 3 or fewer nodules with the largest lesion not >4.5 cm in diameter and total diameter of all tumours not >8cm), and without evidence of vascular invasion, then a score of 22 will be allocated to the patient. An additional 2 points will be allocated for every 3 months on the waiting list. If the maximum tumour diameter is ≤2cm there will be no HCC MELD points allocated to the patient. This patient's score will be the standard MELD score only.

<sup>a</sup> <http://www.unos.org/resources/meldpeldcalculator.asp>

## 6.2.2 Exclusion criteria

Patients who are estimated to have less than a 50% likelihood of surviving at least five years after liver transplantation, and patients who are predicted to have an unacceptably poor quality of life post-transplant, are considered ineligible for wait-listing. Exclusion criteria therefore include those conditions or circumstances (medical or psychosocial) that would make the risk of mortality at five years post-transplant exceed 50%. The assessment of risk associated with coexisting conditions is complex and many patients require detailed appraisal by specialists across multiple fields before determining whether a patient should be excluded from entry to the waiting list. The NHMRC Ethical Guidelines underpin the specified exclusion criteria.<sup>2</sup> Past behaviours such as intravenous drug use or alcohol dependence are not acceptable as reasons for exclusion from the liver transplant waiting list, but if these behaviours are ongoing then they would be considered exclusionary as they threaten the outcome of the transplant. The following list of contraindications to liver transplantation is indicative but not exhaustive:

- Malignancy (prior or current, except for HCC within UCSF criteria);<sup>6</sup> these cases often require detailed discussion between transplant units and oncologists prior to the patient being assessed for transplantation because the prognosis of different cancers varies widely
- Active infection (other than hepatitis B, hepatitis C, or HIV)—tuberculosis for example
- Coronary artery disease that is irremediable or associated with a poor prognosis
- Cerebrovascular disease that is irremediable or associated with a poor prognosis
- Severe metabolic syndrome (hypertension, morbid obesity, hyperlipidaemia, and type II diabetes, with or without obstructive sleep apnoea)<sup>7</sup>
- Extreme inanition or frailty not thought to be reversible by liver transplantation
- Patients at risk of alcohol recidivism. For those patients where alcohol was a contributing factor in their liver disease, careful assessment by a multidisciplinary team of the risk to post-transplant outcomes posed by recidivism is required. As a general rule, a period of abstinence of not less than six months will need to be observed before acceptance onto the waiting list.<sup>8</sup> This time frame has been applied to prevent patients being transplanted with acute alcoholic hepatitis (in this group transplant outcomes are universally poor), and to exclude patients with alcoholic liver disease whose liver function will improve with abstinence to the point where liver transplantation is no longer needed. If assessment of recidivism risk is unfavourable then this is a contra-indication to proceeding with transplantation because of the risk of compromised outcomes
- Ongoing misuse of any substance that might compromise survival of the graft
- A likelihood that the recipient will be unable to adhere to the necessary ongoing treatment regimen and health advice after transplantation
- Tobacco use is a relative contraindication to liver transplantation (because of an increased risk of malignancy and cardiovascular disease)<sup>9,10</sup>
- Inadequate or absent social support is a relative contraindication to liver transplantation (because of an increased risk of non-adherence)<sup>11,12</sup>
- Hepatopulmonary Syndrome—current evidence shows that patients with this condition who have a partial pressure of oxygen on room air of <40 mmHg have an unacceptably high perioperative mortality rate (30 to 40%)<sup>5</sup>
- Portopulmonary hypertension—current evidence shows that patients with this condition who have, despite treatment, a mean pulmonary artery pressure of >35 mmHg and a pulmonary vascular resistance of >250 dynes.sec.cm<sup>-5</sup> (3.1 Woods units)<sup>7</sup> have an unacceptably high perioperative mortality rate (30 to 40%, with patients often succumbing during the transplant surgery)<sup>5</sup>
- Neurocognitive impairment is not an absolute exclusion criterion, but all units are aware that such patients and their carers may find that the outcome of transplantation is not as good as they hoped, with little improvement in quality of life. Patients with severe neurocognitive impairment require an exceptionally careful evaluation.

### 6.2.3 Hepatocellular carcinoma

HCC typically arises in a setting of chronic liver disease and is an unusual malignancy in an otherwise normal liver. Any patient with cirrhosis has an increased risk of HCC, but that risk is greater in liver disease arising from certain causes such as hepatitis B, hepatitis C and haemochromatosis. While patients with a single small HCC can often be treated with liver resection or ablation, others can only be cured by liver transplantation. Establishing which HCC patients are eligible for transplantation is complex. There is substantial heterogeneity in the way that tumours behave, and predicting the natural history of disease progression in the HCC patient is not straightforward. Furthermore, the “severity” or stage of a HCC is variable, and it has been established for more than two decades that there is a high risk of recurrence if liver transplantation is performed in the context of advanced HCC.

In Australia and New Zealand, it has been shown that transplant outcomes are acceptable if the UCSF criteria are used to determine eligibility for liver transplantation.<sup>13</sup> Using these eligibility criteria, five-year post-transplant survival of HCC patients currently stands at 70%, with low rates of HCC recurrence.<sup>1</sup> However, despite acceptable outcomes, the UCSF criteria are imperfect for a number of reasons. They are based on imaging criteria and it is well known that the accuracy of HCC imaging is problematic. Furthermore, the imaging criteria are essentially surrogate markers for the actual features of HCC that are the important determinants of outcome—specifically the presence or absence of vascular invasion and the differentiation status of the cancer. These features of HCC can only be assessed after the liver transplant has been done, when the patient’s own liver can be examined histologically. In addition, recent data indicate that patients with HCC in whom the serum alpha-fetoprotein (AFP) is markedly elevated or rising quickly have poor outcomes after liver transplantation, and therefore transplantation should not be offered in this setting.<sup>14,15</sup> There are also data to suggest that the response of HCC to pre-transplant treatment such as chemoembolisation (TACE) is strongly correlated with the likelihood of post-transplant HCC recurrence.<sup>16</sup> In Australia and New Zealand, patients with HCC are eligible for liver transplantation if their tumour burden lies within UCSF criteria, but the presence of other strongly adverse factors such as a highly elevated AFP (> 1000 mg/L) or poor response to TACE is taken into account and can be a reason for exclusion from the waiting list.

Further advances are being made in the staging of HCC. PET-CT scanning shows promise as a new imaging modality with prognostic capability in patients with HCC.<sup>17</sup> Other tumour markers are also under evaluation internationally and may also find general application in the future.<sup>18</sup>

Another source of complexity in liver transplantation for HCC is the degree of waiting list priority given to such patients. Paradoxically, if all of HCC patients were assigned top priority and transplanted very quickly, then overall outcomes for patients on the liver transplant waiting list may actually suffer because some patients would have aggressive HCC that would recur after transplantation no matter how quickly they were transplanted. Meanwhile, waiting times and therefore waiting list mortality would increase for the other, non-HCC patients. On the other hand, HCC patients often do not have severe enough liver failure to give them priority based on their MELD score, and there is a need to award some degree of priority to enable them to be transplanted before their cancer progresses to the point of ineligibility (but without compromising the prospects of non-HCC patients). The incidence of HCC is rapidly rising and the question of appropriate priority for waitlisted HCC patients is, internationally, a very difficult problem to solve equitably.

### 6.2.4 Retransplantation

Patients are eligible for re-transplantation if they fulfil the same criteria for either acute or chronic liver disease as stated above, with an estimated likelihood of surviving at least five years post-retransplantation exceeding 50%.

## 6.3 Waiting list management

### 6.3.1 Principles of prioritisation for liver transplantation

For patients with chronic liver disease who are waitlisted for liver transplantation, care is provided at one of the Australian or New Zealand liver transplant units, which co-align with organ donation services. It is logistically complex to transport donor livers around Australia and New Zealand; furthermore, organ donation rates are such that it is most efficient to organise liver transplant services at the state level. Therefore livers donated in a given jurisdiction are allocated to patients on the waiting lists of the transplant units that correspond to that donor jurisdiction (unless there is a patient on the urgent waiting list—see Section 6.3.3). It is therefore necessary for each liver transplant unit to be very familiar with the patients on their waiting list and to prioritise them according to clinical urgency in order to minimise waiting list mortality.

Patients on the liver transplant waiting list are grouped according to the blood group of the donor liver that the patient on the waiting list would ideally receive, and then prioritised according to clinical urgency within each blood group. The waiting list is organised in this way to promote equitable outcomes across recipient blood groups. Usually this will mean that recipients will receive only a liver with the identical blood group to their own. However, in some circumstances where a patient is extremely unwell they might receive a liver that would otherwise have been allocated to other blood group lists. For example, a blood group O liver can be transplanted into a patient of any blood group, and this may occasionally be necessary to save the life of a very sick patient of another blood group. Conversely, subtype 2 of blood group A is compatible with blood group O, and hence A<sub>2</sub> livers can be transplanted into O recipients. Blood group incompatible transplants can also be performed, but these are rare and only performed when patient risk assessment suggests that it is justified and certain technical manipulations are undertaken.

Prioritisation is NOT based on the length of time that patients have been on the liver transplant waiting list: the principle is always “sickest first”. Prioritisation is based largely on MELD score, but other features of liver disease (such as encephalopathy) may justify prioritisation above patients with higher MELD scores. In the United States, such patients are termed “MELD exceptions” in recognition that their MELD scores don’t serve them equitably, and there is a complex protocol in place to enhance their priority. An example would be patients with primary sclerosing cholangitis, who are prone to serious recurrent bacterial cholangitis with blood poisoning yet who frequently have low MELD scores. There are also a number of rare diseases where the liver doesn’t fail but has a metabolic defect—in the manufacture of an important protein for example—which leads to life threatening disease in another organ system (amyloidosis is an example). The liver transplant units in Australia and New Zealand individually work out how to prioritise such patients on their waiting lists.

Each unit reviews their waiting list at least weekly and discusses the priority of listed patients. In this way, patients who deteriorate—especially if this isn’t reflected in their MELD score—can be re-prioritised. In Australia and New Zealand, prioritisation occurs by clinical consensus among all members of the transplant unit. At the time of a liver donor offer the selection of a recipient is then relatively straightforward and can be made by one or two individuals rather than the entire clinical group, as patients have been ranked by need ahead of time.

### 6.3.2 Ongoing review

In the same way that a patient listed for urgent liver transplantation can deteriorate to a point where transplantation becomes futile, so might non-urgent patients need to be delisted because their situation has changed in such a way that they are no longer likely to benefit from a liver transplant. The commonest reason for this is cancer progression in patients with HCC, where the tumour(s) has grown to the point where the risk of recurrence after transplant is unacceptably high.

Clinical circumstances can arise that mean that a patient needs to be temporarily removed from the ‘active’ waiting list. An example would be a significant infection, causing an acute illness such that liver transplantation at that time would be hazardous. These patients are placed on a ‘hold’ list that allows them to still be reviewed at the transplant unit clinical meetings and, when appropriate (e.g. after the infection is successfully treated), they

can be returned to the active list or permanently delisted if necessary. Patients are informed of such changes in listing status whenever they occur. The reasons for the status change should be made clear to the patient or, if appropriate, to their next of kin.

### 6.3.3 Acute and urgent patients

There are situations in which the need for liver transplantation occurs suddenly and without a history of pre-existing liver disease. Sometimes this happens, for instance, in patients newly infected with hepatitis B where the liver is rapidly overwhelmed by the virus. Paracetamol poisoning is another example. However, in some patients no cause of acute liver failure can be established. There is also a small risk in patients who have recently undergone liver transplantation that the donor liver may not work, due either to primary non-function or hepatic arterial thrombosis. Many patients with acute liver dysfunction will recover spontaneously as the liver cells overcome the causative insult—only a few patients will actually require urgent liver transplantation. In Australia and New Zealand, the Kings College criteria are used to determine whether a patient needs urgent liver transplantation. It is recognised that the urgency of the situation is not always the same from one patient to another—in the most extreme cases, where the patient is in a coma and on a ventilator (life support), the patient may have less than 24 hours to live and is placed in category 1. Less serious cases, where the data indicate severely impaired liver function but the patient is not yet ventilated, are placed in category 2a.

#### King's College Hospital criteria for liver transplantation in acute liver failure

1. Paracetamol (acetaminophen)-induced liver failure:  
pH of arterial blood (after rehydration) of  $<7.3$ , OR  
All three of the following criteria on the same day:
  - International normalised ratio (INR)  $>6.5$
  - Serum creatinine  $>300$  micromol/L
  - Grade III or IV encephalopathy.
2. Non-paracetamol-induced acute liver failure:  
INR  $>6.5$ , OR  
Three of the following five criteria:
  - Age  $<11$  or  $>40$
  - Serum bilirubin  $>300$  micromol/L; jaundice-to-encephalopathy time of  $>7$  days; INR  $>3.5$
  - Drug induced liver disease or viral hepatitis as aetiology.

For urgent liver transplantation, recipient prioritisation and allocation of donor livers is conducted on an Australia and New Zealand-wide basis (i.e. binational listing). This is because the populations served by the individual jurisdictions (Australian States and New Zealand) are too small to realistically offer a good chance of a donor liver becoming available for urgent patients in the necessary timeframe. It has been agreed that patients fitting the criteria for urgent listing should have access to donor livers across all of Australia and New Zealand. Since less than 10% of liver transplants are performed in urgent patients, this does not seriously impact upon waitlisted patients with chronic liver disease. However, to reduce the possibility that patients with chronic liver disease might be adversely affected by urgent listings, two categories of urgency exist. Extremely sick patients are placed in category 1: any donor liver that becomes available anywhere in Australia or New Zealand is automatically offered to a patient in category 1. It is possible, however, that there might be patients with chronic liver disease who are on the waiting list and, although not listed as urgent, may be at greater risk of dying than an urgent patient in Category 2a. Thus, when a donor liver becomes available in a given jurisdiction and there is a category 2a patient listed elsewhere in Australia or New Zealand, a discussion needs to occur between the jurisdiction listing the category 2a patient and the jurisdiction where the liver is available to ensure that the liver is in fact directed to the sickest patient. In practice, this is nearly always to the category 2a patient.

There are two further types of category 2 patients: Category 2b, which refers to children with hepatoblastoma in whom liver transplantation needs to occur quickly at the conclusion of chemotherapy treatment so that cure can confidently be achieved; and Category 2c, which refers to patients who need combined liver and intestinal (small bowel) transplantation. It is exceptionally difficult to find suitable grafts for Category 2c patients, who also present

a formidable surgical challenge as well as having a high risk of dying whilst they await transplantation. It has been agreed across all liver transplant units that Category 2c patients will be accorded national prioritisation; however it has also been agreed that donor livers will not be sent to the National Intestinal Transplant Unit (part of the Liver Transplant Unit Victoria) if the jurisdiction in which the liver was donated has a patient on their waiting list with a MELD score of 25 or greater (such patients have a 50% chance of death within a month). In the case of both Category 2b and Category 2c patients, discussion regarding liver allocation needs to take place between the urgent listing unit and the jurisdiction in which a donor liver has become available before allocation takes place.

**Table 6.2:** Categories of patients eligible for urgent liver transplantation

<b>Category 1</b>	
Patients suitable for transplantation with acute liver failure who are ventilated and in an ICU at risk of imminent death. When such patients are listed, allocation to them is mandatory.	
<b>Category 2</b>	
When a donor liver becomes available, discussion occurs between the urgent listing unit and the local retrieving unit to determine optimal allocation.	
<b>Category 2a</b>	Patients suitable for transplantation with acute liver failure from whatever cause who are not yet ventilated but who meet the King's College criteria. This includes patients who have acute liver failure because of vascular thrombosis in a liver allograft. In addition, this category includes paediatric candidates with severe acute or chronic liver disease who have deteriorated and are in a paediatric intensive care unit. When such patients are listed, allocation to them is usual but not mandatory. It is subject to discussion between the directors (or delegates) of donor and recipient state (or New Zealand) liver transplant centres.
<b>Category 2b</b>	Paediatric patients suitable for transplantation who suffer from severe metabolic disorders or hepatoblastoma (after initial treatment) for whom a limited time period exists during which liver transplant is possible.
<b>Category 2c</b>	Patients awaiting combined liver-intestinal transplantation by the National Intestinal Transplantation programme in Victoria. If a potentially suitable donor is identified, the home unit must discuss allocation of donor organs with the Victoria unit unless the home unit has a suitable liver recipient with a MELD score of 25 or greater.

### Listing and delisting of acute and urgent patients

The assessment of patients needing urgent liver transplantation is complex, and the situation is never static. Some acute patients improve while they are waiting for a donor organ, and therefore can be removed from the waiting list (delisted) because they no longer need a transplant to survive. Other patients unfortunately deteriorate while waiting for an urgent liver transplant and may reach a point where transplantation is futile, in which case they must be delisted. An example of this would be the onset of brain swelling when, even if a transplant is undertaken, the ensuing brain damage cannot be reversed and would prove fatal.

Patients listed for urgent liver transplantation must be frequently re-assessed. The listing automatically expires after 72 hours for category 1 and category 2a patients, and after 7 days for category 2b patients, so that patients must be formally relisted at these time points if liver transplantation is still required. Category 2c are exempted from the relisting requirements because they are not in a situation where their condition is expected to improve (however they may require delisting if there is a change in circumstances such that transplantation is no longer appropriate).

## 6.4 Donor assessment

All donor organs are precious, and the altruistic act by donor families of consenting to deceased donation in the most difficult and tragic of circumstances is gratefully and respectfully acknowledged. The goal of organ transplantation is to save and improve lives; in some circumstances, however, a potential donor liver may carry some risk of not achieving this goal. The worst case scenario is that the liver does not function after transplantation, in which case the recipient of that liver will die (unless a second donor liver quickly becomes

available). There is also the potential transmission of infection or cancer from the organ donor to the recipient via the donor liver. Chapter 2 of this document provides more detailed information about risks of disease transmission and donor eligibility. Organs from persons with HIV for example are not used in Australia and New Zealand, likewise persons who have active cancer are not eligible to be organ donors (except some of the less serious forms of skin cancer and some primary brain cancers).

The assessment of donor eligibility and the suitability of organs for transplantation is one of the most difficult and complex areas of liver transplantation. Decision-making is frequently not straightforward: patients on the waiting list are at risk of dying without a transplant so it may be preferable to accept a higher-risk donor liver when offered rather than wait for a lower-risk one, not knowing how long that wait might be. Of course, the risk-benefit calculation is not the same for all patients. The HCC patient with a tumour that is approaching the size threshold for delisting will present a different risk-benefit scenario with regards to utilisation of a higher-risk donor liver as compared to stable a patient with cirrhosis from hepatitis C. Balancing the risks associated with a given donor organ against recipient urgency is one of the most difficult tasks faced by liver transplant units.

During the assessment and workup of potential liver transplant recipients, donor-related risk as it relates to the individual patient needs to be thoroughly explained as part of the consent process. Thus, a patient who is very unwell and at high risk of imminent death may be advised to accept a higher-risk liver—for example, a liver retrieved from a donor carrying the hepatitis B virus. The recipient of this graft may then require lifelong anti-viral treatment, but this may be acceptable if such a donor liver represents the only opportunity for this very sick patient to receive a transplant. On the other hand, a liver from a hepatitis B-positive donor or other higher-risk donor might not be suitable for a young child.

As well as the general donor eligibility criteria described in Chapter 2, there are some specific donor considerations relevant to liver transplantation. In contrast to the considerations related to higher-risk donor organs, it is also possible to identify donor livers that carry very low risk of either immediate or long-term dysfunction. In the case of low-risk livers, there is a commitment in Australia and New Zealand that these will be “split” wherever possible—typically generating a small left-sided graft and a larger right-sided one. Thus the single donor liver can be transplanted into two people. This is especially relevant to the transplantation of children, who usually only require a small graft—the left side being ideal. Such donors are young (less than 50 years of age), have been diagnosed with brain death, have no risks factors for infection or malignancy, and their management in ICU has been straightforward, without any cardiovascular instability and little requirement for blood pressure support with drugs.

### 6.4.1 Donor-related risk

#### Risks to liver function

Certain donor-related factors are likely to influence the post-transplantation outcomes of their liver, including:

- Age
- Length of hospital stay
- Length of ICU stay
- Cold ischaemia time
- Fatty liver
- Cause of death
- Donation after circulatory death (DCD).

Risk assessment of liver donors is recognised to require considerable experience in the field of liver transplantation. The Donor Risk Index (DRI), developed in Michigan, is an “integrated” measure of liver donor risk widely used in the United States.<sup>19</sup> However, the United States DRI has been found to have poor discriminatory power when applied to European donor cohorts, and would be expected to perform similarly poorly if applied in Australia and New Zealand. Efforts are therefore underway to develop an Australian and New Zealand DRI and it is likely that this tool will be available in the next 5 years. Extra investigations may also sometimes be helpful in determining suitability for liver donation, such as a biopsy of a donor liver to examine the extent of steatosis (fat) in the liver (severe steatosis can pose a severe threat of a liver transplant failing to function).

## Risk of donor transmitted disease

Although HIV is considered an absolute contraindication to organ donation, some persons with chronic infections can be considered as potential donors. Hepatitis C infection does not always damage the liver and infected donor livers can be used for transplantation into patients with pre-existing hepatitis C.

A common and more difficult scenario is when there is a potential risk of viral transmission, which may be small but is not zero. An example would be an intravenous drug user who dies of an overdose and is then considered as a potential organ donor. Even if tests for viral infection are negative, there is still a small possibility that infection is present and viral transmission could occur. However, if there is a patient on the waiting list who is in imminent danger of death or delisting, the risk of viral transmission might be acceptable to them. Critical to this decision process is the provision of adequate counselling for the potential recipient in order that they can give properly informed consent if they choose to proceed with transplantation in these circumstances.

## Technical considerations

Very small donor livers such as those retrieved from newborn babies present great technical difficulties to transplantation. On rare occasions, there might be a young child in such desperate need of liver transplantation that this would be undertaken. This is an area of practice that is currently under re-evaluation, but at the present time the use of neonatal organ donors is not established in clinical practice.

With the increasing number of referrals of older potential donors, the possibility of severe vascular disease in organs from older donors is noted. On occasion, this can be so severe that the donor liver cannot be safely transplanted.

## 6.5 Allocation

### 6.5.1 General allocation principles

Given the adverse impact of longer ischaemia times on transplant outcomes, the transportation of donor livers over long distances is considered to be undesirable. Therefore, for efficiency and optimal transplant outcomes, the allocation of donor livers is organised at the level of the states and New Zealand (as opposed to binational allocation for urgently listed patients). The principle of allocation is to provide the best possible outcome for the highest priority patient on the waiting list for whom that liver would be a suitable match. Organ quality is not uniform, and therefore liver allocation must strike a balance between the expected outcomes of transplantation with a particular donor liver (i.e. benefit/utility) versus the risk of remaining on the waiting list for an unknown length of time (i.e. urgency/justice).

There are fewer problems of tissue compatibility in liver transplantation than there are for other forms of solid organ transplantation. Mismatches of HLA tissue types are of little relevance in liver transplantation and hence tissue cross-matching is not taken into consideration. In contrast, however, while liver transplantation between incompatible ABO blood groups is possible, it is a complex and higher-risk undertaking (with the exception of very young children). Therefore, the first principle of liver allocation is to match donors with recipients of the same, or at least a compatible, blood group. It is appreciated that there is the potential for blood group O livers, because they are universally compatible, to be allocated to recipients of other blood groups to the detriment of blood group O patients on the waiting list. All units make every effort to avoid this situation. Additionally, there is an argument in favour of transplanting blood group A subtype 2 (A<sub>2</sub>) livers into blood group O recipients (blood types A<sub>2</sub> and O are compatible) to redress some of the inequity in allocation faced by the blood group O waitlisted population.

Other factors to be considered in liver allocation include organ size, risks of poor or delayed graft function, and hepatitis C status of the donor. Gross size discrepancy between the organ donor and the recipient may lead to situations where the donor liver is too big to be physically transplanted into the recipient or, conversely, where it is too small to support life. More difficult, however, are allocation decisions in a situation where the donor liver

carries several risk factors that indicate it may not function well post-transplant. On the one hand, such a liver may prove disastrous if transplanted into a very sick recipient who would tolerate graft dysfunction poorly. On the other hand, that patient might die if they were to wait for another, hopefully better, organ. Allocation decisions are often very difficult to make but are guided by the principle of trying to provide the best possible outcome for the highest priority patient on the waiting list for whom that liver would be a suitable match.

Allocation decisions occasionally deviate from the predetermined order of waiting list priority. For example, if a unit were undertaking two liver transplants in one day, resources may be stretched and therefore the second liver may be allocated to a lower priority patient who is anticipated to be more straight-forward surgically. It is therefore important that allocation activity and decision-making is recorded, audited, and reviewed at the binational level. For some years, the Liver and Intestinal Transplantation Advisory Committee (LITAC) have annually reviewed allocation decisions made by all transplant jurisdictions in Australia and New Zealand. Recently, LITAC has determined that the results of this annual audit will in future be made available to the public.

### 6.5.2 Allocation pathway

Any liver becoming available from a deceased donor within Australia or New Zealand is first to be offered to patients listed as urgent. If there are no suitable urgent (including paediatric) candidates on the waiting list, the liver will go to the ABO blood group identical recipient with the highest clinical priority (see Section 6.3).

Often, but not always, clinical priority will align with MELD/PELD score ranking. However, there are other considerations that influence how a donor liver is allocated. The following factors may be relevant (and the reasons for the variance in allocation must be prospectively recorded):

- The presence of a patient on the list with HCC
- The quality of the donor liver—higher-risk donor livers may be utilised but can be problematic in patients with very high MELD scores (although it is recognised that such patients also have a higher risk of dying whilst waiting for a better liver to be offered)<sup>1-3</sup>
- 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\*
- Donor size—overly large size discrepancies result in poor outcomes, therefore size matching may mean that the patient with the highest MELD/PELD score is not allocated a particular liver
- Logistical considerations—transport, cold storage preservation time, surgeon and operating room staff skill mix and availability, and anticipated hepatectomy time may impact on allocation decisions and result in the patients with the highest MELD/PELD score not being allocated a particular liver.

\*In the event that a donor liver is suitable for splitting between a child and an adult, it may be necessary to allocate the left-sided graft to a paediatric recipient and the right-sided graft to an adult smaller than one who would have been chosen had the liver been used whole. If there is a waiting adult patient *in extremis* for whom it would only be suitable to use the liver whole (rather than the small right hemigraft), then sometimes it is not possible to split the liver (unless the potential paediatric recipient is also gravely ill).

### 6.5.3 Paediatric donor liver allocation

Paediatric organ donors comprise only approximately 5% of all organ donors in Australia and New Zealand, however there is a consensus amongst the liver transplant units in Australia and New Zealand that the allocation of these grafts involves considerations that are separate from the rest of the organ donor pool. It has been agreed that livers retrieved from donors less than 18 years old will be used for paediatric recipients. The reason for this is partly that the grieving parents of a paediatric organ donor may be comforted by knowing their child's liver has gone to another sick child. However, this is also a situation where to do otherwise would potentially deny the possibility of finding an ideal donor for an older child (for whom it can sometimes be very difficult to find a suitably sized liver), and secondly would permit a marked donor-recipient age mismatch. In some cases a paediatric donor liver is big enough to split into 2 grafts, in which case the agreed principle is to use one part for a child while the other part may be allocated according to the usual priority criteria. While there is no minimum

age or weight for paediatric liver donation, it is recognised that the transplantation of livers retrieved from very small donors, particularly neonates, is extremely technically difficult and would usually only be undertaken when there is a child in urgent need of transplantation.

Since the number of children awaiting liver transplant in Australia and New Zealand is low (typically less than 10 at any given point in time), it is often necessary to consider the whole list of children waiting for liver transplantation in Australia and New Zealand to achieve the goal of allocating paediatric donor livers to paediatric recipients.

#### 6.5.4 Organ sharing and rotation

It is important that all donor livers suitable for transplantation are used. After determining that there are no urgent patients to whom a donor liver must be allocated automatically, the organ is available for allocation to the local waiting list in the jurisdiction of retrieval according to the allocation principles already described. On occasion, no suitable local recipient can be identified. In this situation, the liver is offered on to other units around Australia and New Zealand for allocation. This happens infrequently, but an agreed rotation system exists for interstate offers in this situation.

### 6.6 Multi organ transplantation

There are patients who have multi-system diseases for whom to transplant only one organ would not improve their survival. Cystic Fibrosis (CF), for example, not only affects the lungs but also may affect the liver (as well as other body systems). Uncommonly, both the lungs and the liver may need to be transplanted for an improvement in survival to be gained.

The ethical tension that exists in multi-organ transplantation arises because one patient receives organs that could otherwise have saved the lives of two or more patients. However, to give a patient one organ when they need two (or more) is also inefficient because it may not lead to the desired improvement in survival.

#### Combined liver and kidney transplantation

Transplanting a kidney in conjunction with another organ is the commonest form of multi-organ transplantation. Australian eligibility criteria for combined liver-kidney transplantation are as follows:

- Known end-stage kidney disease requiring dialysis
- Chronic kidney disease not requiring dialysis but with an estimated GFR of <30 mL/min and proteinuria of >3 g/day, or with a GFR of <20 mL/min for >3 months
- Acute kidney injury (including hepatorenal syndrome) not requiring dialysis but with an estimated GFR of <25 mL/min for >6 weeks, and
- Known metabolic disease including hyperoxaluria, atypical haemolytic uraemic syndrome with H factor deficiency, or familial amyloidosis affecting primarily the kidney.

Patients who meet these criteria can be considered for combined liver-kidney transplantation. These criteria are concordant with those currently defined by the United States United Network for Organ Sharing.<sup>20</sup> The decision to list a patient for a combined liver/kidney transplant should be taken after workup and assessment by, and discussion between, both the liver and renal transplant teams.

### 6.7 Emerging issues

The field of liver transplantation is constantly evolving, although occasionally there is also a major shift in practice as a result of new developments in science or medicine. An example of this is the introduction of effective antiviral agents for hepatitis B infection. Prior to this, the results of liver transplantation in hepatitis B-infected

patients were unacceptably poor; now, with the availability of these antiviral drugs, survival outcomes for hepatitis B-infected recipients are better than those for recipients transplanted for many other indications.<sup>1</sup> A similar shift in practice and patient outcomes will now likely be observed for patients with hepatitis C as a consequence of the recent development of highly effective antiviral agents for hepatitis C infection. Until now, patients undergoing liver transplantation for hepatitis C would universally infect their transplanted liver. If the transplanted liver subsequently failed, then re-transplantation was typically not offered because results were often poor owing to even greater recurrence of hepatitis C-related liver disease in a second transplant. With the introduction of effective therapy to eradicate hepatitis C infection, such patients should no longer be at risk of losing their graft from hepatitis C recurrence.

The incidence of HCC is forecast to continue to rise for the next two decades, and this will translate into increasing demand for liver transplantation. There is a possibility that HCC patients might place such a demand on the waiting list in the future that outcomes for other patient groups would be compromised. The specific practical difficulty is how much priority to assign wait-listed HCC patients. In the USA, extra HCC-MELD points are currently given, but it is recognised that the weighting given to HCC patients may be excessively generous and it is likely that this will be recalibrated again in the near future. The same difficulty faces Australian and New Zealand liver transplant units, who have not yet settled on a final HCC prioritisation protocol. There is an urgent need to better understand the biology and behaviour of HCC so that eligibility criteria for liver transplantation can be refined, patients appropriately prioritised, and outcomes maintained without compromising other wait-listed patient groups. There is interest in Australia and New Zealand in conducting studies into the effects on waiting list mortality and post-transplant outcomes of pre-transplant down-staging, stratification of risk by tumour marker levels, and assessment by the use of PET-CT imaging.

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# 7 Lung

## 7.1 Preamble

Lung transplantation is a highly effective treatment for advanced lung disease. Generally, a 60% five-year and 40% ten-year survival rate are expected following lung transplantation.<sup>1,2</sup> However, only approximately one in twenty of those individuals with severe lung disease who might benefit from a lung transplant will actually receive one.<sup>3-5</sup>

Due to the scarcity of donor lungs, lung transplantation is offered only to patients who have a two-year likelihood of survival predicted at less than 50% without transplantation and who have no alternative treatment options. Infant and toddler lung transplants (currently not available in Australia and New Zealand) and living-related lung transplants have their own specific issues and are not discussed in this document.

Lung transplantation is a complex therapy with significant risks, and therefore the careful evaluation of all organ systems (with appropriate specialist advice as needed) is a mandatory part of the assessment to evaluate a potential patient's risk of short and long-term morbidity and mortality post-transplantation. As significant contraindications may exist, it follows that not all potential recipients will prove suitable for lung transplantation.<sup>1-7</sup>

It is also possible that, even after active listing for lung transplantation, an individual may subsequently develop a new complication or become too frail to successfully undergo transplantation. In this circumstance, an individual may then be delisted temporarily (if the situation can be resolved) or permanently (if the condition is unresolvable). Intensive interventions such as mechanical ventilation or extracorporeal membrane oxygenation (ECMO) may be used to provide a short-term 'bridge' to lung transplantation, but these are complex therapies that can themselves be associated with patient deterioration to the extent that ultimately transplantation may not be feasible.

The guidelines of the International Society for Heart and Lung Transplantation on patient eligibility for lung transplantation were revised in 2014 with input from Australia and New Zealand, and Australian and New Zealand units follow the recommendations contained within these guidelines.<sup>4-6</sup>

## 7.2 Recipient eligibility criteria

### 7.2.1 Inclusion criteria

Indications for lung transplantation are:

- Progressive respiratory failure despite optimal medical, interventional and surgical treatment, and/or
- Poor quality of life, potentially with intractable symptoms and repeated hospital admissions (e.g. New York Heart Association [NYHA] Class III-IV).

#### **Additional disease-specific candidate selection criteria**

Chronic obstructive pulmonary disease:

- Forced expiratory volume in one second (FEV<sub>1</sub>) <20% of predicted
- Body-mass, airflow obstruction, dyspnea and exercise (BODE) index  $\geq 7$
- Severe exacerbation with hypercapnic respiratory failure or recurrent exacerbations

- Moderate to severe pulmonary hypertension
- $PCO_2 >50$  mmHg and/or  $PO_2 <60$  mmHg.

Cystic Fibrosis:

- Frequent hospitalisation
- $FEV_1 <30\%$  of predicted especially if a rapid downward trajectory is observed
- Increasing antibiotic dependence or resistance
- Life threatening haemoptysis or pneumothorax
- Requirement for non-invasive ventilation
- Development of pulmonary hypertension
- $PCO_2 >50$  mmHg and/or  $PO_2 <60$  mmHg.

Pulmonary Fibrosis:

- Decline in forced vital capacity (FVC) of 10% or more and in diffusing capacity of the lungs for carbon monoxide (DLCO) of 15% or more within the prior 6 months
- Development of pulmonary hypertension
- Hospitalisation because of respiratory decline, acute exacerbation or pneumothorax
- Significant exercise-associated desaturation or requirement for oxygen.

Pulmonary vascular diseases:

- NYHA Functional class III or IV despite escalation of pulmonary vasodilator therapy
- Refractory or progressive right heart failure
- Right heart catheter measurements of mean right atrial pressure  $>15$  mmHg, cardiac index of  $<2$  litres/minute/m<sup>2</sup> and mean pulmonary artery pressure (PAP)  $>50$  mmHg.

## 7.2.2 Exclusion criteria

Contraindications to lung transplantation include any condition or combination of conditions that result in an unacceptably high risk of mortality or morbidity, limiting the likely survival benefit from transplantation or the predicted gain in quality of life. Common examples include (but are not limited to):<sup>4-6</sup>

- Active malignancy other than non-melanoma skin cancer remains an absolute contraindication, with a five-year disease-free interval considered prudent. A two-year disease-free interval with a low predicted risk of recurrence may be reasonable in some cancers, although in these circumstances lung transplant assessment needs to be individualised and includes careful consultation with the patient's oncologist. Some malignancies such as prostate cancer have a high prevalence in the community, and in selected cases (e.g. a low Gleason score) patients may still be considered eligible for lung transplantation even with a disease-free interval of under two years
- Irreversible, significant dysfunction of other organs or body systems is a contraindication to lung transplantation: combined organ transplantation (e.g. heart/lung) may be considered in some cases, however patients must fulfil the eligibility requirements for both organs and an agreed strategy for organ allocation must be in place with the agreement of both individual transplant services at the time the patient is placed on the active waiting list
- Some chronic infections may be an absolute contraindication (e.g. *Burkholderia cenocepacia*, *Mycobacterium abscessus*) if there is no viable post-transplant treatment strategy available. Patients with hepatitis B or C may be suitable for lung transplantation, depending on viral load assays on peripheral blood, absence of chronic liver disease and response to antiviral eradication therapy
- *Mycobacterium tuberculosis* infection: treated pulmonary TB is not a contraindication to lung transplantation, but may require confirmation of adequacy of therapy prior to acceptance for transplantation
- Documented non-adherence, or inability to comply with complex medical therapy or office follow-up (e.g. untreatable psychological or psychiatric condition)<sup>8-10</sup>

- Substance addiction (e.g. alcohol, tobacco or illicit drug use) that is either current or was active within the last 6 months
- Uncorrected atherosclerotic disease with end-organ dysfunction including coronary artery disease not amenable to revascularisation
- Significant chest wall or spinal deformity causing severe restriction
- Body mass index (BMI) >35.0 kg/m<sup>2</sup> is an absolute contraindication; BMI 30.0 – 34.9 kg/m<sup>2</sup>, particularly central obesity, is a relative contraindication that is influenced by ethnicity (e.g. Maori and Pacific Islanders have a higher normal BMI)
- Severe progressive malnutrition
- Complicated diabetes as indicated by established end-organ complications of microvascular disease, diffuse vascular disease and poor glycaemic control (HbA1c >64 mmol/mol or >8%)
- Uncorrectable bleeding
- Absence of an adequate and reliable social support system
- Severely limited mobility with poor rehabilitation potential.

It is likely that the presence of multiple comorbidities in patients over 65 years of age will exclude the majority of such patients from consideration for lung transplantation.<sup>11</sup>

### 7.2.3 Retransplantation

Retransplantation may be an appropriate consideration if an individual deteriorates after receiving a lung transplant and re-qualifies for listing according to the inclusion and exclusion criteria stated above.

## 7.3 Waiting list management

Lung transplant units will generally review patients listed for lung transplantation every 4-8 weeks in an outpatient clinic. A monthly blood test is performed to enable serum collection for cross-matching at the time of organ allocation. Most units perform six-monthly Luminex testing to update the patients' anti-HLA antibody profile.

### 7.3.1 Urgent patients

Urgent patients are allocated deceased donor lungs as per the National Notification document—see Appendix F.

### 7.3.2 Paediatric patients

The nationally funded centre for paediatric lung transplantation resides at the Alfred Hospital in Melbourne, Victoria, with a recommended age range for referral from six to sixteen years.

## 7.4 Donor assessment

### 7.4.1 Donor-related risk

Table 7.1 outlines standard criteria for lung donation. Historically, approximately 35-40% of deceased donor lungs offered for donation in Australia and New Zealand have been considered acceptable for clinical transplantation.<sup>12</sup> This compares with international procurement rates of only 15-20%.<sup>13,14</sup> Specific management protocols have evolved for the potential lung donor that address common scenarios such as retained secretions, aspiration, ventilator-associated pneumonia, barotrauma prevention, atelectasis and neurogenic pulmonary oedema. A higher-risk lung donor is one who has characteristics that may adversely influence the early and/or long-term

transplant outcomes of the chosen recipient. Traditionally, a higher-risk donor has been defined as possessing one of the following characteristics: age >60 years, smoking history >20 pack years, PaO<sub>2</sub> <300 mmHg, chest x-ray positive for infiltrates or trauma, persistent purulent secretions at bronchoscopy or prolonged ischaemic time. Nonetheless, many potential donors with these characteristics will prove suitable for lung donation following careful organ assessment and procurement.<sup>15-17</sup> The evolution of ex-vivo lung perfusion (EVLP) will further enhance acceptance rates for lung donation especially those donors considered very high risk or with multiple risk factors. The EVLP system consists of a perfusion circuit with tubing and a reservoir, enabling lungs to be sustained ex-vivo at normal temperature with an extracellular perfusate rich in human albumin to maintain high colloid pressure. The principles of EVLP are to reduce interstitial oedema within the donated lung and to perform manoeuvres to facilitate alveolar recruitment, whilst monitoring the trajectory of key physiological measures including PO<sub>2</sub>, pulmonary vascular resistance and lung compliance.

**Table 7.1:** Suitability criteria for lung donation<sup>18-22</sup>

Criteria	Comments
General organ donor criteria	See Chapter 2
Age 5-70 years	
No significant untreatable lung disease	Also no known significant pleural disease in the case of DCD lung donation
Arterial blood gases on 100% fractional inspired oxygen (FiO <sub>2</sub> ) and 5 cm positive end-expiratory pressure (PEEP) >250 mmHg	Or equivalent partial pressure of oxygen in the blood (PaO <sub>2</sub> )/FiO <sub>2</sub> - ratio

## 7.4.2 Donor information and testing

**Table 7.2:** Donor information required for lung allocation

1	Accurate lung disease and treatment history	Especially smoking (cigarettes and cannabis), asthma, and aspiration may determine single versus bilateral lung transplant considerations Any past history of TB or contact with TB
2	Accurate height and race	Used to estimate total lung capacity
3	Weight	Only used in consideration of combined heart/lung transplant
4	Investigations	ABO blood group Arterial blood gases on 100% FiO <sub>2</sub> and 5 cm PEEP Chest x-ray and lung field measurements within 24 hours Fibreoptic bronchoscopy (if possible)* CT Chest (selected patients)* Donor/recipient lymphocytotoxic cross-match Donor/recipient CMV serology Donor/recipient EBV serology (if available)

\*See Appendix E. Ante mortem interventions such as lung bronchoscopy are commonly deployed in all jurisdictions with variations between states and, in some jurisdictions, between hospitals.

## 7.5 Allocation

### 7.5.1 General allocation principles

The recognised lung transplant unit in the home state is offered the donation as detailed below and given 30 minutes to respond to the offer.

State of donor hospital	Lung Transplant Unit
NSW, ACT	NSW
VIC, TAS	VIC
QLD	QLD
WA	WA
SA, NT	On rotation through above states

If the home state declines the offer, the lung donation offer is made to the non-home state lung transplant units—with a 30-minute response time—based on a rotation kept by each state donor coordination team. If all lung transplant units refuse the offer, it is then rotated through any units that have non-nationals awaiting transplantation.

The acceptance of lungs by a transplant unit depends on a large variety of technical and logistic factors, including the existence of a suitable recipient (see below). Although it is known that a variety of factors may manifest as apparent donor lung ‘quality’ (and be measured as oxygenation, chest X-ray abnormalities and bronchoscopy findings), no specific higher-risk donor category is used when allocating lungs or making acceptance decisions.

## 7.5.2 Allocation algorithm

Considerable logistical issues and the various combinations of potential lung and/or heart transplantation that a cardiothoracic transplant unit must consider when donor organs are offered complicate the allocation of donor lungs.<sup>21-25</sup> A decision regarding the configuration of single, double, or lobar transplantation will reflect these logistic issues, the quality of the donor organs, and any pre-determined specific requirements of a potential recipient. The final allocation decision is made by the accepting lung transplant unit according to the criteria in Table 7.3.

**Table 7.3:** Individual patient allocation criteria for donor lungs

1	ABO compatibility
2	Size compatibility based on chest x-ray measurements and total lung capacity values
3	Absence of a positive T-cell cross-match and acceptable anti-HLA antibody profile on Luminex testing
<i>Where more than one potential recipient meets the above criteria, the first choice will be determined by the following process</i>	
4	Clinical urgency* Logistics** Long-term outcome benefit*** CMV status of donor and recipient
5	Recipient waiting time, all other factors being equal

Notes:

\* Clinical urgency: Graded by level of support required and evidence of rapidity of deterioration of underlying indication for transplant.

Level of support includes, but not limited to the following:

- Extracorporeal membrane oxygenator (ECMO)
- Invasive mechanical ventilation
- Non-invasive ventilation
- High-flow O<sub>2</sub> requirement
- Low-flow O<sub>2</sub> requirement
- Prolonged or recurrent hospitalisation
- Other support devices such as continuous intravenous therapies

Rapidity of deterioration includes, but not limited to:

- change in NYHA functional Class or Medical Research Council (MRC) grade
- significant fall in lung function parameters
- significant fall in PaO<sub>2</sub>
- significant rise in partial pressure of carbon dioxide in the blood (PaCO<sub>2</sub>)
- 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
- development of refractory right heart failure

\*\* Logistical considerations include: operation type (lobar, single, bilateral, heart/lung); availability of required team members for the retrieval, lung transplant(s) and related cardiac transplants (paired donor heart or domino heart transplant); timely availability of all recipients; coordination between all involved transplant units arranging and performing the transplant procedures.

\*\*\* Consideration of long-term outcome benefit includes: comorbidities such as osteoporosis, gastroesophageal reflux, known coronary or peripheral vascular disease, carriage of pan-resistant organisms, poor rehabilitation potential, history of malignancy, advanced age, lack of compliance, morbid obesity or malnutrition and other relative contraindications for lung transplantation which have been shown to be associated with an inferior outcome benefit.<sup>21,22</sup>

## 7.6 Multi-organ transplantation

Patients with respiratory failure and concurrent disease of another solid organ—typically heart, kidney or liver—may be considered for combined organ transplantation. The general eligibility criteria for multi-organ transplantation follow the individual eligibility criteria for each organ to be transplanted. Nonetheless, multi-organ transplant is a more complicated surgical procedure with associated unique medical and other post-operative complications. As such, it is reserved for younger patients with functional reserve and with an ability to withstand the heightened surgical risks and prolonged rehabilitation associated with this complicated procedure.

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# 8 Pancreas and Islet

## 8.1 Preamble

Pancreas transplantation is undertaken as a treatment for type 1 diabetes in two ways:<sup>1</sup>

- Either the whole pancreas organ is transplanted,<sup>2</sup> or
- The insulin producing pancreatic islet cells are separated from the organ and transplanted.<sup>3</sup>

There are three units in Australia and New Zealand that perform solid organ pancreas transplantation (see Appendix H). The vast majority of solid organ pancreas transplants are undertaken as simultaneous pancreas and kidney (SPK) transplants in recipients with both type 1 diabetes and end-stage (or near end-stage) kidney disease.<sup>4</sup> A small minority of transplants are undertaken as solid organ pancreas transplants alone, either after kidney transplantation or in patients with good kidney function who do not require a kidney transplant. There are only a very small number of patients with exceptional circumstances for whom pancreas-alone transplantation is deemed appropriate.<sup>2</sup>

There are two pancreatic islet isolation laboratories in Australia and New Zealand: Westmead Hospital in Sydney and St Vincent's Institute of Medical Research in Melbourne. Pancreatic islet cell transplantation is currently undertaken in four islet infusion centres: Westmead Hospital, St Vincent's Hospital, Royal Adelaide Hospital and Auckland Hospital.

### Simultaneous pancreas (solid organ) and kidney transplantation

As the solid organ pancreas transplant units are national centres with referrals often coming from interstate, patients must first meet broad minimum eligibility criteria to be referred to and undergo subsequent assessment at one of the three units. Further criteria must then be met in order for patients to be entered onto the solid organ pancreas transplant waiting list.

This two-step waitlisting process allows potential recipients to be seen and preliminarily assessed at a transplant unit before their disease progresses to the point that they meet the final criteria for waitlisting for SPK transplantation. This process also prevents the referral of patients who would ultimately be deemed unsuitable for SPK transplantation. The minimum eligibility criteria for referral are based on data demonstrating poor outcomes in subgroups of patients with, for example, significant cardiac disease,<sup>5-7</sup> increasing age,<sup>8</sup> or obesity.<sup>9</sup> Eligibility criteria are also based on feasibility; for example significant bilateral disease of the iliac vessels or marked obesity in the recipient make transplant surgery technically difficult or impossible.<sup>9-11</sup>

## 8.2 Recipient eligibility criteria

### 8.2.1 Criteria for referral for solid pancreas transplantation

Patients must be referred to a pancreas transplant unit by their treating nephrologist and/or endocrinologist. Patients will be reviewed by the pancreas transplant unit if they meet the following criteria:

- Type I diabetes with insulin dependence;
- GFR <30 mL/min
- Absence of significant cardiac disease, or adequately treated cardiac disease
- Patent iliac vessels bilaterally
- BMI <35 kg/m<sup>2</sup>
- Age ideally <50 years (unless medically fit, see below).

In the case of age, individual subjects older than 50 years may still be deemed eligible for solid organ pancreas transplantation if they are otherwise very medically fit.<sup>6,8</sup> It must be taken into account, however, that patients generally face a waiting time of approximately two to three years from listing to the time of transplantation. As older age affects the likelihood of a successful outcome from SPK,<sup>6,8</sup> alternative transplant options (e.g. kidney-alone transplantation, living donor kidney transplantation) also need to be strongly considered.<sup>12</sup>

In the case of cardiovascular and/or iliac vessel disease, referral may still be considered if the referring team have a strong expectation that these problems can be significantly resolved. Individual cases may need to be discussed directly with one of the national transplant units before the transplant unit can make a decision to formally assess the patient's overall suitability.

### 8.2.2 Inclusion criteria: solid organ pancreas transplant waiting list

Patients may be referred and assessed if they meet the above criteria for solid pancreas transplantation, however they will not be actively listed for transplantation until they also meet all of the following criteria:

- Insulin dependence deemed by the national pancreas transplant unit to be reversible by pancreas transplantation
- GFR <15 mL/min and dialysis impending
- Absence of significant cardiac disease, or adequately treated cardiac disease
- Patent iliac vessels bilaterally
- BMI <30 kg/m<sup>2</sup> (BMI 30–35 kg/m<sup>2</sup> is a relative contraindication)
- Non-smoker or permanent cessation of smoking for more than 3 months (see below).

The expectation that a solid organ pancreas transplant can fully reverse the need for insulin is based on a pattern of insulin deficiency rather than one of insulin resistance (signifying type 1 rather than type 2 diabetes). This is not always straightforward to determine but relies partly on the demonstration of absent or low C-peptide levels (a marker of native insulin production).<sup>13,14</sup>

Smoking has been found to adversely affect transplant outcomes.<sup>6,15</sup> For this reason, patients are expected to demonstrate commitment to permanent smoking cessation before they can be transplanted.

While outcomes are significantly improved if patients can be transplanted early in the course of their kidney disease progression,<sup>16-18</sup> the limited supply of organs and the needs of the kidney-only waiting list restrict the ability to transplant patients before the point of kidney failure. The majority of patients are transplanted after they commence dialysis (typical GFR <10 mL/min), however some may be fortunate enough to receive a transplant just prior to dialysis (10–15%). The ability to transplant patients prior to dialysis is important, as the window of opportunity for transplantation is small for some patients due to the presence of multiple comorbidities. The current mortality rate on the SPK waiting list is approximately 10% per year—significantly higher than age-matched patients on the kidney-only waiting list.<sup>4,19-21</sup>

### 8.2.3 Exclusion criteria: solid organ pancreas transplant waiting list

Exclusion criteria for pancreas transplantation are:

- Exclusion criteria as per kidney-only transplantation (see Section 3.2)
- Significant cardiac disease, or inadequately treated cardiac disease
- Significant vascular disease
- Continuous dual antiplatelet therapy that cannot be safely ceased (in the short term) to allow surgery to proceed (e.g. recent coronary artery stenting at risk of thrombosis); single agent antiplatelet therapy is not an exclusion
- Significant psychiatric disease (affecting ability to cope and comply with surgery and treatment)
- Ongoing cigarette smoking
- Inability to comply with complex medical therapy (e.g. chronic cognitive or neuropsychiatric deficits in the absence of a carer capable of taking on this role)
- Addiction to non-prescription illicit drugs (e.g. narcotic or cannabis abuse).

## 8.2.4 Inclusion criteria: pancreatic islet transplant waiting list

Patients are entered onto the national islet transplant waiting list by recognised Clinical Islet Transplant Programmes. Patients on the national Islet transplant waiting list will be assigned to a recognised Clinical Islet Separation Laboratory by the Clinical Islet Transplant Programme.

Inclusion criteria for pancreatic islet transplantation are:

- Type 1 diabetes for five years or more
- Severe hypoglycaemic unawareness (documented blood sugar level <3mmol/l without awareness) that has not responded to optimal conventional insulin therapy, as assessed by an endocrinologist
- Age >18
- Creatinine clearance >75 mL/min/1.73m<sup>2</sup>
- Serum creatinine <130 umol/L
- 24 hour urine protein estimation <300 mg/day
- Weight ideally <80 kg
- The patient has read and signed the islet-specific informed consent form
- Absence of donor reactive antibodies by Luminex and negative cytotoxic crossmatch
- Willingness to use effective contraception measures
- Ability to understand the protocol and provide informed consent.

## 8.2.5 Exclusion criteria: pancreatic islet transplant waiting list

Exclusion criteria for pancreatic islet transplantation are:

- Weight >80 kg
- C-peptide response to arginine (5 g IV)—exclude any patient with C-peptide greater or equal to 0.3 ng/mL at 2, 3, 4, 5, 7, and 10 minutes post infusion
- Creatine clearance <75 mL/min/1.73 m<sup>2</sup>
- Serum creatinine >130 umol/L
- 24 hour urine protein estimation >300 mg/day
- Baseline haemoglobin <12 g/dL in women or <13 g/dL in men
- Baseline liver function tests outside of normal range
- Insulin requirement >0.7 IU/kg/day
- HbA1c >108mmol/mol (12%)
- Serum cholesterol >10 mmol/l
- Systemic corticosteroid usage
- Treatment with terfenadine, cisapride, astemizole, pimozone, or ketoconazole (that is not discontinued prior to sirolimus administration)
- A positive pregnancy test or desire to fall pregnant following islet cell transplantation
- Malignant disease other than localised and excised skin squamous cell or basal cell carcinoma
- Liver disease, including any form of active viral hepatitis, portal venous abnormality or cirrhosis
- Chronic pancreatitis
- Significant cardiac disease including ischaemic and valvular heart disease
- Respiratory disease including clinically significant asthma, bronchiectasis or obstructive airways disease
- Any form of chronic infection that could, viewed by the transplant team, pose a mortality risk after transplantation
- Any form of chronic or current acute mental or psychiatric illness that could jeopardise patient safety and adherence to medication in the peri- and post-transplantation period

- Allergy to intravenous contrast agents, sirolimus, tacrolimus or anti-thymocyte globulin
- Any other disease that in the opinion of the investigator may pose a significant risk to survival or adherence post transplantation.

### 8.2.6 Retransplantation

SPK retransplantation is technically possible, particularly where an early graft thrombosis has occurred and the pancreas has been removed. Even late failure of both organs might be considered for retransplantation if standard inclusion/exclusion criteria are met. The decision would then have to be made whether to remove both failed organs prior to relisting or at the time of retransplantation.

## 8.3 Waiting list management

### 8.3.1 Solid organ pancreas waiting list

Patients are transplanted in the order in which they were referred for assessment within each blood group, within each transplant unit. The decision whether to accept each individual offer and the management of the solid pancreas transplant waiting list are the responsibility of each of the recognised pancreas transplant units.

Each solid organ pancreas transplant unit allocates organs to the patient who has been waiting the longest, provided they are deemed suitable and ready for transplantation. Patients who are sensitised to HLA antigens may be listed on both the Westmead and the Monash transplant waiting lists if they have been active on the waiting list for over two years and have spent at least one year of that time on dialysis. They will be integrated into the other unit's list in the order of their accumulated waiting time. Essentially this means that there is a common national waiting list within Australia for these highly sensitised patients. Currently, the logistics of distance make it difficult to include highly sensitised patients from New Zealand in this arrangement.

### 8.3.2 Islet waiting list

Each islet transplant programme allocates islets to the blood group-matched patient who has been waiting for the longest time on the islet transplant list and is deemed suitable and ready for the islet preparation made available for transplantation. Patients on the waiting list who require a second islet transplant will take priority over those waiting for a first transplant.

Where donor a pancreas meets the appropriate criteria for both solid organ and islet transplantation, it is first offered for solid organ transplantation. If the pancreas is not accepted by the national pancreas transplant units for this purpose, then the pancreas can be offered to the national islet transplant units.

### 8.3.3 Urgent patients

There is no urgent classification for either solid pancreas or islet transplant candidates.

## 8.4 Donor assessment

### 8.4.1 Donor information and testing

**Table 8.1:** Donor information required and donor suitability criteria for solid pancreas donation

1. Blood group	ABO compatibility (absolute requirement)
2. Body weight	>25kg and ideally <100kg
3. Height	
4. Age	3 – 45 years
5. Abdominal girth	
6. Anatomical information	No past or current evidence of acute pancreatitis No evidence of pancreatic or duodenal trauma (may be considered for islets) No evidence of significant fat infiltration of pancreas at laparotomy
7. History of donor haemodynamic status	Inotrope use, blood pressure
8. Laboratory tests	General organ donor criteria for viral studies: HIV, HBsAg, hepatitis C, CMV Electrolytes, glucose Amylase and/or lipase
9. Medication use	Current use of insulin, dextrose and steroids
10. Medical history	No known diabetes mellitus or insulin dependence (prior to admission to hospital) No history of alcoholism or chronic pancreatitis

A peak and current serum negative test result for lymphocytotoxic cross-match is required for appropriate recipient selection, however this information is not required at the time of allocation (this information is usually available after organ allocation to the transplant unit).

HLA typing is not required for allocation (this information is usually available after organ allocation to the transplant unit).

**Table 8.2:** Donor information required and donor suitability criteria for islet cell donation

1. Blood group	ABO compatibility (absolute requirement)
2. Donor type	DBD only
3. Body weight	>20 kg and ideally <150 kg
4. Height	
5. Age	3 – 65 years*
6. Abdominal girth	
7. History of donor haemodynamic status	Current use of insulin, dextrose, steroids, inotropes, blood pressure Any hypoxia or down time
8. Laboratory tests	General organ donor criteria for viral studies: HIV, HBsAg, hepatitis C, CMV Electrolytes, glucose Amylase and/or lipase
9. Medication use	Current use of insulin, dextrose and steroids

\*Regardless of age, if a donor is accepted for heart, lung, liver and/or kidney donation, then the donor may be accepted for pancreatic islets

## 8.4.2 Donor suitability criteria

Donor suitability criteria are listed in Table 8.1 and Table 8.2. Similar to the selection process for other organs, donor suitability criteria for pancreas transplantation are based on factors that may adversely impact the success of the procedure,<sup>22-26</sup> as well as factors related to recipient safety (e.g. infection risk or transmission of malignancy). DBD and DCD donors are suitable for solid organ pancreas transplantation (usually SPK transplantation), although thrombosis rates are higher from DCD compared with DBD organs. Within DBD organs, thrombosis rates are higher in donors over 35 years of age. Currently, islet yields from DCD donors are insufficient for transplantation, hence these donors are only considered at present for solid organ pancreas donation. Suitability criteria for pancreas donation from DCDs are given in Table 8.3.

**Table 8.3:** Extended suitability criteria for pancreas donation after circulatory death<sup>24,27</sup>

Criteria	Comments
Suitable DCD organ donor	
Age up to 35 years	
No known diabetes mellitus or insulin dependence	
No known pancreatic trauma	May be considered for separate islets
No history of alcoholism or chronic pancreatitis	
Maximum ischaemic time from withdrawal of treatment to organ perfusion <30 min	
Ideally the liver is also deemed suitable for transplantation	Expected to correlate with good pancreatic integrity

## 8.4.3 Organ retrieval

Due to the small number of pancreas transplant units, geographic considerations as well as availability of local expertise need to be taken into account in the process of pancreas retrieval. In some cases the accepting transplant team (the national pancreas transplant unit) will perform the retrieval. Where circumstances make it possible and/or favourable for the local teams to be involved in the process of retrieval and delivery, this will also be considered. Pancreas donations in Western Australia, Queensland and South Australia may involve the local teams, avoiding the need for the staff from the pancreas units to travel interstate for the retrieval process. This process is greatly appreciated by the pancreas transplant units.

## 8.5 Allocation

### 8.5.1 General allocation principles

Organ allocation and distribution currently follow processes that have been established over several years based on referral patterns of recipients and geographical considerations regarding retrieval teams and acceptable ischaemic times. The allocation process for pancreas and islet transplantation is reviewed on an ongoing basis.

As stated above (Section 8.3.1), organs are allocated to the blood group identical patient with the longest waiting time who is a suitable recipient and is currently active on the waiting list. Occasionally allocation may deviate from this general rule if, for example, the donor is very small and the intended recipient is very large, or vice versa. Similarly, where the donor is DCD or higher-risk—necessitating a short cold ischaemia time—and the recipient cannot reach the transplant unit in time, an alternative recipient may have to be chosen.

Very rarely, a patient on the waiting list who is at risk of death from either hypos or lack of dialysis access may be given priority irrespective of waiting time. There is no official definition of an urgent category for this type of

pancreas transplant within Australia and New Zealand.

Patients on the waiting lists are reviewed annually by the pancreas transplantation teams, either by a transplant physician or transplant surgeon. Normally this occurs at an interstate clinic, but occasionally will necessitate the patient travelling to the transplant centre where they are listed.

### 8.5.2 Organ sharing and rotation

Donor pancreata arising in New Zealand are initially offered to the Auckland National Pancreas Transplant Unit. If the Auckland Unit is unable to use the organs (e.g. no suitable recipient currently listed, lack of availability of appropriate surgeons for either the retrieval or transplant procedure) then the Australian National Pancreas Transplant Units (Westmead and Monash) will receive the offer. For logistical reasons it would be rare for this to happen.

Donor pancreata arising in New South Wales, Australian Capital Territory, Northern Territory, Queensland and Western Australia are initially offered to the Westmead National Pancreas Transplant Unit for consideration for simultaneous kidney and pancreas transplantation. If the Westmead Unit is unable to use the organs (e.g. no suitable recipient currently listed, lack of availability of appropriate surgeons for either the retrieval or transplant procedure) then the Monash Unit will receive the offer, followed by the Auckland Unit and the islet units (Westmead followed by Victoria/South Australia).

Donor pancreata arising in Victoria or Tasmania are initially offered to the Monash National Pancreas Transplant Unit for consideration for simultaneous kidney and pancreas transplantation. If the Monash Unit is unable to use the organs (e.g. no suitable recipient currently listed, lack of availability of appropriate surgeons for either retrieval or transplant procedure) then the Westmead Unit will receive the offer, followed by the Auckland Unit and the Islet Units (Victoria/South Australia followed by Westmead).

Donor pancreata from South Australia will be offered on rotation between Monash and Westmead transplant units. If either unit are unable to utilise the pancreas, it will be offered to the other unit irrespective of the rotation. If Monash is offered a pancreas from South Australia (whether it is used or not), they will be offered second when the next suitable donor arises in South Australia and vice versa for Westmead. It is hoped that this arrangement will facilitate the transplantation of South Australian recipients at both the Monash and Westmead pancreas transplant units. This rotation will be carefully audited to ensure that neither unit exceeds its quota to the detriment of the other.

Allocation of the second donor kidney in the case of SPK transplantation is discussed in Chapter 5, Section 5.4.4.

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# 9 Intestine

## 9.1 Preamble

Intestinal transplantation remains challenging and controversial because of the complexity of the intestinal failure patient, the effectiveness of parenteral nutrition (PN), and the risks associated with transplanting the intestine.

The gut is a highly complex, highly immunogenic organ, and is exposed to the external environment of chemicals, parasites, viruses and bacteria. There is a poorly understood symbiotic relationship between the gut and the intestinal flora, which encompass many trillion bacteria. The gut 'microbiota' and the intestinal immune system have a complex relationship that includes tolerance to the native flora. It is therefore not surprising that, following transplantation, the intestine is prone to rejection, loss of the mucosal barrier, and subsequent systemic infection.

Several medical advancements preceded and permitted the development of intestinal transplantation in patients who have intestinal failure. The introduction of PN in the 1970s was followed by the development of intestinal rehabilitation and subsequent remedial intestinal surgery. The concept of a specialised service to manage intestinal failure and rehabilitation is more recent.<sup>1</sup>

While the role of intestinal transplantation in the complex management of intestinal failure is still evolving, PN remains the primary therapy for both adults and children with intestinal failure.

It is estimated that approximately 200 – 250 patients in Australia and New Zealand are currently PN dependant, corresponding to a prevalence of 8 – 10 per million population (personal communication Baxter Healthcare 2015). This would be consistent with prevalence estimates from Europe, which range from 3 – 12 per million population; by contrast, prevalence of PN dependency in the United States is estimated at 30 – 40 per million population.<sup>2</sup> Most patients on PN are stable, and consideration for transplantation is currently limited to those who have no chance of intestinal recovery and have potential life-threatening PN-related complications.

As short-term patient and graft survival have increased, attention has turned to improving the long-term outcomes of intestinal transplantation. Long-term survival must be factored into any decision to transplant an individual patient where survival on PN may approximate or exceed that of intestinal transplantation. The improved outcomes of intestinal transplantation and the potential for long-term survival raises the possibility of considering intestinal transplantation for stable patients who have a poor quality of life or—in high-risk patients—before the development of life-threatening PN-related complications.

Management of intestinal failure patients in dedicated centres with multidisciplinary teams has been associated with improved survival and fewer complications.<sup>3-5</sup> Given the small number of patients who might be considered intestinal transplant candidates in Australia and New Zealand, and the fact that they are scattered over a large area, it has been recommended that there should be a single intestinal transplant programme supported by organised intestinal rehabilitation programmes across the two countries.<sup>6</sup>

### Types of intestinal transplantation

Intestinal transplantation incorporates several transplant procedures, and can range in complexity from an isolated intestinal graft to replacement of the entire abdominal cavity including stomach, duodenum, pancreas, small intestine, liver and possibly colon. Kidney transplantation may also be contemplated.

The decision for an individual patient as to which organs to replace can be difficult. Intestinal failure associated liver disease (IFALD) is common and liver function is important in determining whether the liver should also be replaced. Advanced fibrosis, cirrhosis or severe cholestasis and the presence of portal hypertension mandate the liver should be included in the transplantation procedure.

In surgical practice, the graft options centre around isolated intestinal replacement versus the need to include

the liver. A multi-visceral graft includes the liver, stomach, duodenum, pancreas and small intestine, whereas a modified multi-visceral graft does not include the liver.<sup>7-9</sup> The multi-visceral graft can also include the spleen and colon. The factors that determine the choice of graft 'cluster' include the aetiology of the intestinal failure and the functional state of the liver and gastric motility. The type of graft is tailored to the individual patient. Organs that are functioning will not be replaced.

## 9.2 Parenteral nutrition

There is a medical preference for enteric feeding, if at all possible, because of the reduced risk of systemic infection, venous thrombosis and liver dysfunction in comparison with PN. However PN remains the nutritional mainstay for patients who cannot eat or whose gastrointestinal tract cannot support enteral nutrition sufficient to meet the metabolic demands of the patient. The great majority of patients will have short-term surgical or medical conditions with no intention that PN will be used long-term, and an intestine that will allow them to return to full enteral feeding once their condition is resolved.

In patients with irreversible intestinal failure, PN remains the gold standard for treatment. The five- and ten-year survival for children receiving total parenteral nutrition (TPN) is 89% and 81% respectively; the five- and ten-year survival for adults receiving TPN is 70% and 55% respectively.<sup>2,10</sup>

However, long-term PN can result in life-threatening complications. Intestinal transplantation has usually been reserved for patients who develop the following problems:<sup>11-13</sup>

The development of IFALD: this can occur in up to half of all TPN patients and is associated with a dramatic reduction in patient survival.<sup>13</sup> IFALD can result in advanced fibrosis or cirrhosis or severe cholestasis. Portal hypertension may develop, manifested by splenomegaly, thrombocytopenia, gastro-oesophageal varices or stomal bleeding. Liver biochemistry often is a poor indicator of the extent of liver injury, so liver biopsy and/or non-invasive assessment of liver fibrosis are important considerations in the longer-term management of these patients.

Central line access failure: as evidenced by central venous thrombosis of two or more central veins, pulmonary embolism, superior vena cava syndrome or chronic venous insufficiency.

Severe sepsis: usually secondary to catheter-related blood stream infections that require hospitalisation, or a single episode of line-related fungemia, septic shock or acute respiratory distress syndrome.

Severe dehydration: frequent episodes of severe dehydration despite intravenous fluid supplementation in addition to TPN.

### PN in Australia and New Zealand

PN is widely available in Australia and New Zealand. However, there is little coordination and currently no operating central registry or national audit of PN patients.

A distinction should be made between hospitals able to offer PN and those that have a formal intestinal failure/intestinal rehabilitation service. There is a dedicated paediatric intestinal failure service at the Royal Children's Hospital in Melbourne and the Starship Children's Hospital in Auckland, but no other recognised intestinal failure service. Intestinal failure, particularly in adults, is treated ad hoc, largely due to the low incidence of gastrointestinal tract pathology and the wide geographic distribution of the few affected patients.

## 9.3 Intestinal transplantation in Australia

Intestinal transplantation is an emerging therapy in Australia and New Zealand. The low prevalence of intestinal failure across the two countries suggests a need for a single bi-national adult and paediatric transplant centre, as transplantation may be indicated in only four or five patients per year across Australia and New Zealand.

An intestinal transplantation programme has been recently established at the Austin Hospital and Royal Children's Hospital in Melbourne.<sup>11</sup> The first intestinal transplant (liver-intestine) was performed in 2012.<sup>14</sup> A total of three patients have been transplanted (one adult, two children), and there is currently an active waiting list of children and adults.

The intestinal transplantation programme is not currently funded, therefore the funding for transplantation of an individual patient is negotiated on an ad hoc basis with each referring state and New Zealand. This often adds considerably to the time taken to assess the patient, complete their work-up, and activate them on the waiting list.

A single bi-national intestinal transplantation service would ideally be supported by a limited network of intestinal rehabilitation centres that would act as a referral base for intestinal failure patients. Management of patients post-transplantation would likely be done at an existing liver transplant centre with expertise in the management of immunosuppression.

## 9.4 Recipient eligibility

Intestinal failure occurs when intestinal absorption of fluid and nutrients becomes inadequate and life can only be sustained by the use of intravenous PN and fluids. The access line and long-term access can become life-threatening issues, particularly due to the risk of infection and large vein thrombosis.

Approximately 70% of intestinal failure in both adults and children is due to anatomical short gut. However there are multiple other causes, which are summarised in Table 9.1.

**Table 9.1: Causes of intestinal failure**

Anatomical short gut	Dysmotility	Enterocyte failure	Tumours
Congenital malrotation	Pseudo obstruction	Microvillous inclusion	Familial adenomatous polyposis
Necrotizing enterocolitis	Aganglioneosis	Tufting enteropathy	Inflammatory pseudo tumour
Trauma		Autoimmune enteropathy	Desmoid
Volvulus			
Gastroschisis			
Atresia			
Thrombosis/ischaemia			
Crohns disease			

Quality of life is impaired to some degree for many patients with intestinal failure, and to a severe degree for a minority. Survival requires daily intervention. This burden is compounded by the inability to eat and the enormous social dysfunction that this entails. Hospitalisation can become frequent and costly, both financially and psychologically. Patient survival is precarious, and the social impairment and psychopathology of a severe chronic disease are common.

The following anatomical combinations can be associated with full enteral recovery, and hence aggressive attempts at intestinal rehabilitation should be undertaken before intestinal transplantation is considered:<sup>15</sup>

- Residual small intestine of >100 cm with a stoma (no colon in continuity)
- Small intestine >60 cm with jejunocolonic anastomosis (part of the colon in continuity)
- Small intestine >30 cm, including the ileum and ICV, in continuity with the entire colon.

Of the 52 patients that have thus far been referred to Melbourne for consideration for intestinal transplantation, more than 60% were entirely dependent on PN, with the remaining 40% being treated with a combination of PN and enteral/oral nutrition or enteral/oral nutrition plus intra-venous fluids.

Patients with the following are more likely to remain dependent on PN and hence may ultimately become candidates for transplantation:

- Gut length—very short jejunum, no ileum, no ileocecal valve (ICV), no colon
- Mucosal disease
- Motility disorders
- Abdominal wall defects
- Radiation enteritis
- Age—children may do worse on PN
- High-grade intestinal obstruction
- Long duration of PN feeding (>2 years)
- A post-absorptive plasma citrulline level <20 µmol/L (half of normal adult value).

### 9.4.1 Inclusion criteria

It is important to realise that only a small proportion of patients with intestinal failure on PN will be referred for transplantation and subsequently accepted and transplanted. Intestinal transplantation is a recognised treatment for patients with intestinal failure, but will usually not be considered as an option for stable patients who are coping well with PN. Instead, intestinal transplantation is currently considered only for patients with known irreversible intestinal failure who have life threatening complications of PN or fluid management or have significant limitations to their quality of life that have become life-threatening. This so-called “PN failure” has been defined in the USA as one or more of the following:<sup>12</sup>

- Impending or overt liver failure due to IFALD
- Thrombosis of two or more central veins
- Two or more episodes per year of catheter-related blood stream infections
- A single episode of line-related fungemia, septic shock or acute respiratory distress syndrome
- Frequent episodes of severe dehydration despite intravenous supplementation in addition to PN.

In addition to the criteria above, there is a small group of patients who have aggressive, locally destructive abdominal desmoid tumours, who may be eligible for intestinal transplantation in the absence of PN failure.<sup>16</sup>

There is debate about who should remain on long-term PN and regarding the ability to predict success of intestinal rehabilitation in an individual patient. The ability to predict rehabilitation success or failure may facilitate early consideration of intestinal transplantation before the onset of life-threatening complications.

### 9.4.2 Exclusion criteria

Exclusion criteria overlap with those listed for liver transplantation (see Chapter 6).

In summary, contraindications to intestinal transplantation include:<sup>17</sup>

- Potential for intestinal recovery
- Severe wasting and cachexia
- Drug dependence considered likely to impair survival
- Primary or metastatic cancer (with exception of desmoid tumours)
- Ongoing or recurrent infections that are not responding to treatment
- Significant cardiac or pulmonary pathology
- Demonstrated patient non-compliance or significant psychiatric or social risk
- Potential complications from immunosuppressive therapy that are unacceptable to the patient
- Total loss of central line access.

### 9.4.3 Referral for intestinal transplantation

At any instant, 10 – 25% of adults and children on long-term PN may have one of the complications listed in Section 9.4.1 that are an indication for intestinal transplantation. It is therefore estimated that fewer than 10 patients per year in Australia and New Zealand would be considered for intestinal transplantation.

However, determining whether a patient should be transplanted is often difficult. Early referral is preferred as it allows sufficient time to assess the patient, modify treatment and consider the need for transplantation.

In patients for whom loss of central venous access is an indication, referral should be made prior to the patient losing all access as central venous access is necessary to survive the transplant operation, as well as for adequate postoperative care.

Over 70% of Australian patients referred to Melbourne had at least one life-threatening complication of PN at presentation. Five patients (10%) exhibited three life-threatening complications of PN: liver failure, impending loss of venous access and recurrent line sepsis; 11 patients (21%) displayed two complications and 20 patients (38%) presented with one complication.

#### **Outcome of referral of patients with intestinal failure to 2015**

Fifty-two patients have been referred to Melbourne since the intestinal transplantation service was established in 2010, including 35 adults (mean age 40 years) and 17 children (mean age 6 years). Thirty-five (67.3%) have been either deferred or rejected from wait-listing for various reasons (75% with either 'stable' disease or not meeting transplant criteria; 16% too unwell for transplant; 9% unsuitable for psychosocial reasons).

Four patients (8%) have so far died prior to transplantation: two while awaiting transplantation, two during the assessment period. Causes of death included sepsis and intracranial bleed.

Three patients (one adult, two children) have undergone intestinal transplantation (in all cases combined with liver transplantation) with 100% graft and patient survival (median follow up 1161 days) and all have achieved enteral autonomy. Four patients were active on the waiting list for intestinal transplantation as of June 2015.

### 9.4.4 Assessment and acceptance

While there is no specific upper age limit for intestinal transplantation, most potential recipients are likely to be under 50 years of age. Patient adherence to medical treatment is critical to success. A stable social and psychological history is mandatory because of the intensity of the pre- and post-operative procedures and the ongoing medical risks.

Most patients will have undergone multiple abdominal operations that add to the operative risk. The abdominal cavity may be contracted and small with limited space in which to place a new graft.

A detailed assessment of the venous anatomy is mandatory. Thrombosis of the major vessels is common due to the prolonged intravenous access associated with PN. This may include complete thrombosis of the innominate or jugular veins, the superior vena cava and inferior vena cava. Vein mapping is essential to enable planning of the operation and anaesthetic access. In some patients who have lost major veins and where current intravenous access may be via direct atrial or lumbar caval lines, lack of access may preclude transplantation.

Co-morbidities are common in intestinal failure patients, and will influence the decision to proceed with transplantation. End-stage kidney disease is frequent, often due to long-term hydration issues and occasionally due to renal oxalosis as a complication of short bowel syndrome. In this case, combined kidney and intestinal transplantation may be considered.

Sensitisation and antibody status are critical to the success of intestinal transplantation, which will only be successful where there is a negative cross-match between the recipient and the donor. Preformed HLA antibodies in the potential recipient make donor matching difficult and often impossible. Currently there are attempts to moderate donor specific antibodies (DSAs) in recipients with high titre and high panel reactive antibodies (PRA).

Assessment for intestinal transplantation may take many months, hence early referral is recommended. It usually takes this long to assess the patient and their response to various therapies, including surgery, in the hope that intestinal transplantation can be avoided.

### 9.4.5 Retransplantation

Re-transplantation is possible, but has a high failure rate when compared to primary transplantation.<sup>18</sup> This is largely due to immunologic factors which make rejection of the second transplant more likely, the presence of sepsis associated with failure of the primary graft, and other organ system failures. Liver-inclusive intestinal retransplantation offers a better long-term outcome when compared to liver-free retransplantation.<sup>19</sup>

## 9.5 Donor assessment

The selection of appropriate deceased donors is critical to success of intestinal transplantation. In general, only stable donors who meet the criteria described below would be considered for intestinal transplantation. Most of the criteria for liver donor suitability also apply to intestinal donation (see Chapter 6).

The “ideal intestinal donor” is quite uncommon, hence interstate donors will be considered for all potential recipients. An ideal donor would be <50 years of age and donate via the brain death pathway. Donors between 50 and 60 years of age will be considered if other factors are favourable.

Recipients must be ABO-compatible with the donor. Therefore, O universal donors can be considered for A, AB, or B recipients.

In terms of technical factors affecting donor suitability, the gut is sensitive to ischaemia and hypotension therefore intestinal donors must have limited inotrope exposure, low volume or no blood transfusion and stable haemodynamics. The intestine does not tolerate cold storage and should be transplanted in the shortest possible time frame, ideally in under six hours. Irreversible intestinal damage has been observed after approximately five hours of cold ischemia.<sup>20</sup>

Due to previous abdominal surgery the recipient explant operation may take several hours and this will need to be factored into the timing of the donor retrieval operation.

The EBV and CMV status of the donor will influence recipient selection because of the morbidity caused to naive recipients who develop a primary viral infection after transplantation.

Donors and recipients need to be size-matched because of the limited abdominal space. Donors should be between 50% and 100% of recipient weight.

The state of the donor liver will affect the decision to accept the intestine for transplantation. Further, the retrieving surgeon’s opinion of the intestine at the time of surgery and after perfusion is critical to the decision that the transplant should proceed.

Due to a lack of size-matched organs for paediatric recipients, reduced size intestine with or without liver transplantation has been performed elsewhere. It is not anticipated that this will occur in the Melbourne unit in the near future.

An isolated intestine can be retrieved as part of the retrieval of other abdominal organs. Intestinal donation will not interfere with simultaneous liver, whole organ pancreas or kidney retrieval.

### 9.5.1 Tissue typing and cross match

The gut is highly immunogenic and, like the kidney, is sensitive to the presence of circulating donor-specific HLA antibodies. It has become clear that donor-specific HLA antibodies (DSAs) are implicated in medium-long term

intestinal allograft dysfunction and graft loss.<sup>21,22</sup>

Intestinal transplantation will only be performed in a scenario of a negative donor-recipient cross-match. The difficulty in finding a suitable donor for a given recipient can be predicted during the work-up stage by the assessment of recipient DSAs. Recipients with multiple and high-level DSAs will have a high PRA and a high chance of a positive cross-match with most donors.

Although Luminex technology allows for 'virtual' cross-matching, a physical cross-match is done before final recipient selection. This must be factored into the donation process and may delay organ retrieval, especially if the donor is in a regional hospital and the donor's blood needs to be transported to the state tissue-typing laboratory. A cross-match will take the laboratory around 6 hours to perform once the blood is in the laboratory.

## 9.6 Allocation

Competition between recipients is unlikely to be a problem during allocation because of the small number of patients on the intestinal transplant waiting list and the specific requirements of each recipient. ABO matching, DSA status, cross-match results, size-matching and the availability of organs will usually point towards a single recipient.

There is currently no accepted method of ranking wait-listed patients in the context of intestinal transplantation. MELD score is not suitable for intestinal transplantation patients, who may have relatively mild liver disease.

If multiple patients are listed, they will be ranked on clinical criteria based on physician assessment. This will prioritise patients at greatest risk of dying on the waiting list and take into account those likely to have the best post-transplant outcomes. If two recipients are otherwise both well matched, the treating physicians will allocate the donor organs to the recipient assessed to be in the greatest need (i.e. the sickest patient).

The prioritisation system has to assess the different risk factors for death, including liver failure, recurrent sepsis, fluid issues and loss of vascular access. International experience has demonstrated that patients who require a liver-intestine transplant have the highest waiting list mortality of all potential solid organ transplant recipients.<sup>23</sup> For this reason, in December 2012 the Liver and Intestinal Transplant Committee (LITAC) approved a new urgent list category (Category 2c) for all patients awaiting intestinal transplantation who also require liver transplantation. (See Section 6.3.3). Further, the Renal Transplant Advisory Committee (RTAC) has endorsed the allocation of a kidney (if required) to accompany the intestine (and other abdominal organs as necessary), including interstate donors. Individual patient approval will be obtained from RTAC given the infrequent need for this to occur.

The active intestinal/multivisceral transplantation waiting list for both adults and children is reviewed regularly and circulated weekly to all liver transplant units in Australia and New Zealand.

With time, it is anticipated that transplant activity will increase and allocation criteria may need to be reviewed accordingly.

## 9.7 Multi-visceral intestinal allocation versus liver-pancreas allocation

An isolated intestinal graft will not interfere with the retrieval and transplantation of other organs and can be retrieved concurrently. Patients who undergo a multivisceral intestinal transplant may need an organ that would otherwise be allocated to a patient on the liver, pancreas or kidney waiting list. There is no simple way of making this allocation decision between the potential recipients competing for the same organs. Allocation will take account of the competing needs of non-intestinal transplant candidates waiting for organs such as liver and pancreas that may be wanted for the intestinal recipient. A suitable multivisceral intestinal graft may be waived because there is a potential liver recipient who will die without urgent transplantation (e.g. a category 1 listed liver recipient—see Table 6.2).

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# 10 Vascularised composite allotransplantation

## 10.1 Preamble

Vascularised composite allotransplantation (VCA) is the transplantation of a vascularised body part containing multiple tissue types as an anatomical/structural unit. VCA is fundamentally more similar to organ transplantation than to tissue transplantation, and is recognised as such by the United States Department of Health and Human Services, and by the European Parliament.<sup>1</sup> Body parts that meet the definition of VCA include limbs, face, larynx and abdominal wall.

As this is such a new field, protocols for assessing recipient and donor eligibility for VCA are currently developed and applied at the institutional level. Efforts are underway to generate standard international guidelines for recipient and donor eligibility for VCA, with a particular focus on developing standardised psychosocial assessment tools (the 'Chauvet protocol').<sup>2</sup> 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 internationally standardised, evidence-based guidelines will increase.

## 10.2 Recipient eligibility criteria: hand transplantation

Criteria for recipient eligibility for VCA have a number of unique considerations compared to other forms of transplantation:

- The recipient will experience both positive and negative changes to body image: the graft—and therefore rejection—is visible
- Risk of death or return to dialysis are not factors motivating adherence to immunosuppression
- VCA transplantation may decrease rather than increase life expectancy—the goal is not to extend life, but to increase quality of life
- 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.

### 10.2.1 Inclusion and exclusion criteria

**Table 10.1:** Inclusion and exclusion criteria for hand transplantation

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"><li>• Bilateral loss of hands/forearm or unilateral loss with significant contralateral dysfunction as a result of trauma/illness &gt;1 year ago</li><li>• Patient aged 18 years or older</li><li>• Psychologically well and stable, including the ability to form a therapeutic alliance with the transplant team*</li><li>• Able to understand the complexity of the procedure, as well as the risks, benefits and alternatives, and able to communicate their informed decision</li><li>• A reasonable post-transplant life expectancy, defined as an 80% likelihood of surviving for at least five years after transplantation</li></ul>	<ul style="list-style-type: none"><li>• Significant uncorrected chronic comorbid disease, e.g. cardiovascular, respiratory or kidney disease, which results in undue risk from anaesthetic or immunosuppression</li><li>• Active chronic infection</li><li>• Active malignancy or one with high five-year likelihood of recurrence</li><li>• Congenital abnormalities of limbs</li><li>• Proximal amputation and/or proximal neuromuscular dysfunction</li><li>• Inability to comply with long term, complex medical and rehabilitative therapy</li><li>• Untreated/active psychiatric illness</li><li>• Active cigarette smoking</li><li>• Active drug or alcohol abuse/addiction</li><li>• Pregnancy</li></ul>

\*An ability to work cooperatively with the transplantation team throughout work-up, transplantation and follow-up.

A criterion that requires further discussion before inclusion in local protocols is a requirement that the patient have tried and failed with prosthetics. Financing of prosthetics in Australia means that access is an issue; however, there would likely be value to the potential recipient in being assessed for and trialling basic prosthetics to gain an understanding of what the sensation of the transplant will be like.

### 10.2.2 Assessment and acceptance

As for other solid organ transplantation, potential VCA recipient evaluation includes the major criteria of preoperative surgical suitability, infectious disease screening and malignancy screening. There are additional assessments specific to VCA and the patient assessments required in the case of hand transplantation are listed in Table 10.2.

**Table 10.2:** Patient assessments required prior to listing for hand transplantation

VCA-specific assessment	Non VCA-specific criteria
<ul style="list-style-type: none"> <li>• Hand surgeon assessment of suitability of proximal stump for transplant based on anticipated outcome</li> <li>• Immunology physician review</li> <li>• Anaesthetic review</li> <li>• Psychological review</li> <li>• EMG for proximal muscle condition</li> <li>• Prosthetics assessment</li> <li>• Imaging:               <ul style="list-style-type: none"> <li>- Xray</li> <li>- CT angiography</li> <li>- MRI and MR angiography</li> <li>- MRI</li> </ul> </li> <li>• Preoperative Functional assessment:               <ul style="list-style-type: none"> <li>- DASH score</li> <li>- Michigan Hand Score</li> <li>- Jebsen assessment</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Preoperative investigation</li> <li>• FBE, coagulation profile</li> <li>• ABO serology</li> <li>• Donor specific antibody</li> <li>• Renal function – U+ E/Cr, GFR estimation, urinalysis</li> <li>• Liver function tests</li> <li>• Infectious disease serology – HIV antigen, HTLV I and II antibody, HIV I and II antibody, hepatitis C virus, hepatitis B core antibody, Hep B Surface Ag, syphilis, cytomegalovirus, herpes simplex virus, Toxoplasmosis and varicella-zoster antibody</li> <li>• Pulmonary function tests, chest x-ray</li> <li>• ECG and Echocardiogram</li> <li>• Dental consult</li> <li>• Sinus imaging if indicated</li> </ul>

### 10.2.3 Retransplantation

There is currently no intention to exclude candidates on the basis of prior VCA transplant. 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 VCA transplantation.

### 10.2.4 Criteria for activation on waiting list

As for other solid organ transplant procedures, the decision to activate a recipient for a VCA is based on agreement between all of the teams involved (surgical, medical and psychological). Given the ethical and health implications for the patient of a negative transplant outcome, a robust approach to risk minimisation is encouraged.

The recipient consent form developed by the St Vincent's Hospital Melbourne team includes information on the transplant operation, the potential long-term effects of transplantation, and what the recipient should expect from the transplant and the rehabilitation process. Potential recipients are informed of the following:

- Hand transplant does not prolong life, instead benefits are measured in improved quality of life
- Studies so far indicate that the function of the transplanted hand is better than that of prosthetics
- 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

- Technical success of the surgery will be apparent in two to three days; by two to three months it is expected that the recipient will be able to make a fist, but it will be at least a year before finer finger moments and sensation to the skin develop
- A hand transplant is not the best option for everyone, and risks include:
  - risks related to the operation (infection, bleeding), those related to the anaesthetic and other post-operative complications which make, rarely, result in death
  - rejection, which in some cases may lead to the hand needing to be surgically removed
  - potential to develop certain infections, cancers, diabetes and heart disease as a consequence of immunosuppressive medications
- Inclusion in the International Hand Transplant Registry ([handregistry.com](http://handregistry.com))
- Responsibilities of the recipient include:
  - daily blood tests for the first 30 days, and weekly skin biopsies
  - medication adherence
  - hand physiotherapy
  - clinic visits
- Considerations of the donor family—in order to protect and maintain the privacy of the donor family, the recipient is requested not to share details of the transplant with the media.

It is further recommended that the consent process incorporate a cooling off period whereby, after the recipient gives their initial consent, the recipient considers their decision for approximately 4 weeks and is then asked to re-consent. This cooling-off period is an important ethical safeguard in the consent process.<sup>3</sup>

### 10.3 Recipient eligibility criteria: face transplantation

Though Australian recipient eligibility criteria for face transplantation have not yet been developed, other international groups have well-developed protocols. The Brigham and Women’s Hospital in Boston has performed multiple partial and full face transplants since gaining institutional review board approval for the procedure in 2008. The recipient eligibility criteria specified under the protocols of this institution are listed in the Table 10.3, adapted to reflect Australian hand transplant eligibility criteria (see Section 10.2).

#### 10.3.1 Inclusion and exclusion criteria

**Table 10.3:** Recipient inclusion and exclusion criteria specified under Brigham and Women’s Hospital protocols for face transplantation,<sup>4</sup> adapted for the Australian context

Inclusion criteria (Brigham and Women’s)	Exclusion criteria (Brigham and Women’s)
<ul style="list-style-type: none"> <li>• Most difficult or impossible to reconstruct facial defects</li> <li>• 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</li> <li>• Outcome of an alternative reconstructive method considered unfavourable or unsatisfactory</li> </ul>	<ul style="list-style-type: none"> <li>• Pregnancy</li> <li>• Active psychiatric illnesses are considered individually</li> <li>• Unable to guarantee adequate coverage of follow-up care and immunosuppression</li> </ul>
Inclusion criteria (from hand VCA, Section 10.2.1)	Exclusion criteria (from hand VCA, Section 10.2.1)
<ul style="list-style-type: none"> <li>• Patient aged 18 years or older</li> <li>• Psychologically well and stable, including the ability to form a therapeutic alliance with the transplant team</li> <li>• Able to understand the complexity of the procedure, as well as the risks, benefits and alternatives, and able to communicate their informed decision</li> <li>• A reasonable post-transplant life expectancy, defined as an 80% likelihood of surviving for at least five years after transplantation.</li> </ul>	<ul style="list-style-type: none"> <li>• Significant uncorrected chronic comorbid disease e.g. cardiovascular, respiratory or renal, which results in undue risk from anaesthetic or immunosuppression</li> <li>• Active chronic infection</li> <li>• Active malignancy or one with high five-year likelihood of recurrence</li> <li>• Active cigarette smoking</li> <li>• Active drug or alcohol abuse/addiction</li> </ul>

### 10.3.2 Assessment and acceptance

Similarly, Australian protocols for face transplant candidate evaluation have not been developed. The protocols for face VCA candidate evaluation used by Brigham and Women’s Hospital provide an example of the steps involved in this process.<sup>5,6</sup>

## 10.4 Donor assessment

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. Secondly, because VCA 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 specialised protocols that account for the sensitivity of the request and a lower willingness to consent to donation. Protocols are also required for the fitting of prostheses to replace the donated allograft post-mortem. Further, cold ischaemia time—and therefore travel time—between retrieval and implantation must be minimal. The length of time that a potential recipient will wait for a suitable donor may therefore be extensive: this is a consideration that must be factored into recipient evaluation and informed consent.

Table 10.4 lists the inclusion and exclusion criteria for hand donation that are currently applied in Australia.

**Table 10.4: Inclusion and exclusion criteria for hand donation**

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> <li>• Age 18 – 65 years</li> <li>• Documented brain death with hemodynamic stability</li> <li>• Aesthetically and physically matched to recipient gender, skin tone, race, age, and size (within 15% of recipient size)</li> <li>• Compatible with donor—matched for viral status and blood type</li> <li>• The donor should not require excessive vasopressors to maintain blood pressure prior to retrieval</li> </ul>	<ul style="list-style-type: none"> <li>• Untreated sepsis, HIV, active cytomegalovirus, Epstein-Barr virus, active tuberculosis, hepatitis B, hepatitis C, viral encephalitis</li> <li>• Malignancy</li> <li>• Current intravenous drug use</li> <li>• Tattoo within past six months</li> <li>• Systemic or limb-related neuropathies</li> <li>• Extensive arthritis</li> </ul>

Australian protocols concerning eligibility for face donation have yet to be developed. The Brigham and Women’s Face VCA unit have established criteria that include factors common to hand donation, such as ABO compatibility and age, gender and skin colour match. In addition—again in keeping with hand VCA donor assessment—the presence of active sepsis, active viral infections, tuberculosis and active/recent malignancy are considered contraindications to donor acceptance. Specific to face VCA are the exclusion criteria of congenital craniofacial disorder, facial nerve palsy, a history of significant craniofacial or neck trauma and/or surgery, or a plan by the family to hold an open casket funeral.

## 10.5 Allocation of VCA organs

Given that only one VCA has been performed in Australia as of February 2016, and as yet there are not multiple candidates simultaneously waiting for VCA, an allocation policy has not been developed. The UNOS/OPTN protocol for VCA allocation provides benchmark against which a local policy might be developed in the future. Under the UNOS/OPTN allocation protocol, the host OPO offers VCA organs to candidates with a compatible blood type and similar physical characteristics to the donor. The OPO will first offer VCA organs to candidates that are within the OPO’s region, and secondly to candidates that are outside of the OPO’s region according to proximity. Proximity of the donor and recipient is a relevant factor in allocation given the importance of short ischaemia time.

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.<sup>7</sup> Other factors that may be incorporated into allocation criteria include urgency and waiting time. Given the small size of the potential donor pool, HLA matching will not be feasible.

## 10.6 Multi-organ transplantation

There should be no impediment to undertaking a quality-of-life-improving VCA at the same time as a life-sustaining solid organ transplant. In this instance, the main ethical challenge of a VCA—that of a potential reduction in life years due to immunosuppression in an otherwise healthy recipient—are mitigated. Multiple VCA transplants (i.e. dual hand transplants) are less commonly undertaken internationally due to the challenging and prolonged recovery period for the patient, and none have yet been undertaken in Australia. For suitable candidates, however, multiple VCA would be considered.

## 10.7 Emerging issues

### Ethics assessment in VCA transplantation

The ethical complexity of VCA is unlike any other area of transplant medicine. Clinical ethicists are often members of VCA teams, assisting with the development of protocols, policies, procedures, and forms. The VCA clinical ethicist can also be involved in screening the potential recipient 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 the patient and surgical teams may conflict. It is important to understand these matters, as well as the motivations and motivation level of the potential recipient. The philosophical meaning attached to the hand/face/etc. by the patient must be understood, as well as the values, behaviours and emotions that are linked to these body parts. It is important to 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. The involvement of a clinical ethicist may therefore be a part of local VCA transplantation protocols in the future.

### 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 and 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 their 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.<sup>6</sup> 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.<sup>2</sup> 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.

In an effort to move towards standardised psychosocial assessment of candidates for hand transplantation, the Innsbruck Psychological Screening Programme for Reconstructive Transplantation (iRT-PSP) was developed in 2011.<sup>2</sup> This assessment method measures cognitive functioning, affective status, psychosocial adjustment, coping, quality of life and life satisfaction based on a semi-structured interview, standardised 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. The application of standardised psychosocial assessment tools will, in the future, be a part of the VCA candidate assessment process.

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# Appendices

# Appendix A

## TSANZ Advisory Committees & Working Groups, terms of reference

The TSANZ Advisory Committees and Working Groups represent the interests and views of their organ-specific special interest groups in Australia and New Zealand. The Working Groups are informal networks whereas the Advisory Committees have a more structured work process. There is some variation in the constituency and mode of operation of the individual groups, but the areas listed below are a set of 'minimum requirements' for each Advisory Committee.

Each Advisory Committee acts as the peak body for the organ group it represents. It is broadly representative of the individuals, units and states taking part in the given transplantation area, and has the capacity to formulate clinical standards and policies in this area. Some Advisory Committees hold two face-to-face meetings each year, whereas others meet once during the TSANZ Annual Scientific Meeting. Additional teleconferences are held as required throughout the year. Decisions are normally made by consensus, but when consensus cannot be reached decisions are made by vote.

The Chair of each Advisory Committee reports to the TSANZ Council on a regular basis via the Chair of the Advisory Committees and Working Groups.

Key functions of the Advisory Committee are to:

- Act as the peak body for their special interest group in areas of recipient eligibility, donor organ retrieval, allocation and standards of practice
- Formulate standards of practice and conduct regular audits and reviews (including audits of the interstate exchange of organs and of allocation processes)
- Oversee and regularly review the eligibility criteria and allocation algorithms for their organ group
- Provide a forum for discussion of new or emerging therapies or practices in their field of transplantation
- Provide advice to TSANZ Council on current, new or emerging therapies or practices in their field of transplantation, engaging relevant stakeholders in the process
- Regularly review the information that they make available on the TSANZ website for accuracy and current applicability.

The terms of reference of the Advisory Committees oblige them to foster sound governance by having

- Auditable and transparent processes and operation.
- A process for effective engagement with their constituencies
- Consumer and community representation as required of any peak body
- Documented processes for election of members and the Chair, including specification of tenure.

Any change to standards or policies initiated by the Advisory Committees undergoes a process of consultation that involves endorsement by TSANZ Council, ATCA and OTA.

# Appendix B

## Process report

### Background

The Organ and Tissue Authority (OTA) was established on 1 January 2009 with the aim of creating a nationally consistent and coordinated approach to organ and tissue donation for transplantation. Prior to the creation of OTA, the allocation of organs for transplantation was guided by state-specific guidelines, hospital protocols and protocols developed by the Transplantation Society of Australia and New Zealand (TSANZ) and the Australasian Transplant Coordinators Association (ATCA).

On 16 January, 2009, as part of the Australian Government's National Reform Agenda—A World's Best Practice Approach to Organ and Tissue Donation for Transplantation, the Australian Government Department of Health and Ageing (subsequently transferred to the Organ and Tissue Authority) provided funding to TSANZ to enhance the role of its Advisory Committees and to convene a multidisciplinary working party of transplant clinicians, health-care professionals and consumer representatives to develop nationally uniform eligibility criteria and allocation protocols for deceased donor organ transplantation. The members of the original working party comprised a panel of transplantation clinicians in the specialty fields of cardiology, nephrology, respiratory medicine and surgery (Table B.1).

The initial draft of this document underwent a comprehensive public consultation process from August 2009 to April 2010. Version 1.1 of the TSANZ *Organ Transplantation from Deceased Donors: Consensus Statement on Eligibility Criteria and Allocation Protocols* (the Consensus Statement) was released by TSANZ in June 2011, and subsequent revisions were published in versions 1.2 in May 2012 and 1.3 in January 2014; version 1.4 was released in April 2015.

In light of new scientific evidence and emerging technologies and practices, a full review of the Consensus Statement was deemed necessary. Concurrently, the National Health and Medical Research Council (NHMRC) commenced the development of *Ethical Guidelines for Organ Transplantation from Deceased Donors* (the Ethical Guidelines). The revisions to the Consensus Statement were conducted in parallel with the development of the Ethical Guidelines, and as a consequence have been informed by the content of this document. The Consensus Statement is now replaced by the *Clinical Guidelines for Organ Transplantation from Deceased Donors* (the Clinical Guidelines), with version 1.0 of this document released in April 2016.

**Table B1:** Membership of the working party that developed the Consensus Statement on Eligibility Criteria and Allocation Protocols.

<b>Chairperson</b>	Peter Macdonald
<b>Heart transplantation representative</b>	Peter Macdonald and Paul Jansz
<b>Kidney transplantation representative</b>	Scott Campbell
<b>Lung transplantation representative</b>	Greg Snell
<b>Liver transplantation representative</b>	Stephen Munn
<b>Pancreas and islet transplantation representative</b>	Jeremy Chapman OAM, John Kanellis
<b>Executive Officer</b>	Rosemary Allsopp
<b>Senior Project Officer</b>	Maria-Jose Velasco

## Development

The Clinical Guidelines have been written in a way that makes them accessible to the wider community, however the primary target audience is health professionals within the donation and transplantation sectors. The Clinical Guidelines have incorporated the latest national and international evidence and reflect current practice in Australia and New Zealand. Decisions with respect to the content and wording of each organ-specific chapter were made by the relevant TSANZ Advisory Committee, with the leadership of the respective Advisory Committee Chairs.

The development of the Clinical Guidelines was managed by a specialised project team within TSANZ and with the support of OTA. The Project Team comprised Iman Ali (Project Officer), Sarah White (Project Manager/Medical Writer) and Steven Chadban (TSANZ President), with support from staff at OTA.

The following issues were declared outside the scope of the Clinical Guidelines:

- The process of organ donation
- Transplantation of human tissue
- Transplantation of organs from living donors to a related (emotionally or biologically) recipient
- Transplantation of gametes, ovarian or testicular tissue, or embryos for reproductive purposes
- Xenotransplantation.

**Table B2:** Contributors to the content development of the TSANZ Clinical Guidelines for Organ Transplantation from Deceased Donors (version 2.0, 2016)

<b>TSANZ</b>	Steven Chadban
<b>OTA</b>	Shari Jensen, Eva Mehakovic, Helen Opdam
<b>Cardiac Advisory Committee</b>	Peter Bergin, Enzo de Angelis, Lawrence Dembo, Paul Jansz, George Javorsky, Robert Larbalestier (Chair), Peter Macdonald, Jo Maddicks-Law, Peter Ruygrok, Robert Weintraub, Peter Wicks
<b>Renal Transplant Advisory Committee</b>	Allocation subcommittee and working group: Scott Campbell, Philip Clayton, Nicholas Cross, Rhonda Holdsworth, Ashley Irish, John Kanellis (Chair), Fiona Mackie, Carl Pedersen, Graeme Russ, Christine Russell, Kate Wyburn RTAC members: Scott Campbell, Steven Chadban, Jeremy Chapman, Toby Coates, Tina Coco, Nicholas Cross, Luke Datson, Ian Dittmer, Paolo Ferrari, Anthony Griffin, Rhonda Holdsworth, Peter Hughes, Ashley Irish, John Kanellis (Chair), Lloyd D'Orsogna, Carl Pederson, Graeme Russ, Christine Russell, Narelle Watson, Angela Webster, Jenni Wright, Kate Wyburn
<b>Liver and Intestinal Transplant Advisory Committee</b>	Jonathan Fawcett (Chair), Glenda Balderson, Annette Wickens, Robert Jones, Graeme Macdonald, Michael Crawford, Geoff McCaughan, Michael Fink, Mark Brooke-Smith, John Chen, Gary Jeffrey, Winita Hardikar, Helen Evans, Diana Aspinall, Ed Gane, Libby Johns, Luc Delriviere
<b>Lung Advisory Committee</b>	Daniel Chambers, Helen Gibbs, Allan Glanville, Emily Granger, Michelle Harkness, Jamie Hobson, Peter Hopkins (Chair), Robert Larbalestier, Sharon Lawrence, Trish Leisfield, Bronwyn Levy, Monique Malal, David McGiffin, Tanya McWilliams, Michael Musk, Steve Peuschel, Greg Snell, Glen Westall
<b>Pancreas and Islet Advisory Committee</b>	Jeremy Chapman, Toby Coates, David Goodman, Wayne Hawthorne, Kathy Kable, Tom Loudovaris, Bill Mulley, Stephen Munn, Philip O'Connell, Helen Pillmore, Henry Pleass (Chair), Paul Robertson, Allan Saunders, Pat Siciliano, Angela Webster
<b>Vascularised Composite Allotransplantation Working Committee</b>	Tim Bennett, Jamie Burt, Robyn Langham (Chair), Karen Dwyer
<b>Other contributors</b>	Katrina Bramstedt, Brooke Chapman, Peter de Cruz, Adam Testro, Karen Waller

## Consultation

Targeted consultation on the draft Clinical Guidelines occurred between the 2<sup>nd</sup> of September and 16<sup>th</sup> of October, 2015. Written submissions arising from the targeted consultation were then considered by the relevant TSANZ Advisory Committee and revisions made where appropriate. Submissions were not made publically available.

**Table B3:** List of organisations invited to submit comments on the draft Clinical Guidelines, 2<sup>nd</sup> September to 16<sup>th</sup> October, 2015.

Australasian Transplant Coordinators Association
Australian and New Zealand Intensive Care Society
Australian Liver Association
Australian and New Zealand Paediatric Nephrology Association
Australian and New Zealand Society of Nephrology
Biotherapeutics Association of Australasia
The Cardiac Society of Australia and New Zealand
Consumer Health Forum of Australia
Eye Bank Association of Australia and New Zealand
Gastroenterological Society of Australia
Gift of Life Foundation
Kidney Health Australia
National Aboriginal Community Controlled Health Organisation (NACCHO)
National Health and Medical Research Council Australian Health Ethics Committee
National Renal Transplant Leadership Team and National Renal Transplant Service of New Zealand
Organ Donation and Transplant Foundation of WA
Organ and Tissue Authority
Royal Australasian College of Surgeons
The Thoracic Society of Australia and New Zealand
Transplant Australia
Transplant Nurses' Association
Transplantation Society of Australia and New Zealand

## Ongoing Revision

To maintain clinical relevance and community acceptability, eligibility criteria and allocation protocols for deceased donor organs must undergo periodic revision to account for evolving national and international evidence, clinical best practice, and trends in donor availability and acceptability criteria.

It is anticipated that the Clinical Guidelines will be updated on an annual basis by the TSANZ Advisory Committees. On occasion it may be necessary to update aspects of the Clinical Guidelines on an ad hoc basis to reflect changes in clinical practice.

# Appendix C

## Kidney allocation algorithms

### National Allocation formula

Base score	0 HLA mismatches, Peak PRA not <50%	{Level 1}	60 000 000
Base score	1 HLA mismatch, Peak PRA >80%	{Level 2}	59 000 000
Base score	2 HLA mismatches, Peak PRA >80%	{Level 3}	58 000 000
Base score	0 HLA mismatches, Peak PRA <50%	{Level 4}	57 000 000
Base score	0 HLA mismatches at HLA-DR 1 mismatch at HLA-A or HLA-B Peak PRA not >80%, and Centre credit difference <=-3	{Level 5}	56 000 000
Base score	0 HLA mismatches at HLA-DR 2 mismatch at HLA-A or HLA-B Peak PRA not >80%, and Centre credit difference <=-6	{Level 6}	55 000 000
Base score	When base score is null and centre credit difference <=-20	{Level 7}	54 000 000
Paediatric bonus	If age <18, first dialysis before age 17, and on dialysis for >1 year		+30 000
Recipient at same centre as donor			+50 000
Centre credit balance		1000+patient centre credit	
Patient waiting period >0			+ wait in months*1
If score is <54 000 000 go to the relevant state-based algorithm			

N.B. PRA will be determined using HLA Class 1 and Class 2 antibodies tested by Luminex assay and will be calculated on the basis of authorised antibodies listed for exclusion (i.e. a calculated PRA). PRA was previously determined (prior to March 1, 2016) using CDC-detected HLA class 1 antibodies only.

### National override list

In rare situations there may not be enough patients in a given state to be able to accept the available kidneys. Most often this occurs if the donor has a rarer blood group, such as AB. If there are not enough patients to receive the kidneys locally, a national override list is run. This list incorporates patients from across the country, to ensure that the kidneys do not go to waste.

Base score		0
Paediatric bonus	If age <18, first dialysis before age 17 and on dialysis for >1 year	+30 000
Peak PRA >50%		+1000*(Peak PRA%-50)
Patient dialysis waiting period >0		+Wait in months*100

N.B. PRA will be determined using HLA Class 1 and Class 2 antibodies tested by Luminex assay and will be calculated on the basis of authorised antibodies listed for exclusion (i.e. a calculated PRA). PRA was previously determined (prior to March 1, 2016) using CDC-detected HLA class 1 antibodies only.

### New South Wales formula (NSW, ACT)

After the national allocation has been taken into consideration, kidney allocation within NSW from deceased donors is according to the NSW NOMS Programme. This algorithm takes into account both the donor and recipient match and waiting time. With increasing time spent on dialysis, waiting time becomes more important.

Extremely marginal renal allografts on occasion may be offered as a dual allograft based on donor criteria, findings at procurement and allograft biopsy results.

<b>State HLA</b>		
Base score	If no mismatches at HLA-DR	50 000 000
	For each mismatch at HLA-A	-1 000 000
	For each mismatch at HLA-B	-1 000 000
Paediatric bonus	If age <18, first dialysis before age 17, and on dialysis for >1 year	+100 000
Patient waiting period >0		+ wait in months*100
If score is <48 000 000, go to the state waiting algorithm		
<b>State waiting</b>		
Base score		40 000 000
Paediatric bonus	If age <18, first dialysis before age 17, and on dialysis for >1 year	+100 000
Patient waiting period >0		+ wait in months*100
<b>Urgent patients</b>		
Base score		0
Urgency bonus when urgency index >0		+100*urgency index (1-10)

## Victorian formula (VIC, TAS)

If Victorian patients do not fit the criteria for national allocation, Victorian NOMS Programme assigns a starting score of 40 000 000. Patients lose 20 000 000 for each HLA- B or HLA-DR mismatch. Therefore if a Victorian patient has 2 HLA-B and/or HLA-DR mismatches their score reduces to zero and any added scores are for months on dialysis. i.e. waiting time only applies. However waiting time also applies in the matching list. For example if a patient has one donor HLA-DR mismatch and has been waiting 60 months for a graft, the score will be 20 000 060.

<b>State HLA</b>		
Base score		40 000 000
	For each mismatch at HLA-B	-20 000 000
	For each mismatch at HLA-DR	-20 000 000
Paediatric bonus	If age <18, first dialysis before age 17, and on dialysis for >1 year	+100,000
If total mismatches at HLA-B and HLA-DR is >2, then reset score to 0		
For each month waiting on dialysis		+ 1
<b>Urgent patients – no score set, patients listed in urgency listing</b>		
Base score		0
Urgency bonus when urgency index >0		0

## Queensland formula

The Queensland NOMS programme primarily determines who will receive kidneys by HLA matching, or by the time a patient has been on dialysis. Firstly all patients on the waiting list, who are of the correct blood, group are matched against the donor. If there are any very well matched patients (no more than 2 mismatches out of 6) then the NOMS programme allocates it to the patients with the best match.

This happens about 50% of the time. The other 50% of the time, there is nobody on the waiting list who is well matched with the donor. In these cases NOMS ignores the HLA matching altogether, and produces a list of ABO blood group compatible patients, in order of who has been on dialysis longest. A patient's renal physician should be able to give the patient an approximate idea of how long it will take them to be allocated an organ for their blood group, and whether there are any special circumstances that might make it harder than usual for them to get a kidney.

<b>State HLA</b>	
Base score	50 000 000
For each mismatch at HLA-A	-1 000 000
For each mismatch at HLA-B	-1 000 000
For each mismatch at HLA-DR	-1 000 000
Patient waiting period >0	+ wait in months*100
If score is <48 000 000, go to the state waiting algorithm	
<b>State waiting</b>	
Base score	40 000 000
Patient waiting period >0	+ wait in months*100
<b>Urgent patients</b>	
Base score	10 000 000
Urgency bonus when urgency index >0	+100*urgency index (1-10)

## South Australian formula

The South Australian NOMS programme determines who will receive kidneys by HLA matching and by the time a patient has been on dialysis. Firstly all patients on the waiting list, who are of the correct blood group are matched against the donor. If there are any very well matched patients (no more than 3 mismatches out of 6) then the NOMS programme allocates it to the patients with the best match. This happens about 30% of the time. The other 70% of the time, there is nobody on the waiting list who is well matched with the donor. In these cases NOMS ignores the HLA matching altogether, and produces a list of ABO blood group compatible patients, in order of who has been on dialysis longest.

<b>State HLA</b>	
Base score	30 000 000
For each mismatch at HLA-A	-10 000 000
For each mismatch at HLA-B	-10 000 000
For each mismatch at HLA-DR	-10 000 000
If total mismatches is >3, then reset score to 0	
Patient waiting period >0	+ wait in months*1
<b>Urgent patients</b> – no score set, patients listed in urgency listing	
Base score	0
Urgency bonus when urgency index >0	0

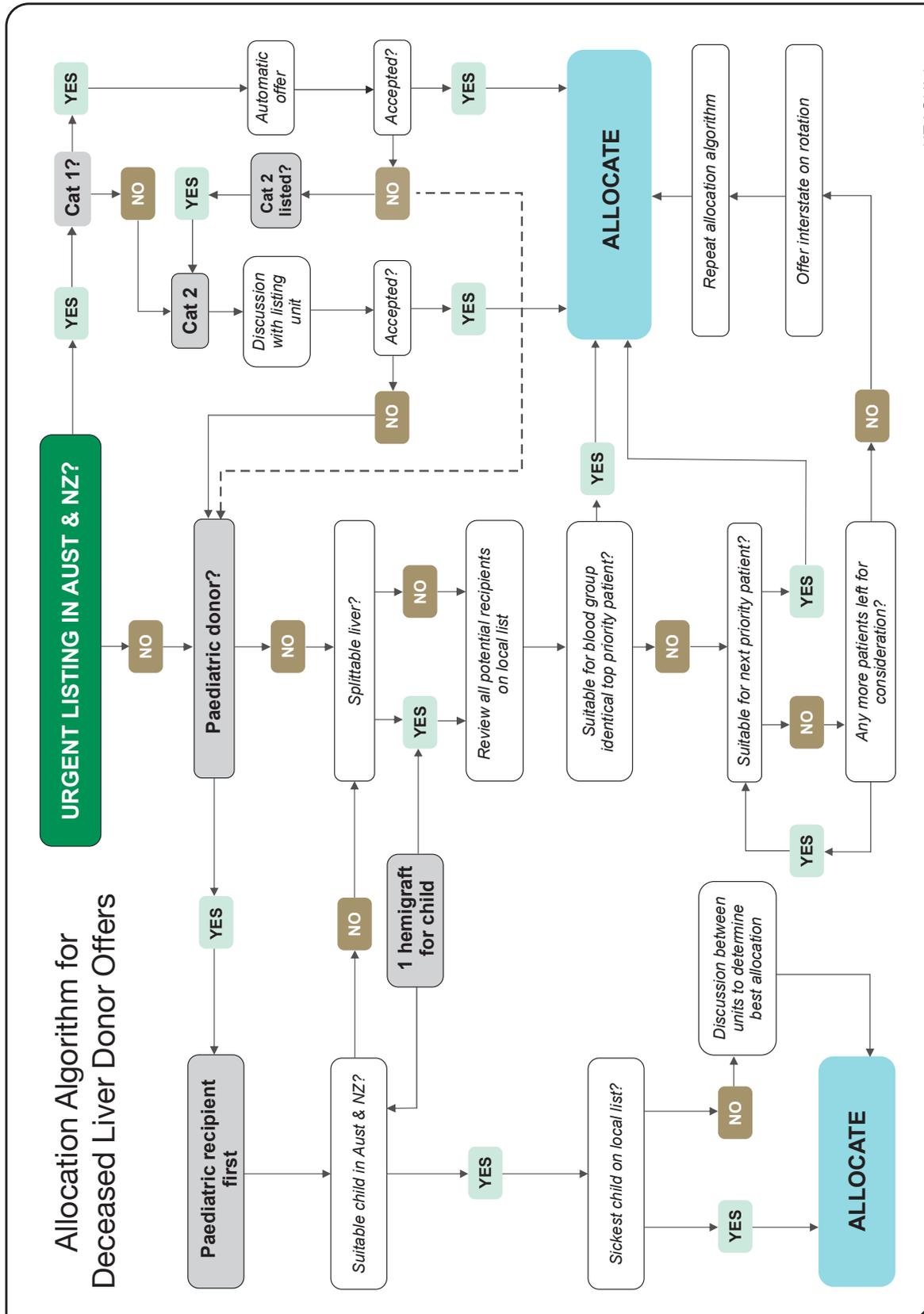
## West Australian formula

The National Allocation Scheme will ensure Western Australian patients, particularly those who are highly sensitised, will be offered well matched kidneys from the National pool when available. After this allocation is taken into account, the Western Australian NOMS Programme allocates kidneys based on a combination of HLA matching (tissue types) and waiting time. For patients with uncommon tissue types, the WA algorithm gives considerable emphasis on waiting time ensuring that with increasing time, they will receive priority above those with a better-matched kidney.

<b>State HLA</b>	
Base score	40 000 000
For each mismatch at HLA-A	-3 000 000
For each mismatch at HLA-B	-3 000 000
For each mismatch at HLA-DR	-5 000 000
Patient waiting period >0	+ wait in months*100 000
Homozygous at HLA-DR and waiting >5 years	+ 5 000 000

# Appendix D

## Liver donor allocation flow diagram



LITACV1.1

# Appendix E

## Guidelines for lung donor bronchoscopy & CT chest

### Purpose

The purpose of this document is to provide guidance to Donation Specialist Coordinators in arranging additional diagnostic investigations of bronchoscopy and CT chest in potential lung donors.

The guidelines described below were last updated on the 27<sup>th</sup> of March, 2015 (ATCA/TSANZ Guidelines G001/2015 Version 1.0)

### Introduction

The guidance document is intended to be used by Donation Specialist Coordinators and trainee coordinators/nurses. The guidelines should be viewed only as recommendations. They do not establish legally enforceable responsibilities.

Mention of specific products or equipment in this document does not represent an endorsement of such products or equipment by the Lung Advisory Committee nor does it necessarily represent preference for those products or equipment over similar competitive products or equipment. It is incumbent on the reader who intends to use any information, forms or procedures contained in this document to evaluate such materials for use in the light of operational requirements associated with his or her facility.

### Lung Donor Bronchoscopy

#### Rationale

- 50% expected to be abnormal in lung donors with findings including mucous/foreign aspirated material/ blood clot plugging, bronchial infection and rarely, endobronchial mass
- Opportunity for acquisition of microbiological specimens to enhance antibiotic regimens early post-transplant.

Most requests for bronchoscopy will be for when the donor is nursed in ICU, before the retrieval team arrives for donor organ evaluation

#### Method/technique

- Local anaesthesia is required in DCD donors
- Visualisation of :
  - site of ETT
  - airway anatomy to assess for variations including right upper lobe tracheal bronchus
  - extent of airway inflammation and vascularity
  - site and extent of secretions, clot, aspirated material, foreign bodies and tumours
- Airway toilet to remove secretions. Small volume aliquots of 5-20ml N/Saline inserted and aspirated via suction: send for urgent microbiology: m/c/s, fungal culture, and AFB.

#### Indications

1. X ray evidence of segmental or lobar collapse
2. Significant burden of secretions on ETT suctioning
3. Assessment of pulmonary infiltrates especially if unilateral
4. History of aspiration or foreign body inhalation
5. Donors with unexpectedly low PO<sub>2</sub> (at the guidance of the requesting transplant physician)

## CT Chest

### Rationale

The plain chest radiograph has a relatively low sensitivity compared with CT imaging in the detection of lung abnormalities in potential lung donors. Whilst CT scans are not considered routine in the work up of a lung donor, indications in either the standard or marginal donor may include:

- Clarification of anomalies suggested on a CXR especially in donors with >20 pack year history of smoking where exclusion of lung malignancy or emphysema is of particular concern
- Donors with history of penetrating or blunt trauma to assess for diaphragmatic tears, lung lacerations, extent of pneumothorax, pulmonary contusions and other infiltrates
- Donor history of aspiration or infection to assess for extent of consolidation as CXR may underestimate structural abnormalities (this may be of particular interest if only single lung donation is being considered)
- All lung donors  $\geq 70$  years of age due to increased incidence of lung pathology.

A CT scan of the chest performed on admission for a lung donor will generally suffice. A formal report from a radiologist is ideal although not always practical. Representative images of lung windows from the upper, mid and lower sections of the thorax should accompany the Electronic Donor Record.

### Method/technique

CT chest (without contrast) to define lung parenchyma and airway anatomy – contrast may be required to outline mediastinal and vascular structures although potential nephrotoxicity needs to be considered.

# Appendix F

## National notification for lung transplantation

### Preamble

Although there is no specific official national priority urgent lung listing category, under some circumstances, a lung transplant wait list patient from one state may be notified to other state Lung Transplant Programmes in an attempt to increase their opportunities for lung allocation and transplantation. This process is termed National Notification.

The process described below was last updated on the 11<sup>th</sup> of June 2014 (Version 1.0)

### 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. Highly sensitised patient > or equal to 6 cross matches with high Panel Reactive Antibody or high titre anti-HLA antibodies, in order to enhance their overall exposure to a larger donor pool. Consideration should be given to initiate national notification for patients with fewer prior positive cross matches under special circumstances such as blood group B or small stature, low TLC blood group O.
3. Unusual technical requirements- size extremes where size-matched organ availability is limited.

NB: These are for general guidance only rather than an automatic trigger for national notification, with institutional factors, prognosis and predicted outcome post transplantation influencing decision making.

### Process

National notification for lung transplantation is at the discretion of the patient's state Lung Transplant Unit Director.

It will be the responsibility of the home state Lung Transplant Unit Director (or his or her nominee) to notify all other Lung Transplant Units in Australia and New Zealand and to inform the state DonatLife agencies outside the home state when a patient is placed on (and removed from) the national notification list. It will not be routine practice to notify the Donation Specialist Coordinators of every such case.

A notification from one state is not binding on other states. A national notification does not override donor lung state rotation policies, or even local allocation practices in a distant state - merely widens the choices of potential recipients.

Despite national notification, the ultimate responsibility for donor lung allocation to such a potential recipient and a decision to proceed to transplant remains under the control of the potential recipient's home state.

It is expected that the majority of individuals placed on the national notification list will either die or be transplanted within 4 weeks of notification. In the event that a potential recipient remains listed beyond 4 weeks, re-notification of all Lung Transplant Units and Donation Specialist Coordinators is recommended at 4-weekly

intervals, except if the indication for listing is sensitization.

## Review

The operation of the national notification list will be subject to annual audit by the Lung Advisory Committee of TSANZ (LAC) and be listed as a standing agenda item at LAC meetings.

# Appendix G

## Issues for further discussion

Simultaneous transplantation of two or more organs sourced from one deceased donor represents a small but growing aspect of transplantation in Australia. Whilst the indications for recipient listing and donor requirements for simultaneous kidney-pancreas transplantation, dual-kidney transplantation, and heart-lung transplantation are well-established, recipient and donor criteria for liver-kidney, liver-kidney-pancreas, heart-kidney, and lung-kidney transplantation are not. This guideline wishes to acknowledge that such transplant procedures have been successfully undertaken and have a role within the scope of transplantation of organs from deceased donors in Australia and New Zealand. The ethical principles to be considered in the allocation of multiple organs to a single recipient have been addressed within the *Ethical Guidelines for Organ Transplantation from Deceased Donors*. The current status of such practices within Australia and New Zealand is mentioned within each of the organ-specific chapters. Developing guidelines for multi-organ transplantation is an ongoing project and such guidelines will be incorporated within the next edition of these Clinical Guidelines. A key focus will be to define and resolve the trade-off between the opportunity cost to those listed for a kidney-alone transplant versus benefits gained by recipients of multi-organ transplants.

# Appendix H

## Currently recognised transplant units

### Heart transplantation units

NSW	St Vincent's Hospital
VIC	Alfred Hospital Royal Children's Hospital (paediatric)
QLD	Prince Charles Hospital
WA	Fiona Stanley Hospital
NZ	Auckland Public Hospital

### Renal transplantation units

NSW	The Children's Hospital at Westmead Prince of Wales Hospital Sydney Children's Hospital John Hunter Hospital Royal North Shore Hospital Statewide Renal Services (Royal Prince Alfred Hospital) Westmead Hospital
VIC	The Alfred Hospital Austin Hospital Monash Medical Centre Royal Children's Hospital The Royal Melbourne Hospital St Vincent's Hospital
QLD	Queensland Renal Transplant Service (Princess Alexandra Hospital and Lady Cilento Hospital)
SA	Royal Adelaide Hospital Women's and Children's Hospital
WA	Fiona Stanley Hospital
NZ	Auckland City Hospital Wellington Hospital Christchurch Hospital

## Lung transplantation units

NSW	St Vincent's Hospital
VIC	Alfred Hospital
QLD	Prince Charles Hospital
WA	Fiona Stanley Hospital Sir Charles Gardiner Princess Margaret
NZ	Auckland City Hospital

## Liver transplantation units

NSW	Royal Prince Alfred Hospital (adult) Children's Hospital at Westmead (paediatric)
VIC	Austin Hospital (adult) Royal Children's Hospital (paediatric)
QLD	Princess Alexandra Hospital (adult) Lady Cilento Hospital (paediatric)
SA	Flinders Medical Centre (adult)
WA	Sir Charles Gardiner Hospital (adult)
NZ	Auckland City Hospital (adult) Starship Children's Hospital (paediatric) – transplants are performed at Auckland City Hospital, but patients are transferred to Starship for post-operative care.

## Simultaneous pancreas and kidney transplantation units

A simultaneous pancreas and kidney transplant unit is defined as a clinical service of a state public hospital that actually performs the relevant transplant procedure. The following units are state-approved transplant programmes:

NSW	Australian National Pancreas Transplant Unit, Westmead Hospital
VIC	Australian National Pancreas Transplant Unit, Monash Medical Centre
NZ	New Zealand National Pancreas Transplant Unit, Auckland City Hospital

## Clinical islet separation facilities

A clinical islet separation facility is defined as a clinical facility of a state public hospital that actually separates islets from human pancreata under a Human Research Ethics Committee (HREC)-approved protocol and has the required regulatory approval/licensing.

NSW	Westmead Islet Laboratory
VIC	St Vincent's Institute of Medical Research

## Clinical islet transplantation and infusion units

A clinical islet transplant unit is defined as a clinical service of a state public hospital that actually performs the relevant transplant procedure under HREC-approved protocols.

NSW	Australian National Pancreas Transplant Unit, Westmead Hospital
SA	The Royal Adelaide Hospital
VIC	St Vincent's Health
NZ	New Zealand National Pancreas Transplant Unit, Auckland City Hospital

## Research islet separation facilities

A research islet facility is defined as a state public hospital or research institute that actually separates islets from human pancreata for research under a HREC-approved protocol with whatever regulatory approval/licensing is required.

NSW	Westmead Islet Laboratory
SA	The Royal Adelaide Hospital
VIC	St Vincent's Institute of Medical Research

## Intestinal transplantation units

VIC	The Austin
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## Vascularised composite allograft units

VIC	Royal Melbourne Hospital
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