

The Transplantation Society of Australia and New Zealand

# Clinical Guidelines for Organ Transplantation from Deceased Donors

Version 1.9 – May 2022

Produced in partnership with



Australian Government  
Organ and Tissue Authority



Version 1.0 of the *Clinical Guidelines for Organ Transplantation from Deceased Donors* (the Clinical Guidelines) was released in April 2016. Updates were made in May 2017 (Version 1.1), December 2018 (Version 1.2), May 2019 (Version 1.3), July 2020 (Version 1.4), April 2021 (Version 1.5), May 2021 (Version 1.6), September 2021 (Version 1.7), and December 2021 (Version 1.8).

The current document, Version 1.9 (May, 2022), replaces these previous versions of the Clinical Guidelines.

## Version control

Version #	Changes made	Approved by	Date
1.9	Updated advice related to organ donation and transplantation from donors with a diagnosis of COVID-19.  Updated advice in Chapter 2; section 2.2 and section 2.3.2.1, including the addition of a flowchart for assessment of potential deceased donors on page 18.	COVID-19 Australian Transplantation and Donation Rapid Response Taskforce, Australasian Transplant Coordinators Association (ATCA), Transplant Society of Australia and New Zealand (TSANZ) and the Organ and Tissue Authority (OTA)	4 May 2022
1.8	Updated advice related to testing in donors for COVID-19.  Addition of advice in Chapter 2; Table 2.1 and section 2.3.2.1.	COVID-19 Australian Transplantation and Donation Rapid Response Taskforce, Australasian Transplant Coordinators Association(ATCA), Transplant Society of Australia and New Zealand (TSANZ) and the Organ and Tissue Authority (OTA)	14 December 2021
1.7	Broad revisions to section 2.4 (Donor derived malignancy).  Changes in relation to Paediatric donors, with revisions to Section 6.5.3 Paediatric donor liver allocation, Chapter 11 (Paediatric Donors): Revision of the criteria for 11.4, Paediatric lung donation and allocation, 11.5 Paediatric heart donation and allocation and the addition of 11.5.1 Paediatric heart-lung blocs and allocation.	Australasian Transplant Coordinators Association (ATCA), Transplant Society of Australia and New Zealand (TSANZ) and Organ and Tissue Authority (OTA), Paediatric Transplant Advisory Committee (PTAC), Lung and Intestinal Advisory Committee (LITAC) and the Cardiac Transplant Advisory Committee (CTAC)	17 September 2021
1.6	The deceased donor kidney allocation algorithm underwent a review that has resulted in broad changes to Chapter 5 (Kidney) and Appendix C. Further enhancements are planned to continue to improve the deceased donor kidney allocation process.	Australasian Transplant Coordinators Association (ATCA), Transplant Society of Australia and New Zealand (TSANZ), Organ and Tissue Authority (OTA) and the OrganMatch Strategic Governance Committee (OMSGC)	4 May 2021

Version #	Changes made	Approved by	Date
1.5	<p>Updated advice related COVID-19 (section 2.3.2.1).</p> <p>Addition of advice in the event of reactive screening antibody results (section 2.3.2.9).</p> <p>Addition of section 2.5 on Risks related to other donor conditions.</p> <p>Updates relating to the Australian and New Zealand paired Kidney Exchange Program (ANZKX) (sections 5.2.5 and 5.4.4).</p>	Australasian Transplant Coordinators Association (ATCA), Transplant Society of Australia and New Zealand (TSANZ) and Organ and Tissue Authority (OTA)	28 April 2021
1.4	<p>Chapter 11 (Paediatric Donors) was added to the Guidelines, providing organ-specific advice on acceptability and allocation of organs from paediatric donors. Each of the organ-specific chapters in Part B were updated to reflect the new recommendations for paediatric donors.</p> <p>Addition of advice on COVID-19 screening in deceased donors.</p>	Paediatric Donor Working Group. Australasian Transplant Coordinators Association (ATCA), Transplant Society of Australia and New Zealand (TSANZ) and Organ and Tissue Authority (OTA)	24 July 2020
1.3	<p>Broad revisions to section 2.2 (Donor assessment) and section 2.3 (Donor transmitted infectious disease).</p> <p>Addition of Appendix I: Summary of recommendations for infectious disease screening in deceased donors</p> <p>References to donor and transplant registry statistics have been updated throughout to reflect the most up-to-date data.</p> <p>Changes to Chapter 4 (Heart): removal of the criterion of at least 10 years expected post-transplant survival (section 4.2); clarification of acceptable duration of warm ischaemia time (section 4.4.1); clarification of policy regarding HCV NAT-positive donors (section 4.7)</p> <p>Changes to Chapter 6 (Liver): updates to Section 6.4.1 'Use of HCV infected livers into HCV negative recipients'</p>	Australasian Transplant Coordinators Association (ATCA), Transplant Society of Australia and New Zealand (TSANZ) and Organ and Tissue Authority (OTA)	31 May 2019
1.2	<p>Changes to Chapter 5 (Kidney):</p> <p>Rewording of the 80% five-year survival criterion for wait-listing eligibility. This now states that "significant benefit" is required from transplantation under section 5.1.</p> <p>An adjustment to the rules surrounding return of deceased donor waiting time in the event of a failed live donor transplant within 12 months under section 5.2.</p> <p>Removal of the 12-month waiting period for paediatric bonus score to be applied to section 5.2.4.</p>	Australasian Transplant Coordinators Association (ATCA), Transplant Society of Australia and New Zealand (TSANZ) and Organ and Tissue Authority (OTA)	17 December 2018
1.1	<p>'Use of HCV infected donor livers into HCV negative recipients' has been added under section 6.4 on page 64.</p> <p>Minor consequential amendments to Recipient Eligibility in Section 1 and Organ Donor Eligibility in Section 2 have also been made.</p>	Australasian Transplant Coordinators Association (ATCA), Transplant Society of Australia and New Zealand (TSANZ) and Organ and Tissue Authority (OTA)	17 May 2017

## Disclaimer

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## 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. The current document (*Clinical Guidelines for Organ Transplantation from Deceased Donors*) replaces the previous Consensus Statement and was developed by the TSANZ Advisory Committees with written feedback sought through a targeted consultation process (see Appendix B). Version 1.0 of the Clinical Guidelines was released in April 2016. The current document, Version 1.9, updates and replaces all prior versions of the Clinical Guidelines.

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). With the introduction of new and safe antiviral therapy for Hepatitis C virus (HCV) infection this should include the possible use of an organ from a HCV infected donor into a recipient without HCV infection. 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 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 or, more recently, the use of HCV positive organs in HCV negative transplant recipients – see Chapter 2) 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 uphold their decision that the patient is not

eligible for listing, however the patient, their family or other advocates 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 not to list. 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 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 be no longer 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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- 15 Ethical Guidelines for Organ Transplantation from Deceased Donors. Australian Government National Health and Medical Research Council, Canberra, 2016.

## 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>2,3,4,5</sup>

### 2.1 The organ donation process

#### 2.1.1 Prerequisites for deceased organ donation

Before organ donation can take place:

- The donor must have been declared deceased by qualified physicians using accepted guidelines that are consistent with the laws and regulations of the jurisdiction in which the donor has died (see ANZICS statement), 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 (ICU). 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 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 no longer to be 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 standstill, 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.

Donation after Circulatory Death 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 16% of organ donors in New Zealand.<sup>6</sup> 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 the required time frames from withdrawal of cardio-respiratory support.<sup>7</sup> The number of potential DCD donors is uncertain and there may be scope for further increase in 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 from cardio-thoracic, liver or renal transplant units who will travel to the donor hospital 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 retrieval surgery 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 retrieval. Arrangements for the transportation of organs are made according to the organ type and whether organs are for local use or for transport interstate or between Australia and New Zealand.

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 non-utilisation 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 Deceased donor and organ assessment

### 2.2.1 General evaluation of deceased organ donors

Organ suitability for transplantation is determined by the answers to two questions: (i) is the donor medically 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>8</sup> That risk may vary depending on the organ and is assessed by considering donor risk factors



and by testing the donor. Donor-derived disease transmission complicates less than 1% of all transplantation procedures (excluding *Cytomegalovirus* [CMV] and Epstein-Barr virus [EBV]) but can result in significant morbidity and mortality.<sup>9,10</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 to an individual patient 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 important that the recipient has an informed view of accepting or rejecting an organ of lower quality and/or increased risk of disease transmission, with an understanding of the likely benefits from transplantation with the organ on offer (in terms of survival and/or quality of life), the likelihood of subsequent organ offers, and the risk of deterioration of their health status whilst waiting for an alternative offer. The conversation with the patient regarding consent to receive organs of lower quality or increased risk of disease transmission should occur early, ideally at the time of consent to waitlisting, and should be revisited periodically to take into account changes in patient priorities and health status.

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

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 the organ post-transplantation. It is also possible to grade the risk of transmissible disease associated with a given donor and 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).

### 2.2.2 Medical and social history

Obtaining a thorough medical, behavioural and travel history of the donor, performing a careful clinical examination and undertaking suitable investigations are critically important to the quality, safety and efficacy of organ donation. The accuracy of this information is critical to the assessment of the degree of risk to which the recipient of an organ from a given donor may be exposed. When interviewing next-of-kin and/or significant others regarding the history of a potential donor, it is important that this is done in a structured and standardised manner, utilising best practice tools, to balance the rigorous requirements of screening with compassion, patience and empathy. In Australia, the donor's medical history, examination and investigations are captured in an electronic donor record (EDR), which is completed for all donors, with the relevant information components provided to transplant units when organs are offered for transplantation. In New Zealand, the donor's medical history, examination and investigations are captured in a Confidential Donor Referral, which is completed for all donors, 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 donor suitability includes obtaining detailed information about the donor's past medical and social history, paying particular attention to:

- History of diseases and surgery, especially those that may affect organ function
- History of diabetes, hypertension and other cardiovascular disease
- Smoking, alcohol intake and non-medical drug use
- History of tumours or cancer—including stage, pathology details, treatment and current status
- Recent symptoms that may be indicative of undiagnosed infection, neurological disease or malignancy
- Suggestion of underlying metabolic disorder
- Risk factors for the transmission of human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), including non-medical injecting drug use, male to male sex, commercial sex work, time in prison, sex with a person at increased risk of these infections, a young child of a mother at increased risk of these infections, or diagnosis with syphilis, gonorrhoea, chlamydia or genital ulcers in the past 12 months
- Risk factors for the transmission of Transmissible Spongiform Encephalopathies (TSE), including family history of early dementia, use of pituitary hormone extract, notification of treatment with pituitary hormone extract
- Place of birth and prior residence in countries outside of Australia and New Zealand
- Travel history, especially recent travel (past six months)
- History of animal contact
- History of COVID-19: it should be ascertained whether the donor has ever been tested for or diagnosed with COVID-19, or has been in close contact with a person known to have confirmed, probable or suspected COVID-19 within 7 days prior to planned organ donation.

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

- Course of illness and cause of death
- Vital signs and cardio-respiratory status, including mechanical and pharmacological supports
- Function of potentially transplantable organs, including pathology, 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).

**There are very few absolute exclusion criteria to organ donation**, with the exception of disseminated metastatic cancer and donors with known specified factors for TSE (see Section 2.3.5.1). All other risk factors should be interpreted in the context of all other donor characteristics and recipient factors.

### 2.2.3 Physical examination

Physical examination provides information relevant to suitability, allocation, and possible disease transmission risks. This should include:

- Height and weight
- General assessment with respect to body habitus and state of health, major abnormalities related to past or present disease (e.g. obvious limb ischaemia, chest or spinal deformities, traumatic injuries)
- Inspection of skin, including the skin of the back and careful examination in skin folds and around the genital and anal areas, looking for surgical scars, skin lesions indicating possible cancers or infections, injection sites/needle track marks suggesting intravenous drug use (IVDU), or lumps, sores, tattoos or rashes
- Palpation for obvious lumps and masses (e.g. neck, groin, axillae, breasts, abdomen).

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.

## 2.2.4 Laboratory investigations

Blood group for ABO and Rhesus are mandatory investigations for all donors. For women of child-bearing potential dying from unexplained intracerebral haemorrhage, testing for beta human chorionic gonadotrophin hormone is recommended to detect metastatic choriocarcinoma. Whilst routine post mortem examination has become an uncommon procedure in clinical medicine, if an autopsy is performed then the results should be followed-up by the donation service up as the autopsy may detect potentially transmittable disease.

The list of possible pathogens for which potential donors might be screened is very long. Which of these pathogens to screen for depends on whether:

- The pathogen is sufficiently prevalent in the population that screening would be useful
- There is evidence that the pathogen in question can be transmitted by organ transplantation
- Transmission of the pathogen could result in significant morbidity or mortality
- A sufficiently accurate, rapid and affordable screening test exists.

The rapid turn-around times necessary in the context of donor screening, the associated logistical and technical limitations, and the need to balance the risk of transmission of infection against the risks to the recipient of dying while awaiting transplantation, make the goals of screening potential organ donors different to screening blood or tissue donors. It is the goal of organ donation and transplantation programs to minimize unexpected infectious disease transmission events while simultaneously maximizing opportunities for transplantation. All infectious disease screening recommendations, therefore, carefully consider turn around times, test performance (i.e. the potential for false positive or false negative results), and other logistical issues that may pose a risk to the donation process and lead to the loss of transplantable organs. These considerations must be weighed against the benefits of screening to patient safety.

The following laboratory investigations to detect infections that may be transmitted by solid organ transplantation are recommended for all donors:

- HIV antigen/HIV-1/2 antibody combination assay (HIV Ag/Ab)
- Hepatitis B surface antibody (anti-HBs or HBsAb)
- Hepatitis B surface antigen (HBsAg)
- Hepatitis B core antibody (HBcAb)
- Hepatitis C antibody (anti-HCV or HCV Ab)
- Nucleic acid testing (NAT) for HBV, HCV and HIV, most commonly using polymerase chain reaction (PCR) assays
- *Cytomegalovirus* (CMV) immunoglobulin (IgG) antibody
- Epstein-Barr virus (EBV) capsid IgG antibody
- Syphilis serology (specific treponemal antibody test)
- Toxoplasmosis serology (IgG)
- Human T-cell-lymphotrophic virus (HTLV) 1/2 antibody
- Coronavirus (SARS-CoV-2) PCR on nasopharyngeal swab' Coronavirus (SARS-CoV-2) PCR lower respiratory tract sample required for potential lung donors.

Urine microscopy and culture is recommended for all donors from whom a urine sample can be obtained, with the results of cultures and sensitivity testing to be followed up as soon as they become available (which may not be until after transplantation has occurred). Blood cultures are recommended only if there is clinical suspicion of bacteraemia. Respiratory tract samples (e.g. tracheal aspirate, sputum or bronchoscopic samples) for microbiological testing should be collected for lung donors or if respiratory infection is suspected.

Table 2.1 provides details of which donors should receive the tests specified above and whether results are recommended prospectively. "Prospective results" in the context of organ donation refers to results that are made available prior to the transplantation of organs (as opposed to prior to organ retrieval). Test results that are not recommended to be made available prospectively should be obtained as early as possible, but transplantation may proceed prior to results being available.

**Table 2.1:** Recommended laboratory investigations for the detection of potentially transmissible infectious diseases in solid organ donors.

Test	Recommended for all donors	Recommended for specified donors	Comments
Serology and nucleic acid testing (NAT):			
HIV Ag/Ab (positive results confirmed with anti-HIV-1/2).	X		Results should be available prior to transplantation proceeding
HBsAg, HBcAb and anti-HBs	X		Results should be available prior to transplantation proceeding
anti-HCV	X		Results should be available prior to transplantation proceeding
HIV/HBV/HCV NAT	X		Prospective NAT is required wherever this is logistically feasible, and is strongly advised for increased-risk donors (see Table 2.2 for definition of increased-risk donors). If results are not available in a timely manner transplantation may proceed at the discretion of the transplant team and with appropriate recipient consent.
anti-CMV (IgG)	X		Prospective results are preferable where possible
anti-EBV (IgG)	X		Prospective results are preferable where possible
anti- <i>T.pallidum</i> (IgG)	X		Prospective results are preferable where possible
anti- <i>T.gondii</i> (IgG)	X		No urgency on test results
Anti-HTLV-1/2	X <sup>a</sup>		Prospective results are preferable where possible
Microbiological testing			
Urine microscopy and culture	X		Microbiological testing should be performed on all donors for whom a urine sample can be obtained, with results of urine culture and sensitivity testing to be followed up as they become available (post transplantation)
Blood culture		X	Recommended where there is clinical suspicion of bacteraemia
Respiratory culture		X	Respiratory tract samples for microbiological testing should be collected for lung donors or if respiratory infection is suspected
Coronavirus (SARS-CoV-2) nasopharyngeal swab for PCR	X		Prospective results are required prior to proceeding with transplantation. In lung donors, a lower respiratory tract specimen is also required
Coronavirus (SARS-CoV-2) lower respiratory tract sample for PCR			Preferable in all donors – diagnostic sensitivity is improved with the addition of testing lower respiratory tract samples. Mandatory in potential lung donors, with a negative result obtained prior to proceeding with lung transplantation - donor transmission is more likely with lung transplantation than that of other solid organs. A tracheal aspirate is generally acceptable, although in potential lung donors presumed recovered from recent COVID-19 infection, a bronchoscopically obtained sample is preferable (e.g. mini- or full broncho-alveolar lavage, bronchial washings).

<sup>a</sup> While HTLV-1/2 screening is recommended for all donors, donors at high risk of HTLV-1 include Aboriginal people from Central Australia and persons born in southwestern Japan, sub-Saharan Africa, the Middle East, the Caribbean, and parts of South America (French Guyana, Peru). Screening is recommended for all donors since information in the donor record might not identify all persons at high risk and outcomes in the rare event of transmission can be extremely severe or fatal. See Section 2.3.2.9.

### 2.2.5 Haemodilution assessment

Where the donor receives multiple blood transfusions or significant infusions of intravenous fluids prior to donation, haemodilution may occur such that circulating antigens, antibodies and targets for NAT are at a low concentration that is difficult to detect, introducing the potential for false negative results. False positive results may also occur due to interactions between serological tests and molecules present as a result of infused products. The degree to which a potential donor's plasma has been diluted is a product of blood loss as well as fluids infused.

Serological tests and NAT have not been validated for use on all haemodiluted samples, and therefore serological screening and NAT should ideally be performed on non-diluted blood samples. For all donors, blood products and colloids given in the 48 hours prior to the date and time the sample was drawn are entered into the EDR (Australia) or Confidential Donor Referral (New Zealand). This information is used to autocalculate whether the sample is haemodiluted. If either plasma dilution or blood dilution exceed defined thresholds, a pre-transfusion/infusion sample should be used for donor screening. If a suitable sample is not available, the risk of false negative results from testing a haemodiluted sample should be communicated to the transplanting teams.

### 2.2.6 Special donor groups

#### Donors under 18 months or breastfed children

Microbiological screening for neonatal and infant donors (of less than 18 months old, or up to 6 months beyond breast feeding) should be performed as for other donors, including HIV/HBV/HCV NAT, taking into account that positive antibody results may reflect passive transfer of antibodies from the mother. The potential for eclipse/window period infections should also be considered, and prospective NAT is recommended in this context.

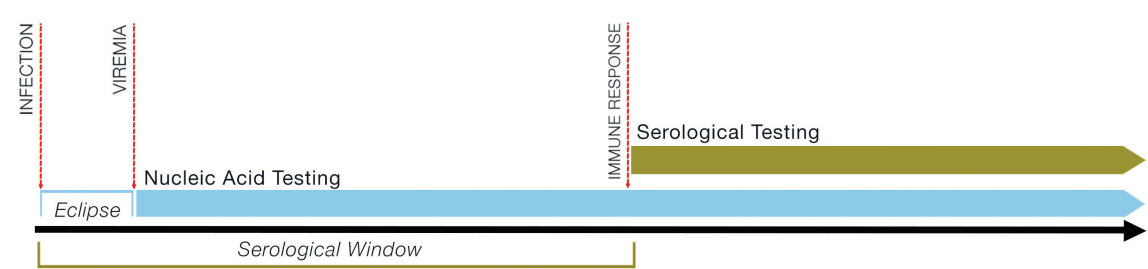
Given the limited volume of blood that can be taken from a neonate or infant for the purposes of screening and the likelihood of haemodilution, complementary testing of the mother is required in these cases. If the mother is not at increased-risk of infectious diseases (see Table 2.2) and is sero-negative for markers of infection, the successful screening of the neonate/infant is less critical. Discussion with an infectious diseases physician or microbiologist is strongly advised.

## 2.3 Risk of donor transmitted infectious disease

Acute or latent infections may be transmitted by the transplanted organ to the recipient. The intentional use of donors with certain infections may be considered where there is an acceptable risk of morbidity to the recipient, mitigated by serostatus matching or by antimicrobial prophylaxis and monitoring. The unexpected transmission of an infectious disease from an organ donor to recipient(s) is a rare event; however when it does occur, it is usually associated with significant morbidity and mortality.<sup>9</sup>

The concept of the “eclipse” or “window” period of infection is critical to understanding donor infectious disease risk mitigation. Following infection by a microbiological agent, there is a period of time during which no microbe can be readily detected in the host; this is classically called the “window period” for serological testing, or the “eclipse period” for NAT (see Figure 2.1: Generalised diagram of eclipse and window periods.). Unexpected transmissions are most likely to occur if the donor has recently acquired the infection and is still in the eclipse/window period before detection is possible. Test results must be interpreted in the context of the patient's full history, and the probability of false negative results needs to be considered against the donor's background of any reported risk factors such as IVDU or high-risk sexual contact. Close attention must also be paid to travel history: potential donors with recent travel to or previous residence in areas where they may have been exposed to endemic pathogens warrant additional screening.<sup>10,11</sup> In the case of a donor with recent risk exposure who is within the eclipse or window period of detection (e.g. a donor with intravenous drug overdose as the cause of death), whether to proceed with donation requires a consideration of the particular risks and benefits from the perspective of the intended recipient(s) and the informed consent of the recipient(s).

**Figure 2.1:** Generalised diagram of eclipse and window periods.



2.3.1 Donors at increased risk of HIV, HBV and HCV

HIV, HBV and HCV have been transmitted through organ transplantation.<sup>10</sup> 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 and NAT assay. Donors are classified as “increased-risk” based on the presence of any of the risk factors listed in Table 2.2. In reality, the risk of donor-derived transmission of HIV, HBV and/or HCV exists on a spectrum, with IVDU and those known or suspected to have HIV, HBV or HCV associated with the highest degree of risk. It should be noted that information about behavioural risk factors obtained from the next of kin may be limited or inaccurate. The donor assessment interview must be supplemented with evidence from physical examination of the donor and/or their medical record. Donors whose social and medical history cannot be obtained should also be treated as increased risk.

The presence of HIV, HBV or HCV in the donor is not necessarily a contraindication to donation. Decisions about whether to proceed with donation and transplantation will depend on recipient informed consent, the nature of the infection, other recipient clinical factors and the availability of effective treatment. Whereas the presence of HIV rules out donation in most circumstances, presence of HCV is becoming less of a barrier to transplantation given the availability of curative treatment. Similarly, recipients who are adequately immunised against or given prophylactic treatment for HBV may be transplanted with organs from donors with the potential to transmit HBV (see Sections 2.3.2.4 and 2.3.2.5). Where uncertainty exists, advice should be sought from a transplant hepatologist or infectious disease physician.

Donor testing for HIV, HBV and HCV using serology and NAT should be undertaken using blood samples obtained from the donor prior to significant haemodilution. Such testing should be undertaken by laboratories with the appropriate accreditation (National Association of Testing Authorities [NATA] and Royal College of Pathologists of Australia [RCPA] or Therapeutic Goods Administration [TGA, licensed]). Serological testing for HIV, HBV and HCV is performed as part of the evaluation of all donors, with results obtained prior to proceeding with organ transplantation. NAT testing for HIV, HBV and HCV is also recommended for all donors, with results required prospectively wherever logistically feasible.

**Table 2.2:** Criteria for identifying organ donors at increased risk for HIV, HBV, and HCV infection (MSM= men who have sex with men; Derived from Seem<sup>12</sup>)

People known or highly suspected to have HIV, HBV and/or HCV infection
People who have injected drugs by intravenous, intramuscular, or subcutaneous route for non-medical reasons in the preceding 10 weeks*
MSM in the preceding 10 weeks
People who have been in lockup, jail, prison, or a juvenile correctional facility for more than 72 consecutive hours in the preceding 10 weeks
People who have had sex in exchange for money or drugs in the preceding 10 weeks
People who have had sex with a person in any of the above groups in the preceding 10 weeks
People who have been newly diagnosed with, or have been treated for, syphilis, gonorrhoea, chlamydia, or genital ulcers in the preceding 10 weeks

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A child who is 18 months old or younger and born to a mother known to be infected with, or at increased risk for, HIV, HBV or HCV infection

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A child who has been breastfed within the preceding 6 months, and the mother is known to be infected with, or at increased risk for, HIV, HBV or HCV infection

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When a deceased potential organ donor's medical/behavioural history cannot be obtained or risk factors cannot be determined

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When a deceased potential organ donor's blood specimen is haemodiluted so that testing for HIV, HBV, and HCV infection is less reliable

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\* 10 weeks represents the longest serological window for detection of any of these three blood borne viruses (i.e. HCV, which has a serological window of ~70 days).

If a donor has recently been infected with HIV, HBV or HCV, it is possible that the donor may still be in the eclipse or window period of infection (see Table 2.3) and transmission may still occur despite negative results on serology and NAT. The degree of residual infection risk associated with a specific donor is influenced by the nature of the donor's risk behaviour(s) and how recently the risk behaviour(s) occurred in relation to the time of donor testing.<sup>13</sup> Higher underlying incidence in an at-risk group or longer eclipse/window periods correspond with a higher residual risk of an undetected infection.

**Table 2.3:** Window and eclipse periods\* for pathogen testing. Modified from Humar.<sup>14</sup>

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

\* Window period = the interval from infection to ability to detect that infection by serological testing; eclipse period = the interval after infection for which infection cannot be detected by either NAT or serological testing.

Table 2.4 lists the estimated risks of undetected HIV, HBV or HCV infection in Australian donors by risk behaviour type, based on Australian epidemiological data.<sup>15</sup> The estimates shown are preliminary, with final results expected to be published in 2019. These estimates of residual risk are based upon the best available local evidence, but are limited where the underlying data were sparse – notably in the case of commercial sex workers and high risk partners. Data on the incidence of HBV in Australia are not available, therefore residual risk estimates were derived from estimates of the prevalence of hepatitis B core antibody (HBcAb) and hepatitis B surface antigen (HBsAg) in each risk group. It is also important to note that these residual risk estimates are based on historical data. Improvements in the treatment of HIV, HBV and HCV (especially HCV) and corresponding reductions in incidence, and/or improvements in testing (resulting in shorter eclipse and window periods), would result in lower residual infection risks.

The risk of an undetected HIV infection is low in all cases. Donors with the highest residual risk, men who have recently had sex with men, have an estimated 1 in 1621 residual risk of undiagnosed HIV based on a negative enzyme immunoassay (EIA) result alone, and a 1 in 5092 residual risk based on a negative EIA + NAT. For recent intravenous drug users, prisoners, commercial sex workers and increased risk partners, the risk of undiagnosed HIV is less than 1 in 10,000.

Risk of undetected HCV is highest among recent IVDU (past 10 weeks), among whom the residual risk of HCV is 1 in 31 based on a negative EIA result alone, and 1 in 299 based on a negative EIA + NAT. The residual risk of HCV is similar among the prison population: 1 in 45 based on EIA alone, and 1 in 344 based on EIA + NAT. The risk of undetected HBcAb (i.e. likely past HBV infection) is highest for recent IVDU: 1 in 103 based on a negative EIA, and 1 in 205 for a negative EIA + NAT. The risk of undetected HBsAg (i.e. active HBV infection) is also highest for recent IVDU: 1 in 1216 based on EIA alone, and 1 in 2430 based on a negative EIA + NAT.

It should be noted that the underlying risk behaviours within each risk factor category are not homogenous. The residual risks reported in Table 2.4 represent conservative estimates of the infectious risks associated with donors in each risk category, however the actual risk of undetected infection in a given test-negative donor may be significantly lower depending on their history. For example, residual risks of HCV among IVDU may be lower



for IVDU participating in needle exchange programs and receiving opioid substitution, compared to IVDU not participating in these programs.<sup>16</sup> For all donors, test results should be interpreted in the context of the donor's personal history, and the residual risk estimates given in Table 2.4 should be used as a guide but not as a definitive numbers.

**Table 2.4:** Residual risk<sup>a</sup> of undiagnosed HIV, HBV or HCV infection for Australian donors at increased risk, by risk factor and testing strategy. Adapted from Waller et al.<sup>15</sup>

Risk Factor	Incidence <sup>b</sup> (95% Confidence Interval) per 100 person-years	Residual infection risk			
		Enzyme immunoassay (EIA) serology <sup>c</sup>		EIA serology +nucleic acid testing (NAT) <sup>d</sup>	
		Risk estimate	Upper risk estimate <sup>e</sup>	Risk estimate	Upper risk estimate <sup>e</sup>
Human immunodeficiency virus					
Men who have sex with men	1.03 (0.72-1.33)	1 in 1621	1 in 1253	1 in 5092	1 in 3936
Intravenous drug use	0.16 (0.11-0.20)	1 in 10,619	1 in 8209	1 in 33,373	1 in 25,797
Prisoners	0.03 (0.02-0.04)	1 in 47,783	1 in 36,937	1 in 150,173	1 in 116,085
Commercial sex workers	0.05 (0.04-0.07)	1 in 31,856	1 in 24,625	1 in 100,116	1 in 77,390
Increased risk partners	0.03 (0.02-0.04)	1 in 47,783	1 in 36,937	1 in 150,173	1 in 116,085
Hepatitis C					
Men who have sex with men	1.3 (0.8-1.8)	1 in 409	1 in 292	1 in 5,719	1 in 4,076
Intravenous drug use	17.5 (10.4-24.5)	1 in 31	1 in 22	1 in 419	1 in 299
Prisoners	11.9 (2.6-21.3)	1 in 45	1 in 25	1 in 613	1 in 344
Commercial sex workers	4.5 (2.7-6.3)	1 in 116	1 in 83	1 in 1,616	1 in 1,152
Increased risk partners	5.6 (3.4-7.9)	1 in 94	1 in 67	1 in 1,301	1 in 927
Hepatitis B core antibody <sup>f</sup>					
Men who have sex with men	1.9 (0.7-3.7)	1 in 444	1 in 224	1 in 887	1 in 446
Intravenous drug use	8.1 (3.1-16.2)	1 in 103	1 in 52	1 in 205	1 in 104
Prisoners	3.5 (1.3-7.0)	1 in 237	1 in 120	1 in 473	1 in 239
Commercial sex workers	0.4 (0.2-0.9)	1 in 1,849	1 in 930	1 in 3,698	1 in 1,860
Increased risk partners	0.2 (0.1-0.3)	1 in 5,315	1 in 2,673	1 in 10,629	1 in 5,346
Hepatitis B surface antigen <sup>f</sup>					
Men who have sex with men	0.4 (0.2-0.9)	1 in 1,933	1 in 973	1 in 3,866	1 in 1,944
Intravenous drug use	0.7 (0.3-1.4)	1 in 1,216	1 in 612	1 in 2,430	1 in 1,223
Prisoners	0.6 (0.2-1.2)	1 in 1,418	1 in 714	1 in 2,835	1 in 1,426

<sup>a</sup> Residual infection risk is the predicted rate of undetected infection in donors who test negative for HIV, HCV or HBV, depending on risk factor and testing strategy, calculated as  $RR = 1 - e^{(-incidence)(eclipse\ period\ or\ serological\ window)}$

<sup>b</sup> Incidence estimates are based on a systematic review and meta-analysis of studies from 2000-2017 reporting original estimates of Australian HIV, HCV or HBV prevalence or incidence. Incidence rates and confidence intervals were estimated using random effects.

<sup>c</sup> Serological window period assumed in the calculation of residual risk estimates based on serological screening (EIA) alone: HIV=22 days, HCV=70 days, HBV=44 days<sup>14</sup>

<sup>d</sup> Eclipse period for NAT testing assumed in the calculation of residual risk estimates based on EIA + NAT: HIV=7 days, HCV=5 days, HBV=22 days.<sup>14</sup>

<sup>e</sup> Upper risk estimate is derived from the upper 95% confidence limit of the risk estimate.

<sup>f</sup> Data on the incidence of HBV in the Australian population are not available. It was therefore necessary to estimate the residual risk of undetected HBcAb and HBsAg separately. These estimates should be interpreted as the risk that, despite a negative test result, the donor is positive for either HBcAb (past, persistent or acute-phase infection) or HBsAg (active infection) respectively.



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

When the transplantation of solid organs is being considered from a donor identified as being at increased risk of HIV, HBV or HCV transmission, standard measures should be taken, including:

- Donor NAT (prospective testing is strongly advised)
- Discussion with a specialist with viral hepatitis and transplantation expertise (e.g. hepatologist or infectious diseases specialist)
- Consideration of recipient status—transplantation may be appropriate for recipients who are immune (for HBV), at risk of reactivation, with existing active infection, or where suitable treatments exist in the event of disease transmission (i.e. HCV)
- Consideration of recipient urgency for transplant – the risk of transplanting organs from increased-risk donors may be more appropriate for patients in urgent need of a life-saving transplant
- Specific informed consent must be obtained from the recipient prior to transplantation
- Post transplant prophylaxis where applicable, in consultation with a hepatologist or infectious diseases specialist
- Post transplant screening for acute infection (see below).

## Follow-up of recipients of organs from increased-risk donors

For all recipients of organs from donors identified as being at increased risk of infection with HIV, HBV or HCV, post-transplant surveillance for the appearance of infection should occur. Given that serological testing may be unreliable in recipients or serological conversion may be delayed, HCV testing should be performed using NAT. Surveillance for appearance of HIV in recipients post-transplant should be performed using the HIV Ab/Ag combination assay or HIV NAT; surveillance for HBV should be performed by testing for the appearance of HBsAg or by HBV NAT.

The first follow-up test should ideally occur within 30 days of transplantation, and follow-up out to 12 months is recommended (with the frequency of repeat testing from months 2-11 at the discretion of the treating physician). In the unlikely event that the recipient is unable to attend follow-up testing within 30 days of transplantation, testing needs to occur at the earliest convenience of the patient. The relevant donation agency should be informed immediately if testing indicates de novo infection with HIV, HBV or HCV in the follow-up period post-transplantation.

### 2.3.2 Viral Infections

#### 2.3.2.1 Coronavirus (SARS-CoV-2) causing COVID-19

Our understanding of the risk of donor-derived COVID-19 (SARS-CoV-2) transmission is evolving and at this point is limited to data from several case series. The importance of assessing potential donors for SARS-CoV-2 infection takes into account the worst outcomes experienced by transplant recipients with COVID-19<sup>17,18,19,20</sup>, especially in the early post-transplant period and in the context of ATG induction<sup>21</sup>, as well as the importance of preventing transmission to healthcare workers, including the organ procurement team.

All potential donors require assessment to determine whether they are currently infected with SARS-CoV-2 or recovering from COVID-19. Risk-based assessment is no longer reliable due to sustained community transmission and widespread vaccination, which reduces the likelihood of symptomatic SARS-CoV-2 infection<sup>22</sup>. The optimal timing of SARS-CoV-2 testing prior to transplantation remains unclear, however routine SARS-CoV-2 testing is recommended for all potential donors ideally within 24 hours of planned donation (no greater than 48 hours from actual donation). Donor-derived COVID-19 in lung transplant recipients, in whom the donor tested negative on nasopharyngeal (NP) swab prior to donation but was positive on bronchoalveolar lavage (BAL) fluid when retrospectively tested has been documented<sup>23,24</sup>. For this reason, potential lung donors require a negative SARS-CoV-2 PCR on specimens from both upper (NP swab) and lower (e.g. tracheal aspirate for most donors, and BAL suggested for donors with a diagnosis of previous COVID-19) respiratory tract ideally within 24 hours of planned donation (no greater than 48 hours from actual donation). If obtaining a PCR within 24 to 48 hours is not achievable due to local testing capacity or logistics, the decision to proceed to organ acceptance will depend on an individual case assessment. Factors to be considered include, but are not limited to; for the donor, the likelihood of hospital- or community-acquired SARS-CoV-2; timing of most recent SARS-CoV-2 PCR; clinical evidence of COVID-19; and the organ(s) being considered for transplantation, and for the recipient, the urgency of transplantation.

There have been no confirmed cases of SARS-CoV-2 transmission via extra-pulmonary organs including from donors with positive SARS-CoV-2 PCRs on NP swabs.

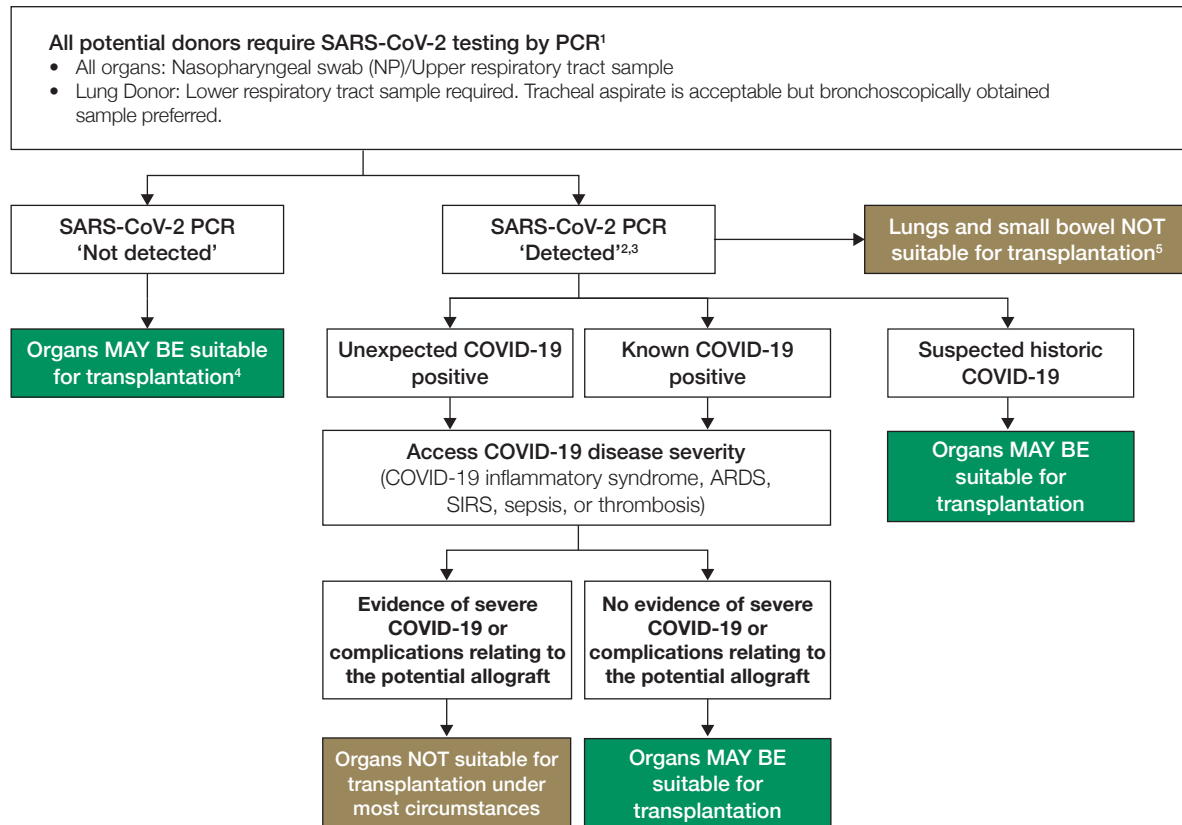
Potential donors may present within the time period where they are considered a “close contact” of COVID-19. During this period, the donor may be in the incubation period of SARS-CoV-2 and thus may test negative on PCR, only to test positive at a later time. Of note, donors may be exposed to SARS-CoV-2 in their pre-terminal hospital admission. Such donors should be assessed for suitability on a case-by-case basis.

There is mounting evidence that it may be safe to transplant extra-pulmonary organs (liver, kidney, heart) from living and deceased donors with a history of COVID-19, who have a positive nasopharyngeal (NP) swab at the time of organ procurement<sup>25,26,27,28,29,30</sup>. In the largest study to date, Gupta et al. analysed the United States Organ Procurement and Transplantation Network database to report on use of organs from COVID-19 infected donors. In this study, 150 donors donated 276 organs to 262 recipients (193 kidneys, 5 pancreases, 18 hearts, 3 lungs, 57 livers, 0 intestine). 72.4% of transplanted organs were from donors who were positive on PCR for SARS-CoV-2 within seven days of organ recovery. The median duration of follow up varied from 62 to 144 days, depending on the organ(s) transplanted. Graft loss was seen only in kidney transplants (n=3, 1.6%) of which two were due to thrombosis on the day of surgery. There were five deaths including one from sepsis and one from respiratory failure. This study did not report on the donor's stage of or complications from COVID-19 or if the recipients received any prophylactic therapy<sup>31</sup>. In addition, several cases have been reported of transplantation of non-lung organs from deceased donors who tested positive for SARS-CoV-2 on PCR of nasopharyngeal swab at the time of organ procurement without SARS-CoV-2 transmission to recipients with and without evidence of immunity at the time of transplant<sup>28,30,32,33</sup>. Long-term allograft outcomes are not yet known.

Concerns have also been raised about the transplantation of small bowel from donors who test positive for SARS-CoV-2, given the high concentration of lymphoid tissue and the high immunosuppression requirement post-transplant, relative to other organs<sup>34</sup>. Pancreas allografts contain a small section of duodenum. The risk of SARS-CoV-2 transmission via pancreas allografts is unclear due to limited data. Pancreas allografts from a donor testing positive to SARS-CoV-2 may be suitable for transplantation, but should be assessed on a case by case basis.

A flow chart for assessment of donors is shown in figure 2.2.

**Figure 2.2:** Flow chart for assessment of donors



<sup>1</sup> Rapid antigen tests are not appropriate for testing potential organ donors

<sup>2</sup> All potential donors who test positive for COVID-19 should be discussed with an infectious diseases physician

<sup>3</sup> Surrogates for viral quantification (i.e. cycle threshold 'CT' values) should not be used as the sole indicator to assess COVID-19 disease activity due to variation based on specimen quality and lack of standardization between tests. Routine serologic testing is not recommended.

<sup>4</sup> Donors with SARS-CoV-2 not detected on PCR may have been classified as a COVID-19 'close contact' within the 7 days prior to donation. This is inconsequential when considering acceptance of non-lung organs. The risk of transmission of SARS-CoV-2 via lung allografts in the setting where the donor is in the 'eclipse period' (time between infection and test positivity) is of theoretical concern but thought to be very low and should be considered on a case-by-case basis.

<sup>5</sup> Pancreas transplantation includes transplantation of a small portion of duodenum. The risk of SARS-CoV-2 transmission and/or adverse graft outcomes from SARS-CoV-2 positive donors is unclear. Each donor-recipient pair should be assessed on a case-by-case basis. Avoid transplanting organs from donors with severe COVID-19 as per other non-lung allografts

Recipients being offered organs from donors who test positive for SARS-CoV-2 or have recovered from COVID-19 should undergo informed consent, given the theoretical risk of transmission.

Refer to the latest advice issued by OTA/TSANZ (on the TSANZ website) and the Communicable Disease Network of Australia (CDNA) for more information on COVID-19 screening in the context of organ donation and transplantation.

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#### Recommendations

All donors should be tested for SARS-CoV-2 on a nasopharyngeal swab ideally within 24 hours of planned donation (no greater than 48 hours from actual donation). In addition, lung donors should be tested on a sample from the lower respiratory tract.

Lung and small bowel organs from donors with a positive PCR for SARS-CoV-2 from upper or lower respiratory tract sampling are not suitable for transplantation.

Organs other than lung and small bowel from donors with a positive PCR for SARS-CoV-2 may be suitable for transplantation if no evidence of severe COVID-19 or complications relating to the allograft.

All donors should be screened for recent SARS-CoV-2 exposure within the preceding 7 days and if deemed a “close contact” suitability for transplantation should be assessed on a case-by-case basis.

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#### 2.3.2.2 Cytomegalovirus

Over 50% of the Australian adult population is latently infected with cytomegalovirus (CMV), based on rates of seropositivity in population studies.<sup>35</sup> No contraindications exist to organ donation in the case of latent CMV. However, organs from seropositive donors may transmit infection, potentially causing severe disease in the seronegative recipient.

*De novo* CMV infection in the recipient can be largely managed by routine prophylaxis and post-transplant virological monitoring. Selecting CMV seronegative donors for CMV negative recipients avoids *de novo* CMV infection, however in practice there are often competing interests to seromatching.

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#### Recommendation

Organs can be accepted irrespective of the CMV serostatus of the donor. If the donor or recipient is seropositive, suitable prophylaxis should be given and post-transplant virological monitoring is required.

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#### 2.3.2.3 Epstein-Barr virus

Over 90% of Australian adults are latently infected with Epstein-Barr virus (EBV).<sup>36</sup> Epstein Barr virus causes lifelong infection, and organs from seropositive donors may transmit infection to a seronegative recipient, increasing the risk of post-transplant lymphoproliferative disease (PTLD). The risk of PTLD is approximately six-times higher in cases of donor-derived primary EBV infection versus cases of EBV reactivation in seropositive recipients.<sup>37</sup>

Antiviral prophylaxis has not been shown to reduce the incidence of PTLD, therefore monitoring for the appearance of EBV deoxyribonucleic acid (DNA) and early treatment should be considered for all donor-positive/recipient-negative (D+/R-) transplants. In cases of suspected acute mononucleosis in the donor, diagnosis should be made on the basis of investigation of EBV-DNA in peripheral blood and EBV nuclear antigen.

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#### Recommendation

Organs can be accepted irrespective of the EBV serostatus of the donor. If the donor is seropositive and the recipient seronegative, post-transplant virological monitoring is suggested.

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#### 2.3.2.4 Hepatitis B virus

When screening for HBV in potential organ donors, HBsAg, HBcAb and HBsAb are all required to identify and distinguish between current infection, prior cleared infection, vaccination or no exposure.<sup>38</sup> HBV-NAT is also recommended for all donors, especially as persistent latent HBV infection may occur.

Many factors influence the risk of HBV transmission. HBsAg-positive donors pose a high risk of transmission regardless of the organ being transplanted. For donors who are HBcAb-positive/HBsAg-negative, transmission rates are higher for liver transplantation (34 – 86% without prophylaxis<sup>39,40</sup>) than for the transplantation of other solid organs (0 – 5%<sup>41</sup>). Prophylaxis for recipients of livers from HBcAb-positive donors has been shown to be effective, although transmission of HBV has been reported in rare instances despite treatment.<sup>42,43,44</sup> For non-liver organ recipients who are immune prior to transplantation, there is a negligible risk of transmission from HBcAb-positive donors.<sup>43,39</sup>

Use of donors who are HBsAg or HBcAb sero-positive or HBV NAT-positive should be considered on a case-by-case basis in consultation with a transplant hepatologist or infectious disease specialist with transplantation expertise.

##### HBsAg-positive or HBV NAT-positive donors

HBsAg-positive and HBV NAT-positive donors are likely have active HBV infection, and pose a high transmission risk.<sup>45,46</sup> HBsAg-positive/NAT-positive donors can be considered for HBsAg-positive recipients,<sup>47</sup> or in exceptional circumstances for HBsAg-negative recipients after hepatology or infectious diseases specialist advice. For HBV-naïve recipients, the risk of HBV transmission from donors who are HBsAg-positive or HBV NAT-positive is attenuated with use of prophylaxis and in vaccinated recipients.<sup>45,46,48</sup>

In the event of transplantation from a HBsAg-positive/HBV NAT-positive donor, the hepatitis D virus (HDV) status of the donor should be determined, including HDV ribonucleic acid (RNA) and HDV antibody assays. The results of these assays will often not be available until after transplantation. Where there is a risk of HDV transmission, transplantation should be discussed with an infectious diseases physician or hepatologist prior to proceeding.

##### HBsAg-negative, HBcAb-positive donors

Transplantation from HBsAg-negative, HBcAb-positive donors can be considered, though with caution.

Interpretations include:

- Past infection: HBsAb will typically be positive, but may be lost in the case of longstanding past infection. HBcAb of immunoglobulin M (IgM) class indicates a current or recent infection with HBV, while HBcAb of immunoglobulin G (IgG) class generally indicates a past infection
- Persistent infection: the liver is a reservoir for HBV, and HBcAb-positive donor hepatocytes are latently infected with HBV, with reactivation possible at any time in liver recipients<sup>49,50</sup>
- Acute phase infection: after disappearance of HBsAg, before appearance of HBsAb
- False-positive test result.

Individuals who have cleared a natural HBV infection typically become HBsAg negative, HBcAb-positive, and have an HBsAb titre >10 IU/L.<sup>38</sup> However, a donor serological profile with an isolated presence of HBcAb may also indicate a current HBV infection at a point where HBsAg is no longer detectable in peripheral blood (but HBsAb titres have not yet reached levels sufficient to clear the virus or to be detected).<sup>38</sup> Presence of an isolated HBcAb therefore carries the possibility of HBV transmission, although the extent of this risk depends on the organ being transplanted. It is preferred that livers from HBcAb-positive donors be used for recipients with current or previous HBV infection, recipients who have been successfully vaccinated, or in urgent cases. Non-liver organs from donors who are HBcAb-positive and HBsAg-negative/NAT-negative may be used for HBV-naïve recipients after informed consent and with HBsAg and HBV DNA testing of the recipient to at least 12 months post-transplant. Short durations of antiviral prophylaxis (entecavir or tenofovir) for the recipient in this circumstance may be appropriate.

The presence of HBsAb in the blood is indicative of an immunologic response to HBsAg, and there is a rough inverse correlation between donor HBsAb titre and infectious risk.

### Donors at increased risk of HBV

If the donor social or medical history is suggestive of increased risk of HBV infection (see Section 2.3.2), test results should be interpreted in the context of donor risk factors, particularly if NAT results are not available prior to transplantation. See Table 2.4 for the residual risks of an eclipse/window period HBV infection, by risk factor.

**Table 2.5:** Interpretation of results of HBV screening in organ donors and recommendations for utilization

Test results	Interpretation	Implications for liver utilisation	Implication for utilisation of non-liver organs
HBV-NAT +ve	HBV infection	HBV transmission may occur to naïve recipients. Organs may be transplanted in HBV infected recipients, or in exceptional circumstances after specialist advice. If proceeding with transplantation of HBV-NAT +ve organs, test for HDV and discuss results with a hepatologist or infectious diseases physician.	
HBsAg +ve	HBV infection	HBV transmission may occur to naïve recipients. Organs may be transplanted in HBV infected recipients, or in exceptional circumstances after specialist advice. If proceeding with transplantation of HBsAg+ve organs, test for HDV and discuss results with a hepatologist or infectious diseases physician.	
HBsAg -ve HBcAb +ve	Hepatocytes infected, usually no viraemia but possible low-level viraemia should be considered	HBV transmission may occur in naïve recipients: allow transplantation of livers to HBV-infected recipients or recipients with an immune response to vaccination and HBV provide prophylaxis <sup>a</sup>	Transmission is unlikely: transplantation may proceed. <sup>b</sup>

<sup>a</sup> Recipient management would typically involve life-long entecavir or tenofovir with HBsAg and HBV DNA monitoring.

<sup>b</sup> For the non liver recipient with HBsAb>100 IU/L no prophylaxis is required. For the non-liver recipient with HBsAb<100 IU/L, consider short durations of entecavir or tenofovir. Non-liver recipients should be tested by HBsAg and HBV DNA to 12 months post transplant

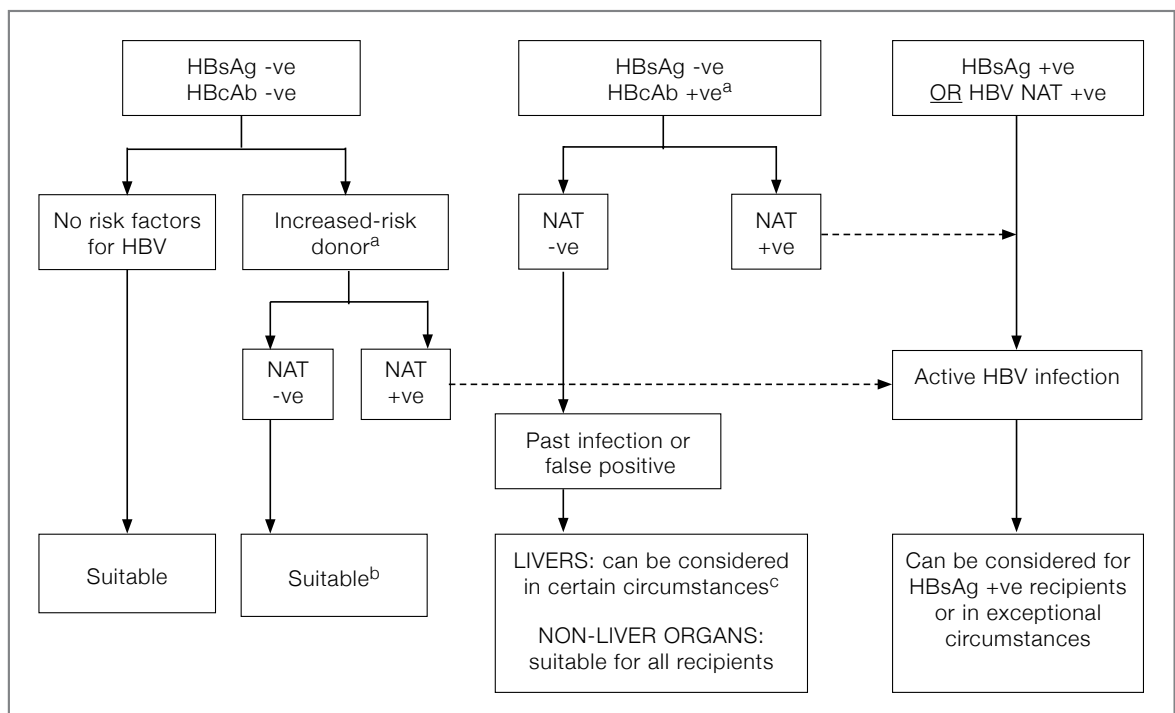
### 2.3.2.5 Hepatitis C virus

A positive HCV-NAT, with or without a positive anti-HCV, is an indication of active HCV infection. A positive anti-HCV with a negative HCV-NAT essentially confirms the absence of chronic HCV infection, given the low level of virus which can be detected with current RNA assays. Both anti-HCV and HCV-NAT are recommended for all donors.

#### Anti-HCV-positive, NAT negative donors

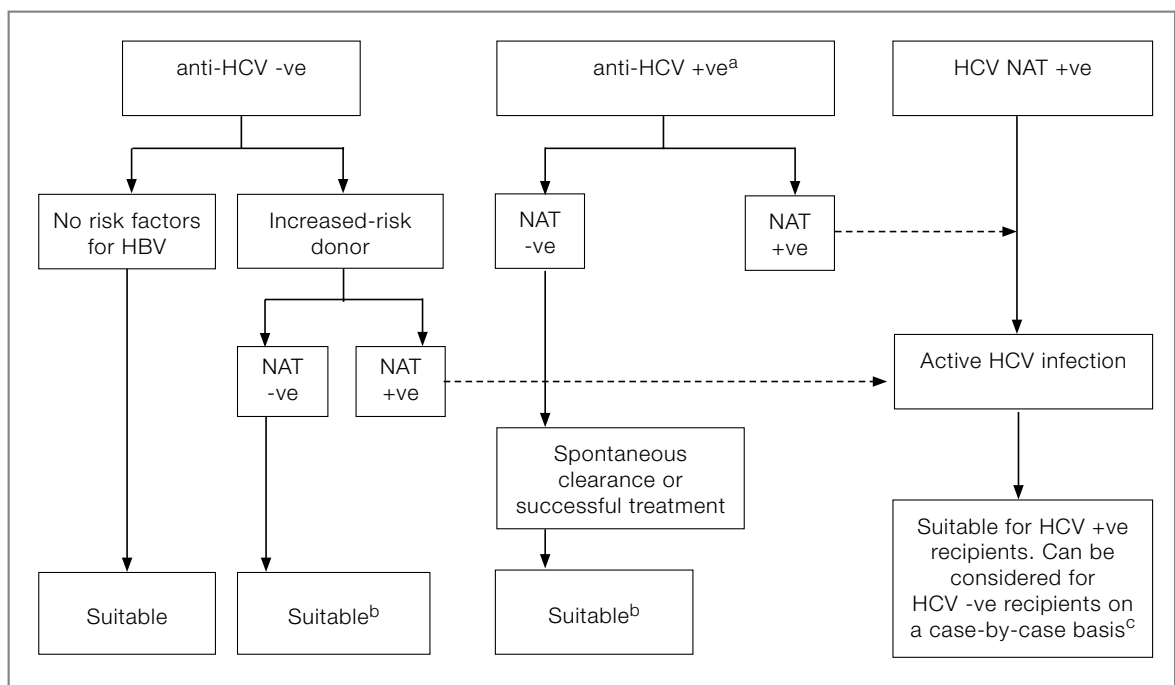
The risk of transmission from NAT-negative, anti-HCV-positive donors is very low. Previous HCV infection is, however, a significant risk factor for reinfection, and the potential for a newly acquired eclipse period infection should be considered in anti-HCV-positive, NAT-negative donors, with close attention paid to any increased-risk behaviours in the previous 10 weeks. For anti-HCV positive, NAT-negative donors with no identifiable risk factors for reinfection with HCV, the risk of HCV transmission to the recipient is negligible. Use of anti-HCV positive, HCV NAT-negative donors is encouraged, with the informed consent of the recipient and appropriate post-transplant monitoring for the appearance of HCV infection. Cohort studies of transplantation involving HCV-negative recipients and anti-HCV positive, NAT-negative donors have shown that seroconversion (without viraemia) is relatively common post-transplant.<sup>51</sup> This is an area of ongoing study and uncertain clinical significance; at this time, potential recipients should be counselled of the likelihood of seroconversion following transplantation with an anti-HCV-positive, NAT-negative organ. In a case series of fifty-five HCV-NAT negative recipients of livers from anti-HCV-positive, NAT-negative donors at high risk of reinfection, 9% of liver recipients developed HCV viraemia at 3 months post-transplant.<sup>52</sup> In the unlikely event that HCV transmission were to occur from a NAT-negative donor, HCV in the recipient is highly treatable.

Figure 2.3: Decision flow-chart for HBV testing and utilisation of HBV-positive donors



<sup>a</sup> If NAT result is not available, follow the pathway for a NAT +ve donor, taking into account the nature of donor risk factors  
<sup>b</sup> Consider the possibility of an eclipse period infection  
<sup>c</sup> Livers from HBcAb +ve/NAT -ve recipients can be considered for vaccinated recipients and recipients with prior HBV infection, or in exceptional circumstances

Figure 2.4: Decision flow-chart for HCV testing and utilisation of HCV-positive donors



<sup>a</sup> If NAT result is not available, follow the pathway for a NAT +ve donor, taking into account the nature of donor risk factors  
<sup>b</sup> Consider the possibility of an eclipse period infection  
<sup>c</sup> Livers from donors with active HCV infection would only be suitable in the absence of significant fibrosis/cirrhosis in the donor

### HCV-NAT-positive donors (active infection)

The reported cure rate of HCV after transplantation with direct acting antiviral therapy is high (>90%),<sup>53</sup> such that organs from donors with active HCV infection can be considered for transplantation into HCV-negative recipients in specific circumstances – for example where the patient has a limited opportunity for a life-saving transplant.<sup>54,55,56</sup> Recipients of actively infected donor organs would then require post-transplant anti-viral treatment for their newly acquired HCV infection. The potential risks, complications, and requirements for post-transplant anti-viral therapy need to be discussed with potential recipients to ensure robust informed consent is obtained. Clinicians should refer to their own jurisdictional governance and legal authorities for advice where there is a lack of clarity or policy direction in relation to informed consent.

### Donors at increased risk of HCV

For donors with negative HCV-serology and/or HCV-NAT, there remains the possibility of a recently acquired infection that is within the eclipse/window period of detection. The likelihood of a window period infection depends on the nature of any increased-risk behaviours and the individual donor's medical history. The highest risk of undetected HCV infection is among IDU, followed by the prison population. Residual risks of HCV transmission by type of risk exposure from a NAT-negative and/or serology-negative donor are given in Table 2.4.

When considering whether to proceed with transplantation, all donor characteristics should be taken into account and the individual donor's risk exposure weighed against the risk to the prospective recipient of not proceeding with transplantation. Given the availability of safe and effective antiviral therapy for HCV, the residual risk of transmission of HCV will rarely outweigh the potential benefits of transplantation. Where a non-infected recipient is transplanted with an increased-risk donor, the recipient should be monitored post-transplant for the appearance of HCV, with the first HCV-NAT performed within 30 days post-transplant.<sup>13</sup>

**Table 2.6:** Interpretation of results of HCV screening in organ donors and recommendations for utilisation

Test results	Interpretation	Implications for organ utilisation
HCV-NAT +ve	Active infection	Organs may be transplanted into actively infected recipients, and may also be suitable for transplantation into HCV-negative recipients in specific circumstances on an individually-determined basis, following provision of informed consent by the recipient.
Anti-HCV +ve HCV-NAT -ve	Active infection unlikely	Represents spontaneous clearance of virus or successful treatment. HCV transmission is unlikely to occur but cannot be ruled out completely based on risk of re-exposure: transplantation should be considered for all recipients.
Anti-HCV +ve HCV-NAT not available	Active infection cannot be ruled out	Organs may be transplanted into actively infected recipients, and may also be suitable for transplantation into HCV-negative recipients in specific circumstances on an individually-determined basis, following provision of informed consent by the recipient.

### 2.3.2.6 Herpes simplex virus

The overall seroprevalence of HSV-1 and HSV-2 in the Australian population is 76% and 12% respectively, although actual rates are highly variable by age group and according to risk factors for acquisition.<sup>57</sup> In the absence of appropriate prophylaxis, life-threatening *de novo* infections have occurred in naïve recipients of organs from latently-infected donors,<sup>58,59</sup> and due to reactivation in latently-infected recipients.<sup>60</sup> Given high rates of donor and recipient exposure, routine prophylaxis seems a more efficient approach than donor and recipient HSV-1 and HSV-2 IgG testing. Routine HSV prophylaxis is supported by a number of guidelines.<sup>61,62</sup> Where it is administered, CMV antiviral prophylaxis will also be effective against HSV. In the event that CMV prophylaxis is not given, acyclovir, famciclovir or valaciclovir would be the anti-HSV agents commonly utilised, usually recommended for at least one month post-transplantation. Active infection in donors should also be considered where there are clinical features suggestive of HSV.



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#### Recommendation

Organs can be accepted from donors with latent herpes family viral infections, and HSV screening is not required where antiviral prophylaxis is routinely administered. Organs from donors with acute herpes viraemia should only be considered with the administration of HSV-active antiviral treatment to the recipient.

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#### 2.3.2.7 Human herpes virus-8 (Kaposi's sarcoma herpes virus)

Human herpes virus-8 (HHV-8) is associated with all forms of Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castelman's disease. Unlike most herpes viruses, human infection with HHV-8 is not ubiquitous and instead has significant geographic and social variation. Seroprevalence is estimated to be <10% in North America and northern Europe compared to between 20-80% in the Mediterranean, parts of Africa and parts of China.<sup>63</sup>

Several cases of donor-derived HHV-8 transmission have been reported,<sup>64,65,66,67,68,69</sup> as well as the development of Kaposi's sarcoma and other HHV-8 related lethal illnesses in recipients following donor-derived transmission.<sup>64,67,68,69,70</sup> Prospective studies indicate 25-30% of seronegative recipients seroconvert after receiving an organ from a HHV-8-positive donor. However, <1% of mismatched recipients develop viraemia and the incidence of HHV-8-related disease among D+/R- pairs is extremely low.<sup>66,70,71</sup> In addition to the low risk of HHV-8-related disease as a consequence of donor-derived transmission, screening donors for HHV-8 is problematic: available routine serological tests for HHV-8 have very poor test performance, are not generally commercially available, and are not performed routinely in Australia and New Zealand. In relation to NAT testing, HHV-8 NAT assays are commercially available, although DNA cannot be detected in all infected individuals and many will test negative on NAT. If a donor does test positive, pre-emptive therapy has not prevented disease.<sup>70</sup> Therapy for established HHV-8 infection is problematic, with variable and generally low responses to antiviral therapies. For these reasons, screening for HHV-8 is not recommended.

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#### Recommendation

Routine screening for HHV-8 is not recommended.

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#### 2.3.2.8 Human immunodeficiency virus

Screening for HIV should be performed using both NAT and a fourth generation antigen/antibody combination immunoassay. These fourth generation antigen/antibody combination immunoassays identify antibodies against both HIV-1 and HIV-2 as well as the presence of p24 antigen. If an initial test is positive, this result should be confirmed with subsequent testing according to jurisdictional policies, which may include separate antibody and p24 antigen assays, commercial western blotting assays, and/or nucleic acid tests.

Although HIV-positive individuals are generally contraindicated from donating organs, in exceptional circumstances a life-preserving donation from an HIV-infected donor may occur, for example for use in an HIV-infected recipient, after discussion with an infectious diseases physician.

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#### Recommendation

All donors should be screened for HIV using an HIV Ag/Ab combination assay and HIV-NAT. Use of organs from an antibody and/or NAT positive donor is generally contraindicated except in exceptional circumstances.

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#### 2.3.2.9 Human T-lymphotropic virus-1

Human T-lymphotropic virus-1 (HTLV-1) is an oncogenic retrovirus that is transmitted predominantly via breast-feeding, sexual intercourse or blood transfusion. While infection is usually asymptomatic, ~2-5% of infected individuals will subsequently develop acute T-cell leukemia/lymphoma (ATL), and a smaller proportion (0.25-4%) will develop HTLV-1 associated myelopathy (HAM).<sup>72</sup> Human T-lymphotropic virus-1 is not a ubiquitous virus;

instead, it is understood to be distributed throughout the world in clusters of high endemicity. A high prevalence of HTLV-1 is found in sub-populations of southwestern Japan, sub-Saharan Africa, the Caribbean, parts of South America, parts of the Middle East, and among Aboriginal people of central Australia.<sup>73</sup> However, large global regions have not been investigated for the prevalence of HTLV-1, and its distribution remains unknown in much of the world. Similarly, outside of central Australia, little is known about the epidemiology of HTLV-1 in Australia and New Zealand. Studies conducted among mostly non-Aboriginal and Torres Strait Islander blood donors living in Australian cities have reported prevalence ranging from 0.001 to 0.032%.<sup>73</sup> It is important to note that HTLV screening assays do not distinguish between HTLV-1 and HTLV-2 infection, however HTLV-2 has not been convincingly associated with human disease.

Worldwide to date there have been 16 published cases of HTLV-associated disease following donor-derived transmission: 14 cases of HAM and 2 cases of cutaneous ATL, with onset of symptoms between 8 months and 4 years post-transplant.<sup>74,75,76,77,78,79</sup> A recent case series from Japan reported a rate of seroconversion of 87% for HTLV-1 negative recipients receiving a kidney transplant from an HTLV-1 positive donor, and a rate of HTLV-associated disease of 40% following donor-derived transmission (median incubation period 3.8 years).<sup>79</sup> Given the morbidity and mortality risk associated with HAM and ATL, utilisation of donors confirmed positive for HTLV1/2 is not recommended.

The HTLV-1/2 positivity rate among Australian organ donors is <0.1%, and to date there have been no reported cases of HTLV-1 transmission by organ donation in Australia or New Zealand. Nonetheless, universal screening of donors for HTLV-1/2 remains recommended at this time given the limitations of our understanding of HTLV-1 epidemiology, the practical challenges of targeted screening (i.e. accurately identifying individuals at high risk), the current lack of therapy for HTLV-1, and the severity of outcomes in the extremely rare event of donor-derived disease. In addition, HTLV-1/2 screening is currently an absolute requirement for eye and tissue donation (with the exception of cornea-only donation). The potential for false positive test results for HTLV-1/2 should be noted, based on international experience.<sup>80</sup> A notable large study of the commonly utilised Abbott Architect rHTLV I/II serology assay, showed that subjects with a signal to cut-off ratio >20 (n=498) were almost all confirmed to have genuine HTLV infection by subsequent testing, while subjects with a signal to cut-off ratio <4 (n=271) were never confirmed to have genuine HTLV infection where follow up samples were available (n=211) [Tosswill JHC, Taylor GP. Interpretation of low reactivity in the Abbott Architect rHTLV I/II assay. *Transfusion Medicine* 2018; 28: 326-330].

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#### Recommendation

HTLV-1/2 screening using serology is recommended for all organ donors, with prospective results preferable where possible. Where a serological screening test is reactive, confirmatory testing should be undertaken and donation should not proceed if HTLV-1/2 infection is confirmed. In the event of reactive screening antibody results which cannot be confirmed by subsequent testing in a timely manner, it is suggested to discuss with an infectious diseases physician or microbiologist the likelihood that results predict genuine HTLV infection, which is influenced by the strength of the test (e.g. signal to cut-off ratio) and the pre-test probability of infection. If a donor is retrospectively confirmed to be infected with HTLV-1 and organs are transplanted, monitoring of recipients for both infection and disease development is recommended.

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#### 2.3.2.10 Seasonal influenza

During each annual influenza season (June, July, August) approximately 5-10% of the population is affected.<sup>81,82</sup> During this period, a potential lung donor has about a 1-2% chance of transmitting influenza, based on 10% of the population being affected and given that influenza virus can be recovered from respiratory secretions of infected persons for approximately one week.<sup>83</sup>

In general, non-lung organs from donors with influenza infection can be safely used. As persons infected with influenza viruses generally do not have virus in non-lung tissues, the risk of transmitting infection to recipients of solid organs other than lungs is low.<sup>84</sup>

Evaluation of potential lung donors for influenza-like symptoms or respiratory tract infection is essential to avoid life-threatening infection in the recipient in the early post-transplant period.<sup>85</sup> In the event of donor-derived influenza transmission, however, successful antiviral treatment is possible.<sup>83</sup>

In the event of circulating influenza strains with antiviral resistance, influenza A subtyping may inform treatment options.

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#### Recommendation

If influenza-like illness in the donor is suspected, influenza-specific NAT should be performed (although it is not essential to wait for the result before proceeding with transplantation). The presence of influenza is not a contraindication to the transplantation of non-lung organs. Utilisation of lungs should be considered on a case-by-case basis. Post-transplant influenza treatment for 5-10 days is suggested for all recipients of organs from a donor infected with influenza.

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#### 2.3.2.11 West Nile virus

West Nile virus (WNV) is a mosquito borne virus commonly found in Africa, parts of Europe, the Middle East, North America and West Asia. West Nile virus infection is asymptomatic or associated with only mild-flu-like symptoms in the vast majority of cases (>99%). However, in some cases – and particularly among immunosuppressed persons – WNV may cause severe neuroinvasive disease, including meningitis, encephalitis and acute flaccid paralysis.<sup>86</sup> Multiple cases of WNV transmission from organ donors to recipients have been reported, with a high rate of adverse outcomes.<sup>86,87</sup> Compared to a mortality rate of 4% among symptomatic WNV cases in the general population, the mortality rate among transplant recipients with symptomatic WNV is approximately 25%.<sup>88</sup>

Suitable vectors for WNV have not been shown to exist in New Zealand, and to date there have been no notified cases of WNV, including cases acquired abroad. In Australia, the Kunjin lineage of WNV is endemic to tropical northern Australia, although notifications of WNV or Kunjin virus infection are rare – on average <2 per year – with some of these cases acquired in endemic countries.<sup>89</sup>

Given that locally acquired cases of WNV in Australia have not been recorded, targeted testing only is recommended for potential donors with compatible symptoms (similar to flu) and a history of recent travel to an endemic country or an area with an ongoing outbreak. The incubation period for WNV is approximately 3-15 days, and infected individuals are viraemic for up to a week, therefore history of travel up to 4 weeks prior is of interest. If WNV is suspected, advice should be sought from an infectious disease specialist regarding testing requirements and how to proceed in the event of a positive test. Testing should be performed using NAT, using PCR at the current time.

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#### Recommendation

Screening of asymptomatic donors for WNV is not recommended. Targeted testing using serology and NAT (PCR) is recommended for potential donors with compatible symptoms and a recent history of travel (<4 weeks prior) to an endemic country or a region with an ongoing outbreak. If a donor is suspected or known to be infected with WNV, an infectious disease specialist should be consulted for advice on testing requirements and whether it is safe to proceed with donation.

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#### 2.3.2.12 Zika virus

Australia and New Zealand do not have local transmission of Zika virus, but suitable mosquito vectors exist in some parts of northern Australia and near neighbours. Of confirmed/probable cases of Zika virus infection diagnosed in Australia and New Zealand in 2017, the majority of these cases were acquired in Tonga, Fiji, Samoa, Mexico or Brazil.<sup>90,91</sup>

Zika virus should be considered in potential donors with compatible symptoms and a history of recent travel (≤4 weeks) to Zika-affected areas (see <https://www.who.int/emergencies/zika-virus/classification-tables/en/>). The median incubation period of Zika virus associated disease is 5.9 days, with 99% of infected individuals clearing the virus within 23.4 days.<sup>92</sup> Although sexual contact with men who have been in an area of Zika virus transmission anytime in the prior 6 months is also theoretically a risk factor,<sup>93</sup> sexual transmission of Zika virus is extremely uncommon in Australia or New Zealand.

Screening for Zika virus in asymptomatic donors is not recommended. For donors with a history of recent travel to Zika virus-affected areas who do not have any symptoms of viral infection, the risk of Zika virus infection is very low and the consequences of Zika virus infection in transplant recipients have not been shown to be severe.<sup>94</sup>

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#### Recommendation

Screening of asymptomatic donors for Zika virus is not recommended. Zika serology should only be used as a diagnostic test in donors with compatible symptoms and epidemiological risk factors (i.e. travel to an endemic area within the previous 4 weeks). If the test is positive, seek advice from an infectious diseases specialist.

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### 2.3.2.13 Other arboviruses

While the potential for donor-derived transmission exists, very little is known about the risks to organ transplant recipients of other arboviruses (dengue, chikungunya, Ross River virus, Murray Valley virus, Barmah forest virus, Japanese encephalitis). Importantly, arboviral infections are transient and there is no evidence for establishment of latency and latent disease. Donor testing is appropriate in the context of potential donors with compatible symptoms who have recently visited an endemic area. Targeted testing in this context would be warranted, typically with IgM, IgG and PCR, and the advice of an infectious disease specialist should be sought to guide appropriate testing and how to proceed in the event of a positive test. Decisions to proceed with transplantation should be made on a case by case basis, dependent on the organ(s) being considered for transplantation and the nature of the infection.

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#### Recommendation

If arboviral infection is suspected in a potential donor with compatible symptoms and a history of travel to an endemic area in the past 4 weeks, advice from an infectious disease specialist should be sought on appropriate testing procedures and what to do in the event of a positive test result.

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## 2.3.3 Bacterial and fungal infections

### 2.3.3.1 Blood stream 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, drug-sensitive pathogens and appropriate prophylactic antibiotics are administered.<sup>95,96</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>9</sup>

The routine culturing of preservation fluids in which organs are transported is of uncertain benefit and is currently not recommended. Contamination of preservation fluids is common, however contaminants are rarely of clinical significance.<sup>97,98,99</sup> In rare cases where contaminants are pathogenic, such organisms would typically be covered by routine prophylactic antibiotics.<sup>97</sup> The burden of clinically irrelevant positive test results that would be generated by routine culturing of bag fluids would outweigh the benefits to recipients.

The culturing of preservation fluids would, however be indicated in exceptional circumstances. Digestive tract breach at the time of multiorgan recovery has been linked to multiple cases of graft-transmitted candidiasis in kidney and liver recipients, resulting in fungal arteritis in several cases.<sup>100</sup> In the event of digestive tract rupture, appropriate specimens should be collected, including culture of organ preservation fluid, and surveillance cultures in the recipient where possible.

Donors with endocarditis should be treated on a case-by-case basis in a manner similar to bacteraemic donors, with consideration given to the potential for septic emboli in transplantable organs.

There is little data regarding donors with fungaemia. Given the difficulty treating fungi, guiding principles would suggest they will generally be unsuitable, however if donation is being considered the case should be discussed with an infectious diseases specialist. The assessment would consider such factors as whether the infection is controlled, whether there are signs of dissemination to the organ, the options for treatment including those relevant to the specific organ (e.g. some antifungals do not penetrate the urinary tract). A full course of antifungal treatment of a minimum duration of 2 weeks should be given to the organ recipients, with culture surveillance for the development of active infection.

For recommendations in the case of bacterial meningitis, see Section 2.3.6 (Central Nervous System Infection).

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#### Recommendation

Bacteraemia is not a contraindication to donation, and organs may be used after the donor has been treated with antibiotics. Recipients of organs from donors with confirmed bacteraemia should receive a full course of antibiotic treatment, with monitoring for evidence of infection. Donors with ongoing sepsis and persistently positive blood cultures should not be utilised. Organs from donors with endocarditis may be transplanted after the donor has been treated with antibiotics and after consideration of the risk of emboli to organs for transplantation. Cases of fungaemia should be discussed with an infectious diseases specialist before proceeding to donation.

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#### 2.3.3.2 Pulmonary infections

Bacterial colonisation of donor lungs is common as (1) the lungs are in constant contact with the external environment and the airways are normally colonized with multiple organisms, (2) most donors require emergency intubation, which may result in aspiration and pneumonia, and (3) the rate of bronchopulmonary infections increases in proportion to the length of time spent in the ICU. Prior to donation, aspiration and consequent pneumonia must therefore be ruled out or treated. In the case of pneumonia without bacteraemia, all other organs can be used safely. Following a period of antibiotic treatment and provided pulmonary function is not impaired, lungs may be considered for donation except where the pathogen is multi-drug resistant.

Invasive fungal infection of the lungs (including with endemic mycoses – e.g. histoplasmosis, coccidioidomycosis, blastomycosis) is very uncommon and the advice of an infectious diseases specialist should be sought in this situation if transplantation is being considered. Much more common is fungal colonisation of the donor airway, which is managed by routine antifungal prophylaxis and/or pre-emptive antifungal therapy according to unit policy.

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#### Recommendation

In the case of pneumonia without bacteraemia, all other organs can be used safely for transplant. Lungs may be used after adequate and effective antibiotic therapy, with a full antibiotic course administered to the recipient. Fungal colonisation of the donor airway is not a contraindication to donation; however, in the case of invasive fungal infection the advice of an infectious diseases specialist should be sought.

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#### 2.3.3.3 Urinary tract infections

Urinary tract infection (UTI), with the risk of pyelonephritis, is common among potential donors due to bacteria or fungi ascending along the urethral catheter. Any suspected UTIs in potential donors should be confirmed by urine culture.

Prior to organ retrieval, the donor should be treated with antibiotics.<sup>96</sup> The final decision about organ utilisation should be made at the time of organ retrieval. Post-transplant treatment of the recipient is expected to reduce the risk of donor-derived infection. In general, however, there is no need to treat the recipient of a non-kidney organ from a deceased donor with nonbacteraemic, localised infection that does not involve the transplanted organ.

*Candida* infection early post kidney transplant has been associated with death and morbidity such as vascular and anastamotic complications.<sup>101</sup> *Candida* in the urinary tract of the donor is commonly thought to arrive there

from contamination by faeces from intestinal perforation, directly infecting the kidneys from the external capsule then progressing inside the kidney. Culture of preservation fluids in cases where a breach of the digestive tract is identified during organ recovery is recommended for the early detection of *Candida* sp. Where donor or early recipient urinary tract cultures are positive for *Candida* sp. ongoing surveillance for complications should occur and antifungal therapy given to the recipient for a minimum 2 weeks.

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#### Recommendation

In the case of UTI without bacteraemia, all non-kidney organs can be used safely for transplant. Uncomplicated UTI/bacteruria is in most cases not a contraindication to utilisation of kidneys if there has been adequate and effective antibiotic treatment and a full antibiotic treatment course is administered to the recipient. Where donor or early recipient urinary tract cultures are positive for *Candida*, ongoing surveillance for complications should occur and antifungal therapy be given to the recipient for a minimum of 2 weeks.

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#### 2.3.3.4 Multi-drug resistant bacteria

Donor exposure to multi-drug resistant (MDR) bacteria in the ICU is an increasing problem, in particular exposure to vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, multidrug-resistant *Pseudomonas aeruginosa*, and carbapenem-resistant *Acinetobacter baumannii*. Prolonged ICU stay, vasopressor use, need for cardiopulmonary resuscitation and injuries involving major blood loss increase the risk of infection or colonisation with MDR bacteria (although nosocomial infections may be acquired even with only a short hospital stay).<sup>102,103</sup> In addition, significant volume and blood product replacement in the donor with traumatic injury may result in a wash-out effect of prophylactic antibiotics and ineffective antibiotic coverage.<sup>103</sup> Donor country of origin/prior residence is also a potential risk factor: donors from countries with high rates of gut colonisation with multi-drug-resistant bacteria pose a higher risk of transmission, as do donors who have previously been hospitalised overseas. Detection of MDR bacteria may be difficult due to antibiotic therapy, which may reduce the bacterial load to a level that is undetectable by standard culture protocols but is still able to transmit infection to an immunosuppressed individual.<sup>104</sup>

At this time there is no need for enhanced microbiological screening of potential donors for MDR bacteria over and above standard ICU practice. If MDR bacteria are identified prior to transplantation, the risks are highest for the bacteraemic donor or where the positive culture is taken from the organ that is to be transplanted: in these cases transplantation should be carefully considered and advice sought from an infectious diseases physician.<sup>105</sup> In all other circumstances, transplantation can be considered in consultation with an infectious diseases physician.<sup>105</sup> Colonisation by MDR bacteria is not a contraindication for donation provided the colonised tissue remains sealed from the rest of the body and any adjacent organs are not affected.

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#### Recommendation

Organs from donors with positive cultures for MDR bacteria may be considered for transplantation with close recipient follow-up. Transplantation should be carefully considered in the event that the organ to be transplanted is itself colonised or the donor is bacteremic. A key consideration is whether safe antibiotic options are available to treat the bacterium. The case should be discussed with an infectious diseases physician and if donation proceeds, a full treatment course should be administered to the recipient.

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#### 2.3.3.5 Mycobacterium tuberculosis

The vast majority of tuberculosis cases in Australia and New Zealand occur in the overseas-born population, with other major risk factors including household or close contact with tuberculosis, employment in the health industry, incarceration, residence in an aged care facility, homelessness, and immunosuppression.<sup>106</sup> In the general Australian population, pulmonary tuberculosis accounts for approximately 60% of tuberculosis cases, with 40% being extrapulmonary.<sup>106</sup>



Reasonable efforts should be made to rule out active tuberculosis in donors with any epidemiological risk factors for tuberculosis or history of tuberculosis infection. However, there are no proven methods for screening deceased donors for tuberculosis. Chest X-ray and direct microscopy of bronchoalveolar lavage for acid-fast bacilli have a low sensitivity, and cultures may take up to eight weeks to turn positive.<sup>107</sup> Tuberculin skin testing and interferon gamma release assays are also impractical in the context of deceased donation given their slow turn-around times. NAT can identify *M. tuberculosis* in clinical specimens from donors with active infection only; a negative result does not definitively rule out infection with *M. tuberculosis*, as organisms can remain dormant in the host without causing disease for decades, without any detectable radiographic abnormality. Conversely, abnormal pulmonary findings from a range of causes are common in deceased donors and may confound donor evaluation.<sup>107</sup>

Given the limitations of tuberculosis screening tools in deceased donors, and given that it is unclear how to proceed on the basis of results from such screening, routine donor screening for tuberculosis is not recommended. Instead, diagnostic testing for tuberculosis is recommended where there is clinical suspicion of tuberculosis infection that is supported by epidemiological factors.

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#### Recommendation

Diagnostic testing for tuberculosis with microscopy (acid-fast bacillus staining) and PCR are recommended where infection is suspected based on epidemiological AND clinical factors that are suggestive of either active or latent tuberculosis. Donation of organs from donors currently being treated for tuberculosis or with positive results (e.g. AFB stain, NAT) is not recommended other than in exceptional circumstances after discussion with an infectious diseases physician. Donors with previous active or latent tuberculosis can be considered, taking into account tuberculosis antibiotic susceptibilities, completeness of donor treatment, and current evidence of infection in the organ. Discussion with an infectious diseases physician, close follow up of the recipient and consideration of tuberculosis prophylaxis for the recipient are recommended.

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#### 2.3.3.6 *Treponema pallidum* (syphilis)

The number of reported cases of syphilis has recently increased in both the Australian and New Zealand general population.<sup>108,109,110</sup> *Treponema pallidum* (syphilis) has been transmitted through organ transplantation.<sup>111,112</sup> All donors should be first screened for *T. pallidum* using a treponemal-specific enzyme immunoassay, with confirmation of positive results by a non-treponemal test such as the rapid plasma reagin (RPR) test. If the non-treponemal test is negative, then a second treponemal test based on different antigens to the original test should be performed. This approach differentiates potential donors who have been previously treated for syphilis from those with untreated or incompletely treated syphilis and those with an initial false positive result.<sup>113</sup> Treponemal test results should be interpreted in the context of what is known about the donor's history of treatment for syphilis and their sexual history, as there is always the possibility of previously treated persons having a recently reacquired syphilis infection.

The stage of syphilis needs to be considered in donors with positive syphilis serology and the case should be discussed with an infectious diseases physician. If secondary syphilis is likely, then the infection may be disseminated and donation should probably not proceed apart from exceptional circumstances. The possibility of tertiary syphilis of the aortic arch should be considered in the case of heart donation. For donors deemed to have primary, latent, or tertiary syphilis, donation may proceed with benzathine or intravenous penicillin prophylaxis given to the recipients with a regimen advised by an infectious diseases physician.

The presence of newly diagnosed syphilis in the donor indicates the donor is at increased risk of having also recently acquired HIV, HBV or HCV, and decisions regarding utilization should be made accordingly.

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#### Recommendation

If primary, latent or tertiary syphilis is detected in the donor, donation may proceed with appropriate prophylactic treatment of the recipient. A donor with secondary syphilis may be bacteraemic with the involvement of many organs, hence caution should be taken if clinical manifestations of secondary syphilis are present.

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## 2.3.4 Parasitic infections

### 2.3.4.1 Malaria

Australia and New Zealand remain free of endemic malaria: all notifications are in travellers or military personnel returning from endemic areas or in refugee arrivals. Despite the absence of endemic malaria, suitable vector mosquitos are present in northern Australia and the area is “malaria receptive”. Limited transmission does also sometimes occur in the Torres Strait following importation.<sup>114</sup>

Although malaria is a rarely reported complication of organ transplantation outside of non-endemic countries and to date there have not been any donor-derived transmissions in Australian and new Zealand, internationally there has been a small number of documented cases of donor-derived malaria transmission involving recipients of kidneys (6 cases), livers (4 cases) and hearts (4 cases).<sup>115,116,117,118,119,120,121</sup> Where donor-derived transmission does occur, if detected early it can be treated effectively.

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#### Recommendation

Donors who have spent more than 3 months in an endemic area for malaria should be tested for *Plasmodium* using NAT or serology or both. If a result is positive, the recipient should be tested and treated routinely for malaria.

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### 2.3.4.2 *Strongyloides stercoralis*

*Strongyloides* is an intestinal nematode that is endemic to tropical or subtropical regions of the world. Once infection occurs, the *Strongyloides* parasite establishes an autoinoculation cycle that allow infection to persist in the host indefinitely. Infection is transmitted by skin contact with soil contaminated with human waste, and prevalence is therefore directly related to sanitation and hygiene conditions. Outside of the endemic regions of Southeast Asia, Central and South America, and Africa, *Strongyloides* infection is also found in poor communities, former war veterans, refugees, immigrants and travellers, and people occupationally exposed to soil (e.g. farmers and miners) in parts of the United States, Europe, United Kingdom, and Australia.<sup>122,123</sup> Groups with high rates of *Strongyloides* infection in Australia include war veterans, immigrants/refugees, and Aboriginal and Torres Strait Islander Australians (particularly children).<sup>124,125,126,127,128,129</sup> Infection with HTLV-1 is associated with increased prevalence of *S. stercoralis* infection.<sup>130,131</sup>

Donor screening with serology, generally using *Strongyloides* IgG EIA, is recommended for donors with past or present risk factors for *Strongyloides* infection – i.e. those from tropical or central Australia or remote communities, and those who were born in or have resided for more than 3 months in endemic areas, including refugees and migrants from developing countries. Because of the longevity of the parasitic infection, screening is warranted even for very remote histories of travel to endemic regions. Similarly, residence in places where the disease was considered endemic decades ago should prompt screening.<sup>132</sup> *Strongyloides* testing may be retrospective, given that there is a window post-transplant in which infection can be treated effectively, although results should still be provided as soon as possible.

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#### Recommendation

Donors who have spent >3 months in an endemic area (including developing countries or central/tropical Australia) should be screened for *Strongyloides*, with results available either prospectively or retrospectively. If the donor tests positive, recipients should receive prophylactic treatment with ivermectin.

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### 2.3.4.3 *Toxoplasma gondii*

Exposure to *Toxoplasma gondii* is extremely common in all parts of the world, including Australia. A study of pregnant women in Australia found 35% had IgG antibodies to *T. gondii*.<sup>133</sup> Following infection, *T. gondii* spreads to organs and tissues and is able to multiply in almost any cell in the body.<sup>134</sup> Immunity does not eradicate the infection, as latent intracellular cysts can persist for years after acute infection mainly in muscle tissues and



the brain (although visceral organs may also be infected).<sup>134</sup> Both acute and latent *T. gondii* infection in the donor pose a transmission risk, and *T. gondii* transmission by organ transplantation has been reported multiple times in the literature, most commonly by heart transplantation but also by kidney liver, bowel and pancreas transplantation.<sup>135,136,137,138,139,140,141</sup>

Numerous serological tests exist for the detection of *T. gondii* antibodies, including both IgM and IgG. IgM antibodies appear sooner after infection than IgG, and disappear following recovery (whereas IgG antibodies do not disappear). NAT can be used to diagnose active infection;<sup>142,143</sup> however, given that active infection is rare and the goal of donor screening is primarily to detect latent toxoplasma in the heart and other organs resulting from past infection, serological testing for toxoplasma IgG alone is recommended, with testing for acute toxoplasma (IgM, NAT) reserved for appropriate clinical scenarios.

While a positive serological test for *T. gondii* is not a contraindication to donation, it may inform the need for prophylaxis in the recipient. Trimethoprim-sulfamethoxazole prophylaxis for at least 3 months post-transplant is currently standard international practice for recipients at risk of *T. gondii* transmission.<sup>144</sup>

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#### Recommendation

*Toxoplasma gondii* screening using serology is recommended for all potential donors, with results available either prospectively or retrospectively. For recipients at risk (donor and/or recipient seropositive), routine *Pneumocystis jiroveci* prophylaxis with cotrimoxazole is protective against toxoplasmosis. If cotrimoxazole is not tolerated, prophylaxis should be chosen which is active against *Pneumocystis* and *Toxoplasma gondii* (e.g. atovaquone, or dapsone plus pyrimethamine, not pentamidine).

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#### 2.3.4.4 Trypanosoma cruzi

*Trypanosoma cruzi* (Chagas disease) is a zoonotic protozoan endemic to Mexico, Central America and South America.<sup>145</sup> Following infection, trypomastigotes circulate in the blood stream, while intracellular amastigotes appear in muscle (including heart) and ganglion cells.<sup>146</sup> Acute infection is typically asymptomatic, with an initial period of high parasitaemia followed by chronic latent infection, which then progresses to cardiac, gastrointestinal and/or peripheral nervous system disease in approximately 30% of those infected.<sup>146</sup> In immunosuppressed persons, acute *T. cruzi* infection is associated with adverse outcomes, particularly where there is cardiac and/or central nervous system involvement.<sup>146</sup>

Routine travel to endemic regions carries a low risk of *T. cruzi* infection; at risk are those who have spent prolonged time in endemic areas (>3 months) and/or stayed in rural/disadvantaged areas. The risk of transmission from *T. cruzi* seropositive organ donors to seronegative recipients ranges from 10-20% for kidneys and livers, to >75% for hearts.<sup>146</sup> Evidence indicates kidneys and livers can be safely transplanted from *T. cruzi* positive donors if close post-transplant monitoring is in place for early diagnosis and treatment, should acute infection occur.<sup>146</sup> Recipients of *T. cruzi* positive organs should be monitored weekly for the first 2 months post transplant, every 2 weeks through months 3-6 and annually thereafter or after intensification of immunosuppression. Monitoring methods include blood microscopy for *T. cruzi*, blood nucleic acid tests, and serology. Given the high rate of transmission in the context of heart transplantation, hearts from donors infected with or screen-positive for *T. cruzi* should not be utilized.<sup>145</sup>

Chronic *T. cruzi* infection should be diagnosed on the basis of epidemiological factors and serological tests, using at least 2 serological methods (e.g. ELISA, indirect haemagglutination assay, indirect immunofluorescence assay) and with inconclusive results confirmed by PCR. Serological tests for *T. cruzi* have good sensitivity but poor specificity in chronically infected persons, whereas PCR has high specificity and low sensitivity.<sup>146</sup> Serological results are unlikely to be available within the donation timeframe but can inform post-transplant interventions.<sup>11</sup> Monitoring for evidence of transmission and prompt treatment of acute infection is preferred to the use of prophylaxis in D+/R- transplants.

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#### Recommendation

Donors who have spent 3 months or more in Mexico, Central or South America at any time in their lives should be screened for *T. cruzi* using serology. Infection with *T. cruzi* is not a contraindication to the donation of non-cardiac organs, however recipients require close follow-up for 24 months post-transplant for the appearance of acute infection. Donors with known *T. cruzi* infection (acute or chronic infection) should be excluded from heart donation.

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### 2.3.5 Central nervous system infection by various pathogens

Most central nervous system (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 point 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, resulting in significant morbidity and mortality in recipients.<sup>147</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 excluded.<sup>148</sup>

Patients with viral encephalitis should generally be excluded as donors, given the potentially fatal risk of transmission of pathogens such as Murray Valley encephalitis, lymphocytic choriomeningitis virus, and bat-related lyssavirus.<sup>146</sup> In the case of encephalitis caused by HSV or Varicella-zoster virus (VZV), provided that the donor has received a period of antiviral treatment and is not viraemic, transplantation may proceed on a case-by-case basis. Recipients in this circumstance should receive a course of antivirals.

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>147</sup>

- Stroke in a patient without risk factors (e.g. young or paediatric, without comorbidities such as diabetes, hypertension or prior cerebrovascular accident) 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 WNV or recent 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 polymerase chain reaction (PCR) and other rapid diagnostic techniques.

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#### Recommendation

Donors should be carefully evaluated for the possibility of CNS infection, with the cause established wherever possible. Donors with microbiologically proven bacterial meningitis are generally suitable for transplantation, provided the donors has been treated with appropriately targeted antibiotic therapy and the recipients receive targeted prophylaxis. Potential donors with viral encephalitis should not be utilised, with the exception of proven and treated HSV/VZV encephalitis. In the latter case, transplantation may proceed on a case-by-case after a period of antiviral treatment in the donor and with recipients receiving a course of antivirals post-transplantation. Donors with CNS infection of unknown origin must not be utilised.

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### 2.3.5.1 Transmissible Spongiform Encephalopathies

Transmissible Spongiform Encephalopathies (TSEs) are a group of rare, transmissible, and lethal neurodegenerative disorders that can occur sporadically, due to genetic causes, or due to exposure to the transmissible agent (prion). Creutzfeldt-Jakob disease (CJD) is the most common human TSE, and can occur in both sporadic (sCJD) and acquired (vCJD) forms. In the hospital setting, sCJD has been transmitted through medical or surgical procedures involving neurosurgical instruments, brain electrodes, tissue (human cornea and dura mater grafts) and tissue extracts (human pituitary hormones).<sup>149</sup> While there have been no known transmissions of vCJD via surgery or tissue or organ donation to date, there have been cases of vCJD transmission via transfusion of red blood cells and plasma.<sup>150</sup>

Prospective CJD surveillance in Australia has been performed since 1993. Persons with suspected CJD are notified to the Australian National Creutzfeldt-Jakob Disease Registry, typically as a result of referral for diagnostic cerebrospinal fluid 14-3-3 protein detection, or alternatively via personal communications from clinicians, hospitals, families or CJD-related groups, and through health record searches.<sup>151</sup> The CJD mortality rate in Australia is <2 per million population per year.<sup>151</sup> Acquired CJD has not been reported in Australia to date.

There is currently no minimally invasive test to detect TSE before the onset of symptoms, nor is the prevalence of asymptomatic TSE known. Definitive diagnosis can only be made, if at all, by neuropathological examination of brain tissue following biopsy or autopsy. In the context of deceased organ donation, minimising the risk of donor-derived TSE transmission relies on screening the patient's history for symptoms consistent with TSE, exposure to human blood, dura mater grafts, pituitary-derived hormones, contact with contaminated surgical instruments and/or prior notification from the department of health as being at increased-risk of TSE due to exposure to one or more risk factors.

The following people are at risk of TSE and should be excluded from the donation of organs and tissues (including blood and plasma):<sup>152</sup>

- People with a family history of CJD
- People who received human pituitary-derived hormones prior to 1986
- People who have received dura mater grafts, contact with contaminated surgical instruments, and/or prior notification from the department of health as being at increased risk of TSE due to exposure to one or more risk factors
- People who die of early onset dementia
- People who die with any obscure undiagnosed neurological disorder.

Residence in the United Kingdom for six months or more between 1980 to 1996 is NOT an exclusion for deceased organ donation in Australia or New Zealand, although it is for blood and tissue donation.

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#### Recommendation

Persons at risk of TSE (as defined above) should be excluded from organ donation.

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## 2.4 Risk of donor transmitted malignancy

Active malignancy generally precludes organ donation, with some exceptions. Transmission of malignancy may nonetheless occur as a result of occult malignancy in the donor, or as a result of past or current malignancy that was judged to have a low chance of transmission at the time of donor evaluation. In these circumstances, transmission of cancer from donor to recipient is believed to occur in <0.1% of solid organ transplants.<sup>153</sup>

Some data on the occurrence of malignancy transmission through organ transplantation are available through tumour registries and other databases (see Appendix J). These data have significant limitations due to incomplete capture of adverse events and the inherent difficulties of attributing cancer in the recipient to donor origin. Registries such as the Israel Penn International Transplant Tumor Registry (IPITTR) rely on voluntary event-based reporting and lack routine follow-up data on all recipients therefore tend to over-estimate risk. Conversely, transplant recipient databases may incompletely track recipients over time and thus under-report the development of cancer, resulting in under-estimation of risk. There are currently no transplant registries with systems in place to capture all cancer diagnoses over the lifetime of the recipient. Nor is there a system to capture instances where donor cancer has not resulted in transmission to the recipient, further complicating the calculation of transmission risk.

When a recipient develops a cancer – even when the cancer is proven to be of donor origin (by HLA or other molecular typing technology) – it is not necessarily the case that the cancer was donor-transmitted, since the transplanted organ may have developed the cancer subsequent to transplantation. That is, cancer in the recipient may be donor-derived but not donor-transmitted. Known examples include late renal cell carcinoma many years post-transplant and cases of donor-origin lymphoma that are likely to have developed through EBV transformation of donor lymphocytes after transplantation, rather than having been transmitted at the time of transplantation.

Practices to avoid donor-transmitted cancer mean that there are relatively few published reports of transmission. These limited reports do not cover the range of cancers for which decisions may be necessary, nor are case reports a reliable indicator of risk for all cancers of a given type. The decision to proceed with a given donor will therefore need to be informed by a combination of:

- i. Reported cases of donor-derived cancer
- ii. Observed lack of transmissions in the case of certain cancers (e.g. low grade, low stage prostate cancer)
- iii. Known biology of cancers in non-immunosuppressed individuals (especially known recurrence rate)
- iv. Known biology of de novo cancers in immunosuppressed hosts.

While it is inevitable that there will always be occasional cases of inadvertent cancer transmission, every effort should be made to identify past or current malignancy and to obtain as much information as possible to assess the risk of cancer transmission. This will inform (i) the decision as to whether the donation of any organ is safe, (ii) the risk-benefit assessment for each potentially suitable organ against individual recipient circumstances, and (iii) necessary steps to mitigate risk if a decision is made to proceed. Investigations should include:

- Obtaining a full donor history, including details of any past cancer diagnosis and treatment and any other information relevant to assessing the risk of malignancy transmission based on current disease status;
- Undertaking a careful physical examination at the time of donor workup and during the surgical retrieval procedure;
- Reviewing test results including those available as part of patient care or routinely undertaken for donor assessment, and any additional tests indicated for further evaluation of cancer risk, including imaging and biopsy;
- Seeking expert oncological and other advice, as required.

#### 2.4.1 Summary recommendations for organ utilisation

Sections 2.4.3 to 2.4.7 of this document provide information on risks and recommendations for organ utilisation in the event of malignancy being detected in a potential donor. The estimated risks of donor-derived transmission associated with cancers of different sites are summarised in Table 2.7 below. Cancer types and stages associated with minimal-to-low risk of transmission and those associated with high-to-unacceptable risk are shown. For recommendations with respect to other cancer types and stages (including those associated with an intermediate risk of transmission), refer to the cancer site-specific section in this document. Recommendations for organ utilisation associated with each risk classification group are given in Table 2.8.

**Table 2.7:** Summary of risks associated with malignancies of different sites in the donor history or detected at procurement.

<b>Risk classification categories:</b> <b>Minimal risk of transmission (&lt;0.1%)</b> – Likely to be acceptable for all organ types and recipients <b>Low risk of transmission (0.1% to &lt;2%)</b> – Likely to be acceptable for many organ types and recipients <b>High risk of transmission (≥10%)</b> – May be acceptable in exceptional circumstances <b>Unacceptable risk</b> – Use of organs is not recommended in any circumstance				
Cancer site and type	Risk classification*			
<b>Bladder</b> (section 2.4.6.14)	Minimal	Low	High	Unacceptable
Single, Grade 1, Stage 0a papillary urothelial carcinoma	•			
Papillary urothelial neoplasm of low malignant potential (PUNLMP)	•			
Single, Grade 1, Stage I papillary urothelial carcinoma		•		
Treated Stage II-IV urothelial cancer >5 years cancer-free			•	
Low-grade urothelial carcinoma diagnosed at procurement (ex PUNLMP)			•	
Recently diagnosed high-grade urothelial cancer				•
Multiple/recurrent urothelial cancer				•
Urothelial carcinoma <i>in situ</i> (CIS)				•
<b>Breast</b> (section 2.4.6.1)	Minimal	Low	High	Unacceptable
Ductal carcinoma <i>in situ</i>	•			
Stage Ia hormone negative breast cancer, >5 years cancer free		•		
Stage Ia hormone negative breast cancer, <5 years cancer free			•	
Stage Ib or higher hormone receptor positive breast cancer			•	
Breast cancer diagnosed at procurement				•
<b>Central nervous system</b> (section 2.4.3)	Minimal	Low	High	Unacceptable
Primary brain tumours (see Table 2.10)	•	•		
Secondary brain tumours				•
Cerebral lymphoma				•
<b>Colon and rectum</b> (section 2.4.6.3)	Minimal	Low	High	Unacceptable
Carcinoma <i>in situ</i> of the colon or rectum	•			
Treated Stage I colorectal cancer (N0/M0), >5 years cancer free (excl familial adenomatous polyposis)		•		
Stage I colorectal cancer diagnosed during procurement			•	
Stage IIa colorectal cancer, >10 years cancer free			•	
Stage II or higher colorectal cancer with ≤10 years cancer free				•

<b>Gastrointestinal tract</b> (section 2.4.6.4 & 2.4.6.7)	Minimal	Low	High	Unacceptable
Treated GIST ≤2cm (N0/M0) with mitotic count ≤5/50 HPFs and >3 years cancer free	•			
Branch duct intraductal papillary mucinous neoplasms (IPMNs) <3cm without a solid component or suspicious nodal disease		•		
Gastric GIST ≤2cm diagnosed during organ procurement		•		
Gastric GIST ≤2cm, mitotic count >5/50 HPFs, treated and >3 years cancer free		•		
Gastric GIST >2-≤5cm, mitotic count ≤5/50 HPFs, treated and >3 years cancer free		•		
Branch duct IPMN >3cm without a solid component or suspicious nodal disease			•	
Gastric GIST >2cm diagnosed at procurement			•	
Gastric GIST >10cm, mitotic count ≤5/50 HPFs, treated and >3 years cancer free			•	
Non-gastric GIST diagnosed during organ procurement			•	
Non-gastric GIST >5cm, mitotic count ≤5/50 HPFs, treated and >3 years cancer free			•	
Non-gastric GIST ≤2cm, mitotic count >5/50 HPFs, treated and >3 years cancer free			•	
Any GIST >2cm with mitotic count >5/50 HPFs, treated and >3 years cancer free			•	
Main duct IPMN >10mm or any IPMN with a solid component or suspicious nodal disease				•
Any GIST diagnosed at procurement or with distant metastases				•
GIST without complete prior surgical excision or GIST with <3 years cancer-free survival				•
Oesophageal, gastric, liver, pancreatic or biliary cancer				•
<b>Gynaecological cancers</b> (section 2.4.6.9 & 2.4.6.15)	Minimal	Low	High	Unacceptable
Adenocarcinoma <i>in situ</i> of the uterine cervix	•			
High grade squamous intraepithelial lesions	•			
Invasive cancer of the uterus or cervix in the donor history with a cancer-free interval >5 years			•	
Invasive cancer of the uterus or cervix diagnosed within the past 5 years				•
Ovarian cancer				•
<b>Head and neck</b> (section 2.4.6.8)	Minimal	Low	High	Unacceptable
Treated low stage oropharyngeal cancer and >5 cancer-free			•	
Oropharyngeal cancer diagnosed at procurement				•
<b>Kidney</b> (section 2.4.6.11)	Minimal	Low	High	Unacceptable
Renal cell carcinoma <1cm, Fuhrman Grade I-II	•			
Renal cell carcinoma >1 and ≤4cm, Fuhrman Grade I-II		•		
Renal cell carcinoma >4-7cm, Fuhrman Grade I-II, diagnosed <5 years ago			•	
Renal cell carcinoma >7cm, Fuhrman Grade I-II, >5 years cancer free			•	
Renal cell carcinoma with extra-renal extension or Fuhrman Grade III-IV				•
Renal cell carcinoma >7cm diagnosed within the previous 5 years				•

<b>Lung</b> (section 2.4.6.5)	Minimal	Low	High	Unacceptable
Any history of lung cancer				•
<b>Prostate</b> (section 2.4.6.10)	Minimal	Low	High	Unacceptable
Prostate cancer with Gleason score $\leq 6$ (Grade 1, Stage I)	•			
Treated prostate cancer with Gleason score 7 (Grade 2/3, Stage II)	•			
Recently diagnosed prostate cancer with Gleason score 7 (Grade 2/3, Stage II)		•		
Prostate cancer with Gleason score $>7$ and extra-prostatic extension (Stage III)			•	
Neuroendocrine prostate cancer			•	
Prostate cancer with distant metastasis (Stage IV)				•
<b>Skin</b> (section 2.4.4 & 2.4.5)	Minimal	Low	High	Unacceptable
<i>In situ</i> cutaneous melanoma	•			
Basal cell carcinoma	•			
<i>In situ</i> squamous cell carcinoma	•			
Cutaneous squamous cell carcinoma T1, or T2 with $>5$ years cancer free		•		
Cutaneous squamous cell carcinoma T2 with $<5$ years cancer free			•	
Cutaneous melanoma $\leq 0.8\text{mm}$ (T1/N0/M0) completely resected			•	
Cutaneous melanoma $>0.8\text{mm}$ (T2-T4/N0/M0) with $>10$ years cancer free			•	
Invasive cutaneous squamous cell carcinoma with nodal involvement or metastasis				•
Cutaneous melanoma T2-T4 with $\leq 10$ years cancer free				•
Cutaneous melanoma with nodal involvement or metastasis				•
Uveal or mucosal melanoma				•
Kaposi's sarcoma				•
Merkel cell carcinoma				•
<b>Thyroid</b> (section 2.4.6.13)	Minimal	Low	High	Unacceptable
Papillary thyroid microcarcinoma (micro PTC)	•			
Differentiated thyroid tumours $\leq 4\text{cm}$ limited to the thyroid (T1/T2)	•			
Newly diagnosed differentiated thyroid cancer $>4\text{cm}$ (T3, M0)		•		
Differentiated thyroid cancer $>4\text{cm}$ with extensive spread (T4), treated and $\geq 2$ years cancer-free		•		
Differentiated thyroid cancer with aggressive histology or angio-invasion (T4b) with $<2$ years cancer-free survival			•	
Medullary thyroid cancer Stage III/IV, treated and $>5$ year cancer-free			•	
Newly diagnosed medullary thyroid cancers.				•
Any history of anaplastic thyroid cancer				•
Thyroid lymphomas, thyroid sarcomas and other rare tumours of the thyroid				•
Treated thyroid cancer with incomplete macroscopic tumour resection				•

Other/multiple sites	Minimal	Low	High	Unacceptable
Grade 1-2 neuroendocrine tumour (N0/M0), >5 years cancer free (section 2.4.6.6)		•		
Grade 3 neuroendocrine tumour (section 2.4.6.6)				•
Neuroendocrine tumour detected at procurement (section 2.4.6.6)				•
Neuroendocrine carcinoma (section 2.4.6.6)				•
Sarcoma determined during procurement (section 2.4.6.12)				•
Haematological cancers, <5 years recurrence-free survival (section 2.4.7)				•
Choriocarcinoma (section 2.4.6.2)				•

## 2.4.2 General recommendations for detecting malignancy in the donor and assessment of transmission risk

### 2.4.2.1 Donor history

At donor assessment, an interview is undertaken with the donor's family by the donation specialist coordinator or other health professional. This includes questions about past history of cancer and removal of any skin lesions, participation in regular cancer screening (e.g. prostate examinations in male donors and regular breast examinations and/or pap smears in female donors) and other factors that may indicate a risk of cancer, including smoking or recent weight loss. Donor assessment should also include a history of genetic testing identifying a cancer predisposition mutation in the donor or their first-degree blood relatives (see Appendix K).

If there is a reported history of cancer, details should be sought about the type, when and where it was diagnosed, treatments (e.g. surgery, radiotherapy, chemotherapy) and follow up. Pathology reports of removed skin lesions are often able to be obtained from the donor's general practitioner or pathology laboratories. Detailed information about a history of cancer should be obtained, including information from the patient's oncologist and treatment centre, stage of cancer, and histopathology reports. Reports related to disease surveillance, including imaging, should also be obtained if possible.

Details of all enquiries made in relation to donor history of cancer should be documented and communicated to the transplant centres. Where investigations were undertaken in response to a history of cancer reported by family, but no information was found, this should also be communicated to the transplant centres.

### 2.4.2.2 Donor physical examination

Physical examination occurs at two steps of the organ procurement pathway: the first by the donation specialist coordinator or other health professional at the time potential donor is being considered, and the second at the time of organ retrieval by the surgical team. The physical examination undertaken by the donor coordinator ideally occurs as soon as possible after the family interview, so that information obtained from the family can be verified at the physical assessment and the coordinator can seek further clarification from the family about unexpected findings (e.g. scars from prior surgery). The physical examination includes a careful assessment to detect scars, skin lesions and obvious lumps or masses. Large scars that may indicate prior excision of a melanoma are of more concern than pigmented skin lesions, which are difficult to precisely identify and unlikely to represent an undiagnosed melanoma. The donor coordinator is not expected to make a precise diagnosis but rather to identify unusual or abnormal findings and seek further details from the donor's medical record as required, as well as documenting and conveying any abnormal findings to transplant units.

The second physical examination undertaken by the surgeon(s) at the time of retrieval may reveal unexpected clinically occult lesions such as bowel cancers, renal or liver tumours. Abnormal lesions identified at this time may require biopsy to further evaluate the risk of malignancy. Perinephric fat should be excised sufficiently to ensure that the kidney is fully perfused. Careful dissection at the renal hilum is not routinely recommended at the donor hospital, but careful palpation of the kidney to exclude any renal mass is recommended.



### 2.4.2.3 Laboratory and imaging results

Pathology and imaging test results may be a) available as part of prior patient assessment, b) obtained as part of routine donation workup, and/or c) obtained through specific additional testing (e.g. imaging and biopsy).

Investigations that were undertaken as part of patient care and for the purpose of cancer treatment prior to the donation process beginning should be reviewed as part of the donor assessment process. These may include blood tests, imaging studies, biopsies or other information. Hospital medical record information, pathology results, and imaging study reports should be reviewed. Sometimes, an absence of any abnormalities is reassuring information that can be used to make a risk determination – e.g. computed tomography (CT) chest imaging revealing a lack of abnormalities in potential lung donors who are older and/or who have a heavy smoking history. If abnormalities are found, further evaluation and investigations may be warranted (see below).

Standard donor workup blood tests include a full blood examination and liver function tests. Occasionally, these can be abnormal as a result of an underlying malignancy. In female donors of child-bearing age, testing for beta human chorionic gonadotrophin hormone is recommended to detect metastatic choriocarcinoma, especially if the cause of death is unexplained intracerebral haemorrhage. In all potential donors, a routine chest x-ray should also be carefully reviewed for any features that may suggest underlying primary or secondary pulmonary malignancy, or that might indicate bone metastatic disease in ribs or spine.

Additional tests, such as imaging, blood tests and/or biopsy, may be appropriate for further evaluation of cancer risk in certain, specific circumstances. Some centre-based or state-based protocols recommend CT chest studies to (i) exclude lung malignancy in potential lung donors aged over 70 years and/or those with a >20 pack year history of smoking, or (ii) further evaluate concerning abnormalities identified on prior chest x-ray (see Appendix E). A CT chest that has already been undertaken as part of patient assessment earlier in the admission will usually suffice. Routine abdominal ultrasound or CT imaging is not recommended.

Similarly, routine screening for tumour markers is not recommended, since false-positive results may lead to unnecessary loss of donation and transplantation opportunities. If there is a confirmed malignancy in the donor history and previous tumour marker results are available, appropriate tumour markers may be tested as guided by oncological advice.

Careful consideration must be given to protocols or individual requests for additional tests, weighing their utility against the impact that undertaking such tests may have. Potential negative impacts include resource use (ICU and hospital), extending the donation workup timeframe and potential loss of family consent for donation as a result, and the potential for adverse impact on other organs. Additional investigations also introduce the risk of incidental findings (e.g. benign lesions identified on imaging, elevated prostatic specific antigen levels in catheterised male donors) that pose no risk to recipients and for which further evaluation is not possible in the donation timeframe, resulting in loss of transplantation opportunities. Hence, ad hoc requests for additional screening tests should only be carried out where there is a sound clinical or epidemiological basis for proceeding.

### 2.4.2.4 Biopsy and histopathology

Where a mass suspected of being malignant is known from the donor history or is found during donor workup and cannot clearly be determined as benign radiologically, a biopsy should be taken as part of the donor workup or planned ahead and performed during organ retrieval. For any mass or lymphadenopathy suspected of malignancy discovered during organ retrieval, an urgent histopathological examination must be performed by cytological smear and/or frozen section before any organ is transplanted. Where possible, discuss the appropriate sampling type with the on-call histopathologist. If possible, the mass should be completely resected and examined, without sacrificing a graft suitable for transplantation. The pathologist should be provided with as much clinical information as possible. If, however, after pathological examination the possibility that a suspicious mass is malignant cannot be ruled out, then the donor should be declined unless there is a suitable recipient facing an imminent risk to life (who has given informed consent).

When a donor malignancy (primary tumour or metastasis) is identified shortly after organ procurement (e.g. during the implantation procedure), all recipient centres involved must be alerted immediately. In cases where organs have already been transplanted and histology reveals a malignancy (e.g. incidental cancer in a lung lobe

discarded due to size reduction), a full donor autopsy should be requested whenever possible to obtain detailed information about tumour origin and dissemination. This is not necessary in cases of small primary renal cell carcinoma found in one kidney, which would not preclude the transplantation of other organs.

While routine post-mortem examination has become an uncommon procedure in clinical medicine, if an autopsy is performed then the results should be followed-up by the donation service up as the autopsy may detect potentially transmissible disease.

#### 2.4.2.5 Assessment of transmission risk

For donors with a known history of cancer or where cancer is detected during donor work-up or organ retrieval, in deciding whether to proceed with donation it is important to not only consider to the natural history of the cancer in the donor, but also the potential impact of transplanting tumour cells of this type into an immunosuppressed recipient. Advice may be sought from the patient's treating oncologist or from oncologists and/or other specialists with particular expertise regarding the cancer under consideration (e.g. urologists who specialise in prostate cancer).

While the precise risk of transmission from donor to recipient of any given cancer is usually unknown, it is possible to broadly categorise the likely risk of transmission based on what is known about the cancer type and stage, its metastatic potential, and its patterns of recurrence in both the transplant and non-transplant setting (see Table 2.8). Newly diagnosed invasive cancer generally poses a higher risk of transmission than a history of treated invasive cancer followed by a significant disease-free interval. For potential donors with a confirmed history of cancer, the risk of transmission will be influenced by the treatment received, the length of the disease-free interval, and follow-up history.

**Table 2.8:** Risk categories for donor malignancy transmission (adapted from Nalesnik et al 2011). In all cases where the risk of donor malignancy transmission is non-standard, specific informed consent should be obtained from the recipient or their delegate prior to proceeding with transplantation.

Risk category	Definition		Recommendations for organ utilisation
	Description	Estimated risk of transmission	
Standard risk	No active malignant tumour or history of malignancy found during donor evaluation	Negligible	Acceptable for all organ types and recipients
Minimal risk	Existing evidence suggests minimal risk of transmission	<0.1%	Likely to be acceptable for all organ types and recipients
Low risk	Existing evidence suggests low risk of tumour transmission	≥0.1%–<2%	Likely to be acceptable for many organ types and recipients
Intermediate risk	Existing evidence suggests intermediate risk of tumour transmission	≥2%–<10%	May be acceptable for some organ types and recipients
High risk	Existing evidence suggests high risk of tumour transmission	≥10%	May be acceptable in exceptional circumstances e.g. where the recipient faces an imminent threat to life
Unacceptable risk	Existing evidence suggests very high risk of tumour transmission	NA	Use of organs is not recommended in any circumstance
Unknown risk	Evaluation for risk factors is incomplete or no literature exists on which to base risk assessment	NA	May be acceptable according to the circumstances and clinical judgement

Organs from deceased donors with cancers categorised as minimal risk may be safely used for transplantation without particular restrictions. Organs from donors with low- to intermediate-risk cancers may also be acceptable and provide benefit for many recipients, depending on organ type and recipient circumstances. Thorough donor assessment can help to inform decision-making, as can advice from oncologists and other specialists.

When donors are at high risk of transmitting cancer, early medical advice regarding suitability is recommended and transplant units should be contacted to determine whether there are suitable recipients in whom the risk

may be deemed acceptable, before proceeding with detailed donor assessment. In particular, liver and thoracic transplant services should be consulted to determine if there are any urgently listed patients who might be considered suitable recipients and may be willing to accept the high risk of cancer transmission.

In all circumstances, it is necessary to weigh the potential risks and benefits of proceeding with transplantation given the characteristics of a donor organ and the circumstances of a particular recipient. This tailored risk assessment will differ according to the donor and cancer risk, the organ being transplanted, the transplant urgency for a given recipient and – if the organ were to be declined – the likelihood of a subsequent more suitable offer being received in an acceptable time period.

Patients who are waitlisted for organ transplantation should receive education about the risks of transplantation, including that of possible donor-derived malignancy. When there is a specific risk associated with the donor organ(s) at the time of organ offer, specific informed consent should be obtained from the recipient or their guardian/delegated decision-maker if the recipient lacks competence (for example, due to young age or illness) prior to proceeding with transplantation.

#### 2.4.2.6 Role of cancer registries

Cancer at most sites is a notifiable disease in Australia and New Zealand. Operational and governance arrangements vary amongst Australian states and territories, however the Australian Association of Cancer Registries encourages a standard approach to cancer data collection and management across Australia.

New Zealand and the Australian states and territories operate cancer registries that assemble information about new cases of cancer and cancer deaths, though the breadth of data collected can vary between jurisdictions (Table 2.9). All registries record location, morphological type, topography, diagnosis date, and basis of diagnosis. The registries are “case-based” data collections: each piece of information provided to the registry is considered in the context of other information about the same person and used to progressively create a complete picture of tumours for that person. Cases are generally identified by name, sex and date of birth. An important exception to mandatory cancer reporting is keratinocyte cancers (particularly squamous cell carcinomas).

In Australia, arrangements exist in some jurisdictions (Table 2.9) for DonateLife staff to query the state-based registry (either directly or indirectly) to obtain the history of a potential donor once appropriate consent for donation is obtained from the next of kin. However, information from the registry is limited to those cancers diagnosed or treated within that state or territory and is identified primarily by name and date of birth. In order to obtain a complete history, it is important to ascertain if the donor previously resided in a different state or territory, and/or may have been diagnosed or treated under a different name. Where the potential donor previously resided in another jurisdiction, DonateLife staff in that jurisdiction would need to be contacted to proceed with further enquires.

The registries forward an agreed list of data elements to the Australian Institute of Health and Welfare (AIHW) annually to a national repository—the Australian Cancer Database—for national reporting and disease monitoring. This data collection is not available for interrogation to obtain the malignancy history of a potential donor.

More information about Australian cancer registries is provided in Appendix L, including an overview of cancer-specific information available through each of the state-based registries. It should be noted that the information in Table 2.9 and Appendix L may change over time through continual improvement in data reporting and capture.

**Table 2.9:** Historic cancer data availability to DonateLife and Organ Donation New Zealand

State	Cancer data availability	
New Zealand	Available to Organ Donation NZ	Planned for 2021
	Method of Access	–
	Availability	–
	Restrictions on use	–
	Earliest year of data available	1948
	Contact details	<a href="mailto:data-enquiries@moh.govt.nz">data-enquiries@moh.govt.nz</a>

NSW	Available to DonateLife	Yes*
	Method of Access	Read-only access via web-based portal
	Availability	24/7
	Restrictions on use	–
	Earliest year of data available	1972
	Contact details	<a href="mailto:CINSW-DARenquiries@health.nsw.gov.au">CINSW-DARenquiries@health.nsw.gov.au</a>   P (02) 8374 3640
VIC	Available to DonateLife	Yes
	Method of Access	Reports accessible on request via secure portal
	Availability	9am-5pm; Monday-Friday
	Restrictions on use	–
	Earliest year of data available	1982
	Contact details	<a href="mailto:vcr@cancervic.org.au">vcr@cancervic.org.au</a>
QLD	Available to DonateLife	Yes
	Method of Access	Read-only real-time access
	Availability	24/7
	Restrictions on use	–
	Earliest year of data available	1982
	Contact details	<a href="https://CancerAllianceQld.health.qld.gov.au">https://CancerAllianceQld.health.qld.gov.au</a>   P (07) 3176 4400
WA	Available to DonateLife	Yes
	Method of Access	Read-only real-time access
	Availability	24/7
	Restrictions on use	–
	Earliest year of data available	1982
	Contact details	<a href="mailto:wacanreg@health.wa.gov.au">wacanreg@health.wa.gov.au</a>
SA	Available to DonateLife	Contact registry
	Method of Access	–
	Availability	–
	Restrictions on use	–
	Earliest year of data available	1977
	Contact details	<a href="mailto:WellbeingSACCSACancerRegistry@sa.gov.au">WellbeingSACCSACancerRegistry@sa.gov.au</a>
TAS	Available to DonateLife	Contact registry
	Method of Access	–
	Availability	–
	Restrictions on use	–
	Earliest year of data available	1982
	Contact details	<a href="https://menzies.utas.edu.au/research/research-centres/tasmanian-cancer-registry">https://menzies.utas.edu.au/research/research-centres/tasmanian-cancer-registry</a>

NT	Available to DonateLife	Yes, once standing approval to receive data is requested from and given by Chief Health Officer under the NT <i>Cancer (Registration) Act</i>
	Method of Access	Email to NT Cancer Registry
	Availability	9am-5pm; Monday-Friday, unless otherwise negotiated
	Restrictions on use	Depends on CHO approval conditions
	Earliest year of data available	1991
	Contact details	<a href="mailto:NTCancerRegistry.DoH@nt.gov.au">NTCancerRegistry.DoH@nt.gov.au</a> P 08 8985 8078   F 08 8985 8075 W <a href="https://health.nt.gov.au/data-and-research/Innovation-and-research/northern-territory-cancer-registry/what-is-the-cancer-registry">https://health.nt.gov.au/data-and-research/Innovation-and-research/northern-territory-cancer-registry/what-is-the-cancer-registry</a>
ACT	Available to DonateLife	Contact registry
	Method of Access	–
	Availability	–
	Restrictions on use	–
	Earliest year of data available	1982
	Contact details	<a href="mailto:cancerregistry@act.gov.au">cancerregistry@act.gov.au</a>

\* A lot of information is captured on the pathology report, the inpatient notification (surgical) or on the radiotherapy/chemotherapy treatment notification, which may not be explicitly listed in a data field.

### 2.4.3 Central nervous system tumours

#### Donor assessment and eligibility

Primary solid central nervous system (CNS) tumours may occasionally lead to death in circumstances where organ donation is possible. Extracranial spread of brain tumours is rare, though there are reports of malignancy transmission to the recipients of organs from such donors.<sup>154,155,156,157,158,159,160,161,162,163</sup>

Wherever possible, full histological characterisation of a CNS lesion should be accessed before any organ is retrieved. Where no histological diagnosis exists, organs from a donor with a CNS lesion should only be used in recipients whose probable waiting-list mortality justifies any extra risk, and only after fully informed consent has been given.

#### Assessment of transmission risk

##### Primary brain tumours

The World Health Organisation grades primary brain tumours from grade I to grade IV, based on biological behaviour and prognosis.<sup>164</sup> Grade IV tumours are cytologically malignant and generally fatal, and this has been interpreted as representing the highest risk of donor-to-recipient transmission. However, a number of transplants from donors with grade IV tumours have been reported that did not result in transmission of malignancy to the recipient. A UK review of 448 recipients of organs from 177 donors with primary CNS tumours, including 23 donors with grade IV gliomas and 9 with medulloblastoma, found no evidence of tumour transmission over a minimum follow-up period of 5 years.<sup>165</sup> A report of the Australian and New Zealand Organ Donor (ANZOD) registry found no transmission events from 46 donors, 9 with high-grade tumours, with organs transplanted into 153 recipients.<sup>166</sup> A UNOS database report that included 642 recipients of organs from donors with CNS tumours between 2000 and 2005, 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>167,168</sup> A Czech report of 42 donors, 11 with high-grade tumours, found no transmission among 88 recipients followed for between 2 and 14 years.<sup>169</sup>

Overall, UK and European guidelines estimate the risk of tumour transmission from WHO grade I and II tumours to be minimal (<0.1%), and the risk of transmission from grade III tumours to be low (0.1 to <2%). WHO grade IV tumours are estimated to have a low-to-intermediate risk of transmission. SaBTO in the UK estimate the risk of transmission of WHO grade IV tumours as 2.2%, although combined data from the registries in the UK, United States and Australia and New Zealand would indicate the risk of transmission is lower than this (<1 in 200). A larger evidence base is needed to definitively quantify the transmission risks associated with grade IV CNS tumours.

Interventions such as brain irradiation, chemotherapy, previous craniotomy and ventriculo-peritoneal shunt may increase the risk of transmission of CNS malignancy from donors to recipients, possibly through breaching the blood brain barrier and so facilitating tumour spread.<sup>170,171</sup> There is considerable debate about the role and significance of such interventions, however, 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 ventriculoperitoneal shunt,<sup>172</sup> though the pattern of metastases is similar in those with and without shunts. The estimated increase in risk of extracranial metastasis attributable to the presence of a cerebrospinal fluid shunt is less than 1%.<sup>173</sup> 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>174</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>174</sup> During the evaluation of a donor with a CNS tumour, a thorough thoracic and abdominal exploration with visualisation and palpation of organs should be performed.<sup>174</sup>

In summary, primary CNS tumours are not automatic contraindications to organ donation (with the exception of primary cerebral lymphoma – see below). In each case where a primary CNS tumour has been identified, the risk of not receiving a transplant should be weighed against the risk of transmission of donor malignancy. Based on reported data, the absolute risk of transmission of a primary CNS tumour is likely to be low, even with a high-grade malignancy. Craniotomy or other breach of the blood brain barrier does not contraindicate donation, though a ventriculo-systemic shunt may slightly increase the risk of transmission.<sup>173</sup> Informed consent of the recipient is required, with the (derived) risk estimates shown in Table 2.10 provided to inform the recipient's decision. More information on the possible transmission risks associated with specific CNS tumour types can be found in the European Guide to the Quality and Safety of Organs for Transplantation.<sup>175</sup>

#### Secondary brain tumours and cerebral lymphoma

Donors with cerebral lymphoma or secondary CNS tumours are considered an unacceptable risk for organ donation. Secondary malignancy in this context refers to metastatic cancer that has spread to the brain from a primary site elsewhere in the body. There is a risk that donors with brain metastases may be misdiagnosed as having a primary brain tumour or intracerebral haemorrhage. 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.

**Table 2.10:** Recommendations on the use of organs from donors with primary CNS tumours, by tumour site. Derived from SaBTO<sup>153</sup> and the 2016 WHO classification of tumours of the central nervous system.<sup>176</sup> For a list ordered by risk category, see Appendix M.

	Risk classification*			
	1	2	3	4
<b>Diffuse astrocytic and oligodendroglial tumours</b>				
Diffuse astrocytoma, IDH-mutant	•			
Anaplastic astrocytoma, IDH-mutant		•		
Glioblastoma			•	
Diffuse midline glioma, H3K27 M-mutant			•	
Oligodendroglioma, IDH-mutant & 1p/19q-codeleted	•			
Anaplastic oligodendroglioma, IDH-mutant & 1p/19q-codeleted		•		

Other astrocytic tumours	1	2	3	4
Pilocytic/ Subependymal giant cell	•			
Pleomorphic xanthoastrocytoma	•			
Anaplastic pleomorphic xanthoastrocytoma		•		
Ependymal tumours	1	2	3	4
Subependymoma/ Myxopapillary ependymoma	•			
Ependymoma	•			
Ependymoma, <i>RELA</i> fusion-positive (II or III)		•		
Anaplastic ependymoma		•		
Other gliomas	1	2	3	4
Angiocentric glioma	•			
Chordoid glioma of the third ventricle	•			
Oligoastrocytoma	•			
Choroid plexus tumours	1	2	3	4
Choroid plexus/ Atypical choroid plexus papilloma	•			
Choroid plexus carcinoma		•		
Pineal tumours	1	2	3	4
Pineocytoma	•			
Pineal parenchymal tumour of intermediate differentiation (II or III)		•		
Pineoblastoma		•		
Papillary tumour of the pineal region (II or III)		•		
Meningiomas	1	2	3	4
Meningioma/ Atypical meningioma	•			
Anaplastic (malignant) meningioma		•		
Embryonal tumours	1	2	3	4
Medulloblastoma			•	
Embryonal tumour with multilayered rosettes, C19MC-altered			•	
Medulloepithelioma			•	
CNS embryonal tumour, NOS			•	
Atypical teratoid/rhabdoid tumour			•	
CNS embryonal tumour with rhabdoid features			•	
Ependymoblastoma			•	
Germinoma			•	
Immature teratoma			•	
Teratoma with malignant transformation			•	
Yolk sac tumour			•	
Embryonal carcinoma			•	
Non-gestational Choriocarcinoma			•	

<b>Neuronal and mixed neuronal-glial tumours</b>	1	2	3	4
Dysembryoplastic neuroepithelial tumour	•			
Gangliocytoma	•			
Ganglioglioma	•			
Anaplastic gangliomyoma		•		
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	•			
Desmoplastic infantile astrocytoma and ganglioglioma	•			
Papillary glioneuronal tumour	•			
Rosette-forming glioneuronal tumour	•			
Central/ Extraventricular neurocytoma	•			
Cerebellar liponeurocytoma	•			
<b>Tumours of the cranial and paraspinal nerves</b>	1	2	3	4
Schwannoma	•			
Neurofibroma	•			
Perineurioma	•			
Malignant peripheral sheath tumour (II, III or IV)		•		
<b>Mesenchymal, non-meningothelial tumours</b>	1	2	3	4
Solitary fibrous tumour/ Haemangiopericytoma (I, II or III)	•			
Haemangioblastoma	•			
<b>Tumours of the sellar region</b>	1	2	3	4
Craniopharyngioma	•			
Granular cell tumour	•			
Pituicytoma	•			
Spindle cell oncocytoma of the adenohypophysis	•			
<b>Cerebral lymphoma</b>	1	2	3	4
Primary cerebral lymphoma				•
<b>Risk classification categories:</b> <ol style="list-style-type: none"> <li><b>Minimal risk of transmission (&lt;0.1%)</b> – Likely to be acceptable for all organ types and recipients</li> <li><b>Low risk of transmission (0.1% to &lt;2%)</b> – Likely to be acceptable for many organ types and recipients</li> <li><b>Low-to-intermediate risk of transmission<sup>a</sup></b> – consider on a case-by-case basis</li> <li><b>Unacceptable risk</b></li> </ol>				

<sup>a</sup> Best available evidence suggests that the risk of transmission from donor to recipient in the case of grade IV CNS tumours is  $\leq 2\%$ <sup>146</sup>

## 2.4.4 Melanoma

Melanoma is the third-most commonly diagnosed invasive cancer in Australia and New Zealand.<sup>177,178</sup> There are numerous reports of donor-derived transmission of cutaneous melanoma in the international literature, mostly where tumour diagnosis was missed in the donor.<sup>167,179,180,181,182,183,184</sup> Due to its high population prevalence, risk of non-detection, and tendency for early micrometastasis, invasive melanoma is the most commonly transmitted tumour type, accounting for approximately 30% of all reports of donor-transmitted cancers.<sup>185,186</sup> Transmission of melanoma from donor to recipient is also associated with a high recipient mortality rate – the IPITTR estimates this at 60%.<sup>181</sup>



The exact risk of cutaneous melanoma transmission is strongly related to Breslow thickness and melanoma stage at diagnosis and treatment.<sup>187</sup> *In situ* cutaneous melanoma is, by definition, non-invasive and poses minimal risk of donor-derived transmission, given that *in situ* melanoma is not associated with metastatic risk. In a case series of 140 transplants with grafts from donors diagnosed with melanoma, including a mix of *in situ* and invasive melanoma, only one case of transmission was reported.<sup>167</sup>

Invasive cutaneous melanoma, in contrast, may recur even after many years of disease-free survival and is associated with a high-to-unacceptable risk of transmission. In non-immunosuppressed individuals, the lifetime risk of recurrence for invasive cutaneous melanoma is greater than 2% for melanomas <0.8mm in thickness (T1a), and greater than 10% for melanomas 0.9-1.0mm in thickness (T1b).<sup>188,189</sup> Melanoma cells may spread to distant sites in the early stages of cancer progression and can stay dormant and clinically undetectable for decades after resection of the primary tumour.<sup>190</sup> Transplantation of an organ with dormant melanoma micrometastases into an immunosuppressed host may lead to metastatic growth in the recipient,<sup>191,192,193</sup> with generally poor survival outcomes.<sup>194,195</sup> Use of life saving organs might still be considered in certain circumstances, however, after discussion with a melanoma specialist and with informed consent of the recipient.

Uveal and mucosal melanoma pose an unacceptable risk to donation, given a high risk of undetected micrometastases, regardless of the length of disease-free survival.<sup>196,197,198</sup> Cutaneous melanoma with a history of nodal involvement or distant metastases also poses an unacceptable risk.

Donors with a history of invasive melanoma should only be accepted in cases where sufficient information is available to make a determination of risk status. If sufficient information is not available to determine risk status, donation should only be considered in exceptional circumstances.

Investigations	Risk	Tumour details	Organs to consider
Obtain data about tumour stage (including depth and ulceration), previous therapy, type of follow-up or recurrence-free time and then evaluate risk of metastasis with a dermatologist before considering for organ donation.  NB: distant historical records of the removal of a melanoma may not be recorded in the donor's current home state cancer registry. Investigations should also follow-up with cancer registries in previous states/territories of residence.	Minimal (<0.1%)	<i>In situ</i> cutaneous melanoma (T0)	All organs may be considered for transplantation
	Low (0.1%-<2.0%)	–	–
	Intermediate (2.0%-<10%)	–	–
	High (≥10%)	History of invasive cutaneous melanoma with tumour thickness ≤0.8mm (T1/N0/M0), completely resected  History of invasive cutaneous melanoma with tumour thickness >0.8mm (T2-T4/N0/M0), completely resected and cancer free >10 years	Consider using organs where the recipient would be at imminent risk of death without the transplant. Consider on a case-by-case basis after discussion with a melanoma specialist and obtaining informed consent from the recipient
	Unacceptable risk	History of invasive cutaneous melanoma >0.8mm (T2-T4) with cancer free period ≤10 years OR with nodal involvement (N1 or higher) OR distant metastasis (M1).  Uveal melanoma  Mucosal melanoma	None
	Unknown	Reasonable suspicion that the potential donor has had a cutaneous melanoma treated in the past and there is a surgical scar to confirm that a skin lesion has been widely excised but no further histological information is available despite extensive enquiry	Consider only in exceptional circumstances where the recipient would be at imminent risk of death without the transplant

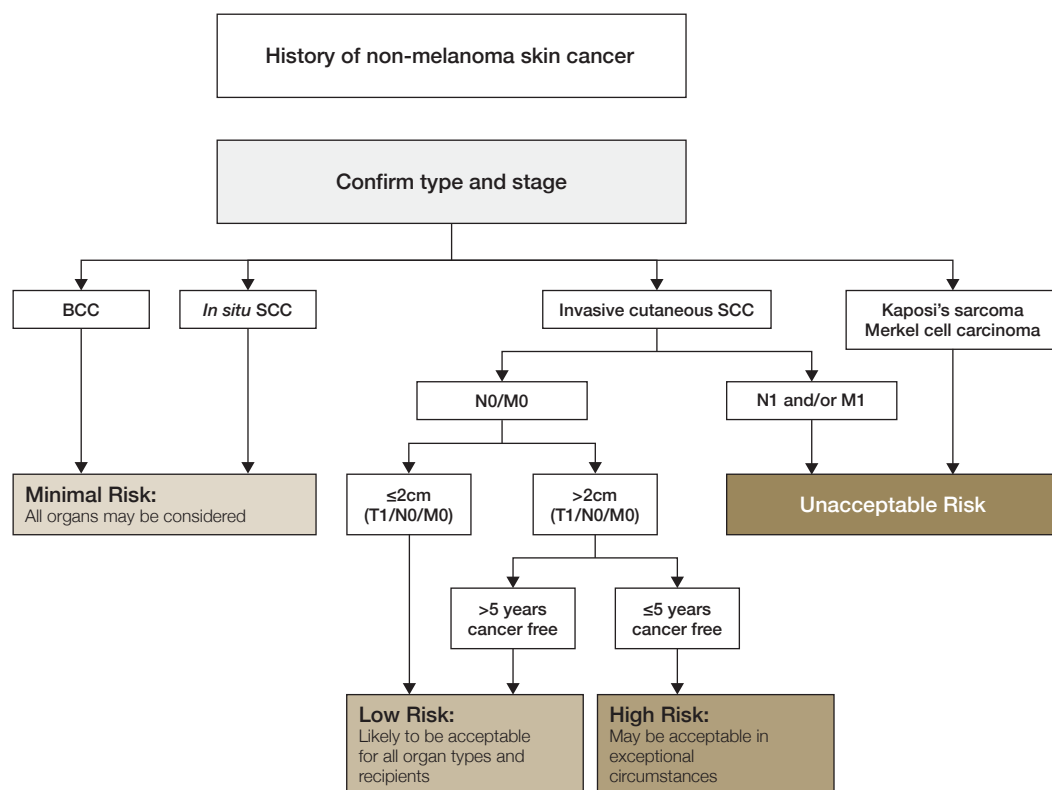
## 2.4.5 Non-melanoma skin cancers

Non-metastatic keratinocyte cancers (basal cell and squamous cell carcinoma of the skin) are the most common malignancy encountered in donors and are not considered a contraindication to donation. All basal cell carcinoma (BCC) and the majority of squamous cell carcinoma (SCC) are considered minimal-to-low risk of transmission: a UNOS database report including 776 recipients of organs from donors with BCC and SCC of the skin reported no incidence of disease transmission.<sup>167</sup>

Potential donors with a history of a large SCC (>2cm) and fewer than 5 years of recurrence free follow-up, however, pose a higher risk of transmission and should be considered on a case-by-case basis.<sup>199</sup> For donors with more than 5 years of recurrence-free follow-up, the risk of SCC transmission is low, regardless of tumour size.

Other types of cancers manifesting on the skin, such as Kaposi sarcoma (see Section 2.3.2.7), spindle cell carcinoma and Merkel cell carcinoma, pose an unacceptable risk to transplantation.

**Figure 2.5:** Decision flow chart for potential donors with a history non-melanoma skin cancer



Investigations	Risk	Tumour details	Organs to consider
<p>Seek to obtain a pathology report for any skin lesion that has been widely excised (particularly on the head and neck) in the context of any reported history of skin cancer. Obtaining the pathology report will minimise the risk of missing a squamous cell carcinoma or melanoma misreported in the donor history as basal cell carcinoma.</p> <p>Consider tumour stage at diagnosis, previous therapy, type of follow-up or recurrence-free time and then evaluate metastatic risk before considering for organ donation.</p>	Minimal (<0.1%)	Basal cell carcinoma <i>In situ</i> squamous cell carcinoma	All organs may be considered for transplantation
	Low (0.1%-<2.0%)	History of invasive cutaneous squamous cell carcinoma, T1 (N0, M0)  History of invasive cutaneous squamous cell carcinoma T2 and above (N0/M0) with curative surgery and cancer free period >5 years	Likely to be acceptable for all organ types and recipients
	Intermediate (2.0%-<10%)	–	–
	High (≥10%)	History of invasive cutaneous squamous cell carcinoma T2 and above (N0, M0) with cancer free period <5 years	May be acceptable in exceptional circumstances e.g. where the recipient faces an imminent threat to life. Consider on a case-by-case basis with informed consent from the recipient
	Unacceptable risk	Kaposi's sarcoma Merkel cell carcinoma History of SCC with nodal involvement and/or distant metastases	None
	Unknown	Reasonable suspicion that the potential donor has had a non-melanoma skin cancer treated in the past and there is a surgical scar to confirm that a skin lesion has been widely excised but no further histological information is available despite extensive enquiry	May be acceptable according to the circumstances and clinical judgement

## 2.4.6 Solid organ tumours

### 2.4.6.1 Breast cancer

Given the potential for late recurrence and metastasis, organs from donors with a history of invasive breast cancer should only be considered where specific criteria indicative a low risk of transmission are met.<sup>200,201</sup> Organs from donors with a history of Stage I (T1A, node-negative) hormone receptor-negative breast cancer may be considered where there has been full treatment and complete remission with follow-up for >5 years.<sup>202</sup> All other invasive breast cancer is considered high-risk of transmission, regardless of the duration of recurrence-free survival. For hormone positive breast cancer, the cumulative risk of recurrence at 20-25 years post-treatment is high, even for Stage 1 disease.<sup>200,201</sup> For Stage I estrogen-receptor positive breast cancer without nodal involvement, there is a 13% risk of recurrence at 20 years.<sup>200</sup> Given the late recurrence associated with hormone-positive breast cancer, donors with a history of cancer of this type have a high risk of malignancy transmission.

While lobular breast cancer is usually of greater clinical concern, in terms of the risk of distant recurrence the risks are similar between lobular and ductal carcinoma of the breast.<sup>203</sup> Hence, in the context of assessing risk of transmission in the case of a Stage I breast cancer with >5 years recurrence free survival, it is reasonable to group lobular and ductal carcinoma together.

Where donors have a known history of invasive breast cancer but critical information on cancer pathology, treatment history, and/or receptor status are unavailable, donation should only be considered under exceptional circumstances for recipients facing an imminent threat to life. Invasive breast cancer diagnosed during procurement poses an unacceptable risk to organ donation.

It is important to verify breast cancer history as reported by donor proxy/next of kin, to rule out the possibility of misreporting. Every effort should be made to establish that breast cancer was present as reported before excluding a potential donor from further investigation.

Ductal carcinoma *in situ* poses minimal risk of donor-derived transmission and does not preclude organ donation.

Investigations	Risk	Tumour details	Organs to consider
Investigations should include a thorough review of donor medical records and pathology reports to confirm existence of prior breast cancer and to determine stage, receptor status, treatment, and follow-up history	Minimal (<0.1%)	Ductal carcinoma <i>in situ</i>	All
	Low (0.1%-<2.0%)	Stage Ia (T1/N0/M0) hormone negative breast cancer treated with curative surgery +/- chemotherapy and no recurrence for >5 years. Risk of transmission is estimated to be similar for lobular and ductal carcinoma with this staging.	All organs may be considered for donation with the informed consent of the recipient
	Intermediate (2.0%-<10%)	–	–
	High (≥10%)	All other invasive breast cancer in the donor history (regardless of recurrence free period)	May be acceptable in exceptional circumstances e.g. where the recipient faces an imminent threat to life
	Unacceptable risk	Breast cancer diagnosed during procurement	None
	Unknown	Where a donor has a confirmed history of invasive breast cancer, but critical information on cancer pathology, treatment history and/or receptor status is unavailable, donors should be considered high risk of cancer transmission	May be acceptable according to the circumstances and clinical judgement

#### 2.4.6.2 Choriocarcinoma

Choriocarcinoma of any stage is considered an unacceptable risk for organ donation. Choriocarcinoma is a highly aggressive, malignant trophoblastic cancer arising after hydatidiform mole, pregnancy, ectopic pregnancy, miscarriage or termination. Cases of undetected choriocarcinoma in donors resulting in multiple transmissions demonstrate the malignancy of choriocarcinoma in immunosuppressed recipients.<sup>181,204</sup> Female donors of child-bearing potential should have their blood levels of beta human chorionic gonadotrophin hormone tested to detect metastatic choriocarcinoma, especially if the cause of death is unexplained intracerebral haemorrhage.

#### 2.4.6.3 Colorectal cancer

Based on an exceedingly low risk of nodal or metastatic disease associated with Stage I (T1, node-negative) colorectal cancers in the general population, a 2003 US consensus conference endorsed the use of such donors in certain circumstances.<sup>205</sup> In donors with Stage I familial adenomatous polyposis, however, the pancreas should be excluded from transplantation due to the increased risk of cancers in the duodenum, although some other organs may be acceptable according to the circumstances and clinical judgement. In donors with familial adenomatous polyposis where the colon remains *in situ*, given the immense number of polyps it would be impossible to rule out the presence of a malignant lesion. The risk of malignancy transmission in this circumstance would therefore most accurately be classified as unknown.

Stage II or higher colorectal cancer diagnosed at procurement, or in the donor history with a cancer-free duration ≤10 years, poses an unacceptable risk of transmission to recipients. It is important that pathology reports are available to definitely establish cancer stage before proceeding with transplantation. Donor surgeons should carefully examine all intra-abdominal and intra-thoracic structures for suspicious lesions.

Investigations	Risk	Tumour details	Organs to consider
Investigations should include a thorough review of donor medical records, pathology reports and colonoscopy reports to confirm existence of prior colorectal cancer and to determine stage, treatment, and follow-up history. Absence of this information does not necessarily rule out donation, but it would be helpful as supporting evidence that the cancer history is low-risk.	Minimal (<0.1%)	Carcinoma <i>in situ</i>	All organs may be considered for transplantation
	Low (0.1%-<2.0%)	Colorectal cancer Stage I (T1/N0/M0) with curative surgery and cancer free survival >5 years (excluding familial adenomatous polyposis)	Likely to be acceptable for many organ types and recipients
	Intermediate (2.0%-<10%)	–	–
	High (≥10%)	Colorectal cancer Stage I (T1/N0/M0) diagnosed during organ procurement  History of Stage IIa (T3/N0/M0) colorectal cancer with curative surgery and cancer free survival >10 years	May be acceptable in exceptional circumstances e.g. where the recipient faces an imminent threat to life
Donor surgeons should carefully examine all intra-abdominal and intra-thoracic structures for suspicious lesions at the time of organ retrieval.	Unacceptable risk	All other colorectal cancer	None
	Unknown	Possible or confirmed history of colorectal cancer reported but pathology report not available  Donor with familial adenomatous polyposis where the colon remains <i>in situ</i>	May be acceptable according to the circumstances and clinical judgement.

#### 2.4.6.4 Gastrointestinal stromal tumour

Gastrointestinal stromal tumours (GIST) account for 4-5% of soft tissue sarcomas and 1-2% of all gastrointestinal malignancies.<sup>206,207</sup> Incidence of clinically diagnosed GIST is relatively low (an estimated 14 cases per million per year in Australia<sup>208</sup> and approximately 10-20 cases per million per year in Europe<sup>209</sup>); however, small, subclinical GISTs are common in adults.<sup>210,211,212</sup> The median age of people diagnosed with GIST is 60-65 years; paediatric GIST is a rare and clinically distinct subset of the disease.<sup>213</sup> GISTs can involve almost any segment of the gastrointestinal tract but most commonly occur in the stomach (60%), jejunum and ileum (30%), duodenum (4-5%), or rectum (4%).<sup>209</sup>

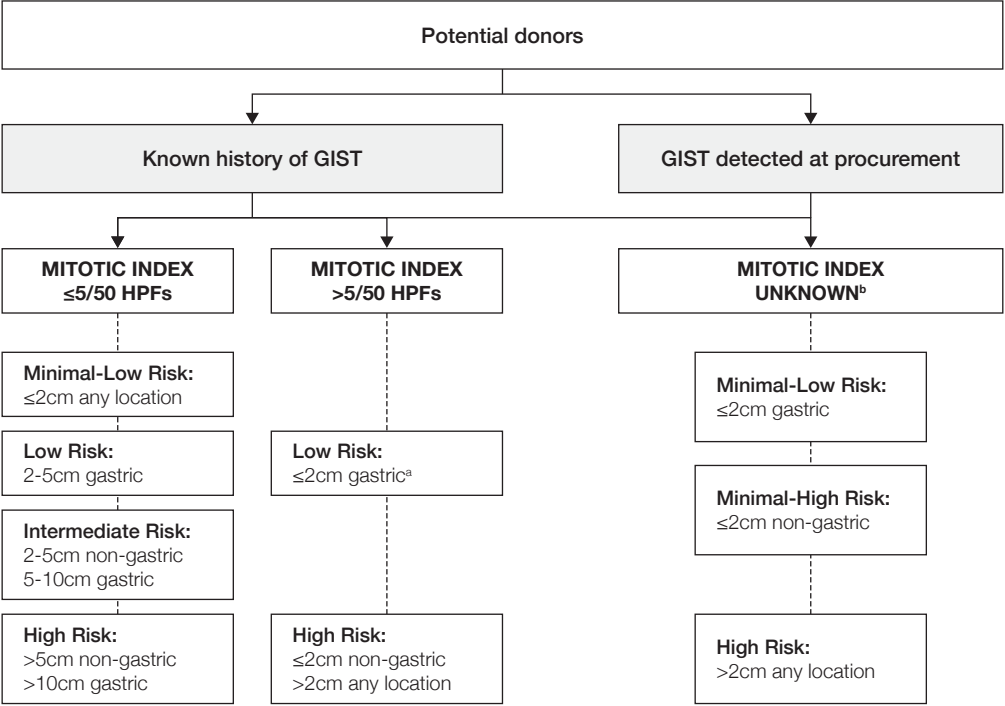
The median disease-free survival after GIST resection is approximately 3 years.<sup>214</sup> The main prognostic factors are: (i) tumour localisation (site and spread) (ii) mitotic index, (iii) tumour size, and (iv) tumour rupture before or during surgery.<sup>214,215</sup> Gastric GISTs have a more favourable prognosis and lower risk of metastases than GIST occurring at other primary sites, such as the small intestine.<sup>209</sup> The metastatic potential of GISTs exists on a spectrum from small, inactive tumours to larger, mitotically active tumours;<sup>216</sup> metastasis, where it occurs, is typically to the abdominal cavity or liver and may occur many years after treatment of the primary tumour.<sup>209,212,217</sup>

European guidelines state that donors with a history of gastric or duodenal GIST <2cm with mitotic index ≤5 per 50 high power fields (HPFs) have a low risk of metastases and may be acceptable for organ donation with low-to-intermediate risk of transmission.<sup>175</sup> A case series from Italy of five GISTs diagnosed during donor procurement, all under 2cm and with mitotic index ≤5/50 HPFs, reported no evidence of transmission after a minimum of 18 months follow up from the three organs transplanted (two kidneys from a single donor and a liver from a second donor).<sup>218</sup> The Miettinen risk criteria define GISTs ≤2 cm as having zero risk of progressive disease over long term follow up, with gastric GISTs up to 5cm associated with a very low risk of progressive disease.<sup>212</sup>

GIST from primary sites other than the stomach that are >2cm and/or have a mitotic count >5/50 HPFs are likely to be associated with a higher risk of malignancy transmission, based on reported relapse rates on long-term follow-up of people with GIST.<sup>212,214,217,219</sup> The exact risk of transmission will also depend on the treatment received, follow-up time and duration of recurrence free survival. A disease-free period of more than 3 years is likely to indicate lower risk of transmission.<sup>214</sup>

In the context of GIST discovered during procurement, the degree of risk is related to where the tumour is located, its size, and its mitotic count. As it is unlikely to be possible to obtain biopsy results and mitotic index in the timeframe required for organ transplantation, in this circumstance all known information about the tumour should be considered (i.e. size, location) and weighed against the risks to the recipient in the absence of transplantation. Gastric GISTS  $\leq 2\text{cm}$  diagnosed at the time of procurement are likely to be low risk, although minimal data are available on which to base recommendations.

**Figure 2.6:** Decision flow chart for potential donors with a history of gastrointestinal stromal tumour (GIST) or GIST detected at the time of organ procurement



<sup>a</sup> Minimal data available on which to base risk assessment

<sup>b</sup> Where mitotic index is not available, all known information about the tumour should be considered and weighed against the risks to the recipient in the absence of transplantation

Investigations	Risk	Tumour details	Organs to consider
<p>For donors with a history of GIST, information on mitotic index, tumour size prior to treatment, tumour site and the treatment delivered should be obtained.</p> <p>Where GIST is diagnosed during donor procurement, excisional biopsy is recommended, noting however that it will be unlikely to be possible to obtain mitotic index prior to transplantation. Mitotic rate should still be requested, however, to support post-transplant management.</p>	Minimal (<0.1%)	History of treated GIST ≤2cm (N0/M0) with mitotic count ≤5/50 HPFs and cancer free survival > 3 years	Likely to be acceptable for all organ types and recipients
	Low (0.1%-<2.0%)	History of treated gastric GIST >2-≤5cm (N0/M0) with mitotic count ≤5/50 HPFs and cancer free survival > 3 years	Likely to be acceptable for many organ types and recipients
		History of treated gastric GIST ≤2cm (N0/M0) with mitotic count ≥5/50 HPFs and cancer free survival > 3 years	
	Intermediate (2.0%-<10%)	Gastric GIST ≤2cm diagnosed during organ procurement	May be acceptable for some organ types and recipients.
		History of treated gastric GIST 5-10cm (N0/M0) with mitotic count ≤5/50 HPFs and cancer free survival > 3 years	
	High (≥10%)	History of treated non-gastric GIST >2-≤5cm (N0/M0) with mitotic count ≤5/50 HPFs and cancer free survival > 3 years	May be acceptable in exceptional circumstances e.g. where the recipient faces an imminent threat to life. Risk of liver metastases may preclude use of the liver from a donor with history of high-risk GIST
		History of treated gastric GIST >10cm (N0/M0) with mitotic count ≤5/50 HPFs and cancer free survival > 3 years	
		History of treated non-gastric GIST >5cm (N0/M0) with mitotic count ≤5/50 HPFs and cancer free survival > 3 years	
		History of treated non-gastric GIST ≤2cm (N0/M0) with mitotic count >5/50 HPFs and cancer free survival > 3 years	
		History of any treated GIST >2cm (N0/M0) with mitotic count >5/50 HPFs and cancer free survival > 3 years	
	Unacceptable risk	Any non-gastric GIST diagnosed during organ procurement	None
		Any gastric GIST >2cm diagnosed at procurement	
	Unknown	Any GIST diagnosed at procurement or in the donor history with the presence of distant metastases.	May be acceptable in exceptional circumstances according to the circumstances and clinical judgement.
		Any history of GIST without complete prior surgical excision or with <3 years cancer-free survival	

#### 2.4.6.5 Lung cancer

A history of lung cancer of any stage poses an unacceptable risk to organ donation. Registry and case reports of transmission of occult donor lung cancer by kidney transplantation, with generally fatal outcomes in recipients, are indicative of very aggressive behaviour of donor-transmitted lung cancers.<sup>220,221,222</sup>

Lung adenocarcinoma *in situ* (AIS) has a low risk of distant metastases and a low risk of recurrence, and therefore theoretically may be associated with a lower risk of transmission from organ donors to recipients. However, a definitive diagnosis of AIS is difficult to determine, as lesions may be multifocal and it is not possible

to guarantee that there are no parts of the lesion with an invasive component. Theoretically – if a definitive diagnosis of AIS could be made – use of non-lung organs might be considered, recognising a small but real risk of disease transmission. In practice, donors with a diagnosis of AIS are unlikely to be suitable for donation of any organs.

Benign pulmonary nodules – such as hamartomas and papillomas – are relatively common especially after 45 years of age, hence it is important to distinguish between benign tumours in the lung and lung cancer in the donor. Donor assessment should include smoking history and appropriate imaging (CT) when indicated on the basis of an abnormality noted on chest x-ray or in the donor history, with review by a radiologist +/- respiratory physician. If available, any prior chest imaging should be reviewed for comparison. Lung bronchoscopy of potential lung donors is commonly deployed in all jurisdictions (where possible) and would permit visualisations of any endobronchial lesions.

Pulmonary hamartomas, which are common benign lesions, can be confidently diagnosed on CT. Other lesions may need to be assessed intraoperatively and a frozen section taken, especially in the context of significant smoking history or any suspicious signs on chest CT.

#### 2.4.6.6 Neuroendocrine neoplasms

Neuroendocrine neoplasms mainly arise in gastrointestinal, lung or pancreatic tissue, but can be detected anywhere and may occur in multiple sites throughout the body. Although neuroendocrine neoplasms are rare, the rate of diagnosis of neuroendocrine neoplasms in Australia has doubled since the early 1980s and they are one of the most common incidental findings on organ retrieval.<sup>223</sup> Neuroendocrine neoplasms are divided based on histological differences into well-differentiated neuroendocrine tumours (NETs), poorly differentiated neuroendocrine carcinomas (NECs), and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs).<sup>224</sup> Well-differentiated NETs are further divided into Grades 1 (low), 2 (intermediate), and 3 (high) based on mitotic rate and Ki-67 proliferation index; NECs are considered poorly differentiated and high-grade by definition and may be of small-cell or large-cell type.<sup>225</sup>

There have been multiple reports of donor-derived transmission of undetected high-grade NETs and small-cell NECs from liver and kidney donors, resulting in explant and/or death.<sup>226,227,228</sup> NETs and NECs detected during organ procurement pose an unacceptable risk for organ donation, given the known metastatic potential of these cancers and the likelihood of undetected micrometastases.<sup>175</sup> There may be certain circumstances of low-grade NETs found at the time of retrieval where the risk might be theoretically acceptable (e.g. small carcinoid tumours or multiple small NETs of the stomach), if supported by a good histological evaluation and if the recipient faces an imminent threat to life. In practical terms, however, it is unlikely that a full histological evaluation including Ki-67 and mitotic count could be performed within the donation window to permit accurate grading and prognostication. Without the additional reassurance of documented, long-term, recurrence free survival, any neuroendocrine neoplasm detected at procurement poses an unacceptable risk to organ donation.

Donors with a history of Grade 1 or 2 NET, successfully treated with a recurrence-free survival of more than 5 years and without lymph node involvement or metastases, may be considered low risk for malignancy transmission, provided the history is well documented and the person had been closely followed up. Limited evidence exists, however, to guide practice with respect to well-differentiated, low-grade neuroendocrine tumours. Even low-grade NET can metastasise, depending on the location, with late metastases up to 20 years after initial resection possible.<sup>229</sup> Factors correlated with higher risk of NET spread include male gender, extra-adrenal location, greater tumour weight, confluent tumour necrosis, vascular invasion and extensive local invasion.<sup>230</sup> All information in the donor history should be taken into account and a careful risk-benefit assessment made when determining whether to proceed with donation.

A history of Grade 3 NET poses an unacceptable risk for organ donation regardless of the duration of recurrence-free follow-up, given the known risk of late metastases. Similarly, a history of MiNEN is an unacceptable risk for organ donation.



**Table 2.11:** Classification and grading criteria for neuroendocrine neoplasms of the gastrointestinal tract and hepatopancreatobiliary organs (source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7003895/>)

Terminology	Differentiation	Grade	Mitotic rate <sup>a</sup> (mitoses/2mm <sup>2</sup> )	Ki-67 index <sup>b</sup>
NET, Grade 1	Well-differentiated	Low	<2	<3%
NET, Grade 2		Intermediate	2-20	3-20%
NET, Grade 3		High	>20	>20%
NEC, small-cell type	Poorly differentiated	High <sup>c</sup>	>20	>20%
NEC, large-cell type			>20	>20%
MINEN	Well or poorly differentiated <sup>d</sup>	Variable <sup>d</sup>	Variable <sup>d</sup>	Variable <sup>d</sup>

MINEN, mixed neuroendocrine-non-neuroendocrine neoplasm; NET, neuroendocrine tumour; NEC, neuroendocrine carcinoma

<sup>a</sup> Mitotic rates are to be expressed as the number of mitoses/2mm<sup>2</sup> as determined by counting in 50 fields of 0.2 mm<sup>2</sup> (i.e. in a total area of 10 mm<sup>2</sup>).

<sup>b</sup> The Ki-67 proliferation index value is determined by counting at least 500 cells in the regions of highest labelling (hot-spots), which are identified at scanning magnification; the final grade is based on whichever of the two proliferation indexes places the neoplasm in the higher-grade category.

<sup>c</sup> Poorly differentiated NECs are not formally graded, but are considered high grade by definition

<sup>d</sup> In most MINENs, both the neuroendocrine and non-neuroendocrine components are poorly differentiated, and the neuroendocrine component had proliferation indices in the same range as other NECs, but this conceptual category allows for the possibility that one or both components may be well-differentiated; when feasible, each component should therefore be graded separately.

Investigations	Risk	Tumour details	Organs to consider
For donors with a history of neuroendocrine neoplasm, information on differentiation, grade, mitotic index, Ki67 and nodal involvement, should be obtained. The type of treatment received (past or present), results from colonoscopies and any imaging for distant metastasis will also be relevant to donor risk assessment.	Minimal (<0.1%)	–	–
	Low (0.1%–<2.0%)	History of Grade 1 or 2 NET (N0/M0) with a well-documented history of cancer-free survival of >5 years	Likely to be acceptable for many organ types and recipients. Histological confirmation of tumour grade and prognostic classification*, details of tumour pathology, and documented follow-up are critical
	Intermediate (2.0%–<10%)	–	–
	High (≥10%)	–	–
	Unacceptable risk	NET or NEC detected at procurement History of Grade 3 NET Any history of NEC History of neuroendocrine neoplasm where pathology reports are unavailable or there is incomplete follow-up	None

NET, neuroendocrine tumour; NEC, neuroendocrine carcinoma

\* WHO 2019 Classification: Grade 1-3 well-differentiated NET defined by histological grade (low/intermediate/high), mitotic rate (<2/2-20/>20mitoses/2mm<sup>2</sup>) and ki67 index (<3%/3-20%/>20%).

#### 2.4.6.7 Oesophageal, gastric, pancreatic, liver and biliary cancers

All oesophageal, gastric, pancreatic, liver or biliary cancers diagnosed during organ procurement pose an unacceptable risk to organ donation. Given the number of fairly common benign liver tumours, however, it is important to confirm whether a tumour identified at retrieval is malignant before ruling out donation.

If identified in the donor history, treated tumours of these sites are also generally considered an unacceptable risk, given the aggressive nature of these cancers and a high risk of recurrence. Theoretically, risk may decrease following curative therapy and >5 years recurrence-free survival; however, given the high mortality rate for these cancers, this is not a common scenario and only a few isolated case reports of malignancy transmission exist involving donors with oesophageal,<sup>231</sup> gastric,<sup>232</sup> pancreatic,<sup>233,234,235</sup> liver<sup>233</sup> or biliary cancer.<sup>236</sup>

In the case of pancreatic cancer, an exception to the recommendations above are intraductal papillary mucinous neoplasms (IPMNs). Intraductal Papillary Mucinous Neoplasms (IPMNs) are considered potential precursors to the development of pancreatic cancer. They are a frequent finding on imaging in the ageing population and are for the most part benign. Persons with branch duct IPMN <3cm without any other “worrisome features”<sup>237</sup> of cancer are at low risk and may be considered for donation (excluding pancreas or islets). Branch duct IPMN ≥3cm is thought to carry greater risk of malignancy and whether to proceed will be at the discretion of the teams involved. Donation would usually not be appropriate in the context of features such as a solid component, suspicious nodal disease, or a main duct IPMN >10mm in diameter.

#### 2.4.6.8 Oropharyngeal cancer

Oropharyngeal cancer diagnosed during organ procurement poses an unacceptable risk to organ donation.

For donors with a history of treated oropharyngeal cancer and recurrence free survival >5 years, there may be certain acceptable risk scenarios, although minimal evidence exists on the outcomes of transplantation from donors with a history of oropharyngeal cancer.<sup>238</sup> In the context of early non-metastatic lesions that verge on being *in situ*-type lesions, donation may be acceptable in exceptional circumstances according to recipient need and clinical judgement. Oropharyngeal cancer associated with human papilloma virus (HPV) may also pose a lower risk of donor derived malignancy transmission, given that HPV-positive head and neck cancers have been demonstrated to respond better to treatment,<sup>239</sup> have better survival outcomes,<sup>240,241</sup> and lower rates of distant metastases than HPV-negative cancers.<sup>242,243</sup> Despite a more favourable prognosis, however, recurrence rates for HPV-positive cancers remain at 13-25% within 2 years, and up to 36% within 8 years of treatment.<sup>244,240,245</sup>

#### 2.4.6.9 Ovarian cancer

Ovarian cancer is considered an unacceptable risk for organ donation.

Although risk may theoretically be diminished in the circumstance of curative surgery and lengthy recurrence-free survival (>10 years), this is an uncommon donation scenario and there are no data to support safe use of such donors.

In the event that an abnormal mass is found on the ovary during procurement, a diagnosis on frozen section should be sought before discarding organs.

#### 2.4.6.10 Prostate cancer

In Australia and New Zealand, there is a high prevalence of low-grade, non-aggressive prostate cancer among men over 50 years of age.<sup>246</sup> Prostate cancer confined to the prostate has a minimal-to-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 23% of those aged 50-59 years, 35% of those aged 60-69 years, and 46% of those 70-81 years had undiagnosed prostate cancer.<sup>247</sup> There is no evidence, however, of increased rates of prostate cancer among transplant recipients relative to the general male population.<sup>248,249</sup> From 120 reports of organ transplants from donors with confirmed prostate cancer, there has been only one case of disease transmission.<sup>250</sup> In this case, prostate adenocarcinoma was transmitted by heart transplantation from a donor subsequently found to have metastatic disease involving the lymph nodes and adrenal gland.<sup>251</sup> A meta-analysis of the outcomes of kidney transplantation from donors with prostate cancer supports the conclusion that the risk of transmitting prostate cancer is lower than the risk of remaining on the waiting list.<sup>252</sup>

For donors with no history of prostate cancer, routine prostate specific antigen (PSA) screening is not recommended. PSA results in this group are likely to be unreliable due to elevation caused by catheterization and routine PSA testing would likely result in unnecessary investigations. In addition, numerous benign prostate pathologies will cause an elevation in PSA.<sup>253</sup>

For donors with a known history of prostate cancer, PSA testing may be appropriate in situations where it is necessary to rule out prostate cancer recurrence or spread; in this circumstance, a PSA level that is undetectable or below 0.1 usually indicates minimal risk of transmission. If PSA is elevated (>6.5), organs may still be acceptable for many recipients. Isolated PSA results must, however, be interpreted with caution. In donors with a history of prostate cancer, results should ideally be interpreted in the context of past measures of PSA for that individual. Of greater importance to risk assessment is the prostate cancer grade, stage and disease-free interval.

For donors diagnosed with prostate cancer at the time of procurement, or where there is a report of prostate cancer in the donor history, whether to proceed with donation will depend on the grade (Gleason score), stage and cancer-free survival for those who have previous surgical treatment. Grade group 1 (Gleason score 6) prostate cancer – which is the majority of prostate cancer diagnosed in Australia and New Zealand – is a largely indolent disease and is associated with minimal risk of transmission by organ donation.<sup>243</sup> There is an almost-zero risk of transmission of prostate cancer out of the prostate to a secondary site when Gleason score is 6.<sup>254</sup> Where Grade group 1 prostate cancer is detected at the time of procurement or in the donor history, all organs may be safely transplanted. A donor history of treated Grade group 2/3 (Gleason score 7) prostate cancer may also be considered minimal risk, provided the tumour was organ-confined and the donor has been cancer-free for more than 3 years.

Where the donor history indicates the donor has previously received anti-androgen therapy (often delivered in conjunction with radiation therapy), consult with a urologist/oncologist before proceeding to donation. Anti-androgen therapy as a single agent therapy is suggestive of more aggressive disease prior to treatment, therefore risk of transmission is higher, even if PSA is low-to-undetectable at the time of donor evaluation.

Investigations	Risk	Tumour details	Organs to consider
<p>Obtain all data about staging, past therapy, type of follow-up or recurrence-free time before considering for organ donation.</p> <p>PSA screening is not routinely recommended and should be used only for donors where there is clinical suspicion of potential for progressive/metastatic cancer, depending on the circumstances and whether prior test results are available to compare against.</p>	Minimal (<0.1%)	<p>Prostate cancer with Gleason score <math>\leq 6</math> (Grade group 1, AJCC Stage I) diagnosed at the time of procurement or in the donor history</p> <p>Past history of organ confined, margin negative, node negative prostate cancer with Gleason score 7 (Grade group 2/3, AJCC Stage II), with cancer-free survival &gt;3 years</p>	All organs may be considered for transplantation
	Low (0.1%-<2.0%)	Organ confined, node negative tumours with Gleason score 7 (Grade group 2/3, AJCC Stage II), in the donor history or diagnosed at the time of procurement	Likely to be acceptable for many organ types and recipients. Consider on a case-by-case basis taking into account treatment type (e.g. anti androgen therapy) and follow-up history. Minimal risk of transmission to female recipients
	Intermediate (2.0%-<10%)	History of organ-confined prostate cancer with Gleason score >7 (Grade group 4, AJCC Stage IIC/IIIA), treated and with cancer free survival >3 years	May be acceptable for some organ types and recipients. Consider on a case-by-case basis after consultation with a urologist/oncologist, taking into account cancer free duration, treatment and follow-up history. Minimal risk of transmission to female recipients
	High ( $\geq 10\%$ )	<p>Extra-prostatic tumour extension, absent of nodal involvement or distant metastases (AJCC Stage III) in the donor history of diagnosed at the time of procurement</p> <p>Neuroendocrine prostate cancer in the donor history or diagnosed at the time of procurement</p>	Consider on a case by case basis for transplantation into female recipients
	Unacceptable risk	Prostate cancer with lymph nodal or distant metastases (AJCC Stage IV)	None
	Unknown	Elevated PSA (>6.5) detected during donor work up and/or unconfirmed report of history of prostate cancer	Consider on a case by case basis

#### 2.4.6.11 Renal cell carcinoma

##### Renal cell carcinoma detected during procurement

There are several case series documenting the safe transplantation of kidneys following renal cell carcinoma (RCC) resection for tumours up to 4cm in size detected at the time of organ procurement. Pavlakis et al report no cases of malignancy transmission from 21 kidneys following excision of tumour (0.1 -2.1cm), as well as no cases of transmission from the transplantation of 47 contralateral kidneys and 198 non-renal organs.<sup>255</sup> Yu et al report 97 cases of kidney transplantation after RCC resection of tumours up to 4cm without transmission; 22 contralateral kidney transplants were identified, with one case of transmission (although the diagnosis of the original donor cancer has been questioned in this instance).<sup>256</sup>

In the case of a solitary, well-differentiated RCC, the risk of malignancy transmission is minimal (<0.1%) where the tumour is  $\leq 1.0$  cm in size, or low (approximately 0.1 – 2.0%) for tumours >1.0 cm to  $\leq 4$  cm in size. All organs may be considered for transplantation in the context of an T1a RCC  $\leq 4$  cm with Fuhrman grade I-II, including transplantation of the affected kidney following tumour resection, provided satisfactory margins are achieved and imaging of the urinary tract has excluded multifocal cancer deposits.<sup>153,257,258</sup>

Ongoing surveillance by annual ultrasound is recommended for (i) recipients of kidneys with a resected tumour, given the small risk of recurrence and/or new primary cancer and (ii) recipients of contralateral kidneys, given the risk of developing a new primary.

#### Renal cell carcinoma in the donor history

If the donor has been diagnosed with RCC <5 years prior to being considered for organ donation, the same risk thresholds defined above for RCC diagnosed at the time of organ procurement apply. If the diagnosis in the donor was made >5 years ago and there has been recent follow up and/or CT scan showing nothing of concern, risk of transmission may be lower. Follow-up surveillance of recipients is recommended.

Donors with a history of treated RCC >4cm to 7cm in size with Fuhrman grade I-II, with cancer-free survival for >5 years may be considered for transplantation of non-renal organs, provided that a recent CT scan shows nothing of concern. Donation of the contralateral kidney in the context of a history of RCC >4-7cm should be considered on a case-by-case basis, after reviewing donor history and follow-up.

A history of invasive RCC (Stage III or IV) or Fuhrman grade III-IV presents an unacceptable risk to organ transplantation.

Investigations	Risk	Tumour details	Organs to consider
A renal USS and/or CT abdo/pelvis should be performed to determine size and position of tumour and presence of tumour in renal vein or IVC.  Have a urology surgeon assess tumour in retrieval surgery if possible.  Do frozen section or H&E stain histology.	Minimal (<0.1%)	RCC <1cm, Fuhrman grade I-II (diagnosed at procurement or in the donor history)	All organs may be considered for transplantation, including affected kidney if tumour is close to the surface and resectable, and provided there are satisfactory surgical margins.
	Low (0.1%-<2.0%)	RCC >1 and ≤4 cm, Fuhrman grade I-II (diagnosed at procurement or in the donor history)	All non-renal organs and the contralateral kidney may be considered for transplantation.  The affected kidney may be considered for transplantation following resection, provided there are satisfactory surgical margins, with the informed consent of the recipient.
	Intermediate (2.0%-<10% risk of transmission)	Donor history of RCC >4-7cm with Fuhrman grade I-II, treated and with cancer-free survival for >5 years	Non-renal organs and the contralateral kidney may be considered on a case by case basis after consulting with a urologist/oncologist and provided a recent CT scan shows nothing of concern. Seek informed consent of the recipient.
	High (≥10%)	RCC >4-7cm and Fuhrman grade I-II diagnosed at procurement or within the previous 5 years  Donor history of RCC >7cm and Fuhrman grade I-II, treated and with cancer-free survival for >5 years	Non-renal organs and the contralateral kidney may be considered on a case by case basis after consulting with a urologist/oncologist and reviewing CT scan (CT needs to be a triple phase CT with 1mm cuts). Seek informed consent of the recipient.
	Unacceptable risk	RCC with extension beyond the kidney (Stages 3 or 4), or Fuhrman grade III-IV  Donor history of RCC >7cm diagnosed within the previous 5 years	None

#### 2.4.6.12 Sarcoma

For recommendations regarding Kaposi's sarcoma (Human Herpes Virus 8) see section 2.3.2.7.

##### Sarcoma detected during procurement

Given the typically aggressive nature of these tumours, sarcoma diagnosed during procurement poses an unacceptable risk to organ donation. While there are a number of low-grade sarcomas, obtaining a definitive diagnosis in the timeframe required for transplantation is unlikely to be feasible.

##### Sarcoma in the donor history

Isolated case reports from the literature demonstrate fatal outcomes of transplantation in the context of unrecognised donor sarcoma.<sup>259,260</sup> However, given the vast array of possible soft tissue and bone sarcomas and their heterogeneity with regards risk of recurrence and potential risk of transmission to recipients, potential donors with a history of treated sarcoma and a substantial recurrence-free period should be considered on a case by case basis.

Sarcoma type and associated long-term risk of recurrence, treatment type and era, and length of follow-up are key considerations in assessing transmission risk. As sarcomas are typically very aggressive, a person who is very late into follow-up (20-30 years) is unlikely to carry a high residual risk of cancer transmission.<sup>261</sup> Long term recurrence rates have reduced further in the current era due to improved treatment protocols. Organs from a donor with a distant history (30+ years) of Ewing sarcoma have previously been transplanted in Australia with good outcomes. The long-term data on recurrence of different sarcoma types should be taken into account when evaluating potential donors – particularly in the case of childhood cancers such as Ewing sarcoma.

#### 2.4.6.13 Thyroid cancer

Over the past 30 years, the annual incidence of thyroid cancer diagnosed in Australia has steadily increased, from an age-standardised incidence rate of 3.3 per 100,000 in 1990, to an estimated rate of 14 cases per 100,000 in 2020.<sup>223</sup> Similar increases in the incidence of thyroid cancer have been reported globally, mostly driven by increases in lower stage papillary thyroid cancer and incidental findings of micro-papillary thyroid cancers during surgery for other conditions of the thyroid.<sup>262</sup> In Australia and globally, mortality from thyroid cancer has remained steady, suggesting a degree of overdiagnosis of thyroid cancer in the general population.<sup>263</sup>

The main types of thyroid cancer are:

- Differentiated (including papillary, follicular and Hürthle cell)
- Medullary
- Anaplastic

Papillary thyroid cancer accounts for approximately 80% of thyroid cancers, and follicular thyroid cancer for another 10%.<sup>264</sup> These cancers generally grow very slowly and are typically low-stage at diagnosis, with only localised spread.<sup>265</sup> Overall, five year relative survival in people with thyroid cancer is 97% and the prognosis for differentiated thyroid cancer is very good until advanced stages of disease.<sup>266,267</sup> Distant metastases develop in 5-23% of people with differentiated thyroid cancer; when these do occur, it is mainly in the lungs and bones.<sup>262</sup> Current clinical practice guidelines recommend total thyroidectomy plus radioiodine for differentiated thyroid tumours greater than 4cm in diameter or tumours of any size associated with multifocal disease, bilateral disease, extra-thyroidal spread (pT3 and pT4a), familial disease or nodal involvement/distant metastases.<sup>262</sup> Post-operative risk of recurrence is low where there is complete resection and the tumour does not have aggressive histology.<sup>268</sup> Late recurrences can occur but can be successfully treated.<sup>262</sup>

The risk of transmission of differentiated thyroid cancer from a donor to a solid organ recipient relates to the size of the tumour and whether it has spread beyond the thyroid. Differentiated thyroid cancers of up to 4cm in size and confined to the thyroid pose minimal risk of donor-derived malignancy transmission, even if detected at the time of organ procurement. It is important to note that thyroid cancers do not seem to be affected by immunosuppression: pre-existing thyroid cancers do not show increased rates of progression and incidence of thyroid cancer is not elevated in recipients of non-kidney organs – in kidney transplant recipients the incidence of

thyroid cancer is not above that of dialysis patients.<sup>269,270</sup> In addition, even widely metastatic differentiated thyroid cancer is amenable to curative therapy, depending on its histology.<sup>262</sup> Hence, even in the event of donor-derived transmission, there could be a reasonable expectation of curative treatment.

Medullary thyroid cancer (MTC) accounts for <5% of thyroid cancer and may be sporadic (approximately 75% of MTC) or familial (approximately 25%).<sup>262</sup> Familial MTC has an earlier age of onset and is more aggressive, with a tendency to spread to the lungs, liver or bones. In confirmed cases of MTC, treatment is total thyroidectomy and central compartment node dissection. Lifelong follow-up is required and there is the potential for local recurrence or distant metastases.<sup>262</sup> For this reason, a history of MTC poses an intermediate-to-high risk to organ donation. A history of MTC with nodal involvement or distant metastasis is an unacceptable risk to organ donation.

Anaplastic thyroid cancer is a rare (approximately 2% of all thyroid cancers) and aggressive form of thyroid cancer that primarily occurs in people over 65 years of age.<sup>262</sup> All anaplastic thyroid cancers are Stage IV with a poor prognosis (5-year relative survival of 7%).<sup>262</sup> Any history of anaplastic thyroid cancer poses a unacceptable risk to organ donation.

Investigations	Risk	Tumour details	Organs to consider
For donors with a confirmed history of thyroid cancer, obtain all data about staging, histology, past therapy, type of follow-up or recurrence-free time before considering for organ donation.	Minimal (<0.1%)	Papillary thyroid microcarcinoma (micro PTC)  Differentiated thyroid tumours ≤4cm in greatest dimension limited to the thyroid (T1-T2), with no spread to the lymph nodes (N0) and no metastasis (M0)	All organs can be considered for transplantation
	Low (0.1%-<2.0%)	Newly diagnosed differentiated thyroid cancer >4cm (T3, M0)  Donor history of differentiated thyroid cancer >4cm that has spread into the neck (T4), treated with total thyroidectomy and ≥2 years cancer-free survival	All organs may be considered for donation with the informed consent of the recipient
	Intermediate (2.0%-<10%)	Differentiated thyroid cancer with extensive spread (T4a) with <2 years cancer-free survival  Donor history of medullary thyroid cancer Stage I or II (N0, M0), treated with total thyroidectomy and >5 year cancer-free survival	May be acceptable for some organ types and recipients. Consider on a case-by-case basis, taking into account cancer free duration, treatment and follow-up history
	High (≥10%)	Differentiated thyroid cancer with aggressive histology or angio-invasion (T4b) with <2 years cancer-free survival  Donor history of medullary thyroid cancer Stage III or IV (N0/M0), treated with total thyroidectomy and >5 year cancer-free survival	May be acceptable in exceptional circumstances e.g. where the recipient faces an imminent threat to life. Consider on a case-by-case basis after discussion with an oncologist and obtaining informed consent from the recipient
	Unacceptable risk	Newly diagnosed medullary thyroid cancers, or history of medullary thyroid cancer with nodal involvement or distant metastasis.  Any history of anaplastic thyroid cancer (diagnosed at procurement or in the donor history)  Other cancers of the thyroid, including thyroid lymphomas, thyroid sarcomas and other rare tumours.  History of treated thyroid cancer with incomplete macroscopic tumour resection.	None

#### 2.4.6.14 Urothelial carcinoma

Superficial, non-invasive papillary carcinoma of the bladder is not a contraindication to organ donation; however, it is important to establish that the cancer is low-grade before proceeding with donation. If urothelial cancer is diagnosed during procurement, the advice of a urologist should be sought in assessing the tumour prognosis/behaviour in the donor.

If urothelial carcinoma is present in the donor history, donors should only be considered if there has been strict follow-up after primary diagnosis and complete histological information is available, given the high risk of recurrence of these tumours. Risk of recurrence increases (i) with increasing Stage and Grade, (ii) with greater tumour diameter, (iii) where multiple tumours are present, (iv) where there have been one or more prior recurrences, and/or (v) where there is concurrent carcinoma *in situ*.<sup>271</sup> A history of muscle-invasive bladder cancer (T2 and above) poses an unacceptable risk to organ donation, unless there is documented evidence of prolonged cancer-free survival. It is possible that the risk of transmission is lower from donors who have previously had a cystectomy and/or chemoradiation and have been cancer-free for >5 years, after which point the risk of recurrence is very low for patients with T1 or T2 disease.<sup>272,273,274</sup> For patients with T3 or T4 disease, the risk of recurrence at 5-10 years post-cystectomy is higher, at around 5%.<sup>274</sup> However, no data are available on the outcomes of transplantation in such circumstances.

Investigations	Risk	Tumour details	Organs to consider
For donors with a confirmed history of thyroid cancer, obtain all data about staging, histology, past therapy, type of follow-up or recurrence-free time before considering for organ donation.	Minimal (<0.1%)	Single low-grade (Grade 1), low stage (Stage 0 – Ta/N0/M0) papillary urothelial carcinoma OR papillary urothelial neoplasm of low malignant potential (PUNLMP)	All organs may be considered for transplantation. Surveillance of kidney recipients recommended due to risk of field changes.
	Low (0.1%-<2.0%)	History of single, low-grade (Grade 1), Stage I (N0/M0) carcinoma	–
	Intermediate (2.0%-<10%)	History of non-muscle invasive low stage (Stage 0-I) high grade (Grade 2-3) urothelial carcinoma, treated with surgery and chemotherapy and with cancer free survival >5 years	Consider on a case-by-case basis for selected recipients after discussion with a urologist. Risk will vary depending on the organ transplanted (e.g. higher risk for kidneys).
	High (≥10%)	Muscle invasive urothelial cancer (Stage II-IV) treated with surgery or radiation +/- chemotherapy and cancer-free survival >5 years  Low-grade urothelial carcinoma diagnosed during donor procurement (other than PUNLMP)	May be acceptable in exceptional circumstances e.g. where the recipient faces an imminent threat to life.
	Unacceptable risk	All other muscle invasive urothelial cancer, all recent high-grade urothelial cancer, donors with a history of recurrent urothelial carcinoma, and/or urothelial carcinoma <i>in situ</i> (CIS)	None
	Unknown	Where a donor has a reported history of urothelial/bladder cancer, but critical information on cancer pathology is unavailable, donors should be considered unacceptable risk of cancer transmission.	None



#### 2.4.6.15 Uterus and uterine cervix cancer

Invasive uterus or uterine cervix cancer (Stage I or higher) diagnosed at the time of organ procurement poses an unacceptable risk to organ donation. For donors with a history of invasive uterus or uterine cervix cancers, transmission risk may diminish after a disease-free interval of >5 years, however there are minimal data from the literature to support a recommendation, and donors should be assessed on a case-by-case basis.

Pre-cancerous cervical cell changes pose little to no risk to organ donation. Low grade squamous intraepithelial lesions (previously graded as CIN1) usually disappear without treatment. High grade squamous intraepithelial lesions (previously graded as CIN2 or 3) and adenocarcinoma *in situ* are pre-cancerous changes but pose minimal risk of donor-derived malignancy transmission.

Investigations	Risk	Tumour details	Organs to consider
For donors with a confirmed history of thyroid cancer, obtain all data about staging, histology, past therapy, type of follow-up or recurrence-free time before considering for organ donation.	Minimal (<0.1%)	Adenocarcinoma <i>in situ</i> of the uterine cervix  High grade squamous intraepithelial lesions	All organs may be considered for transplantation
	Low (0.1%-<2.0%)	–	–
	Intermediate (2.0%-<10%)	–	–
	High (≥10%)	Invasive cancer of the uterus or cervix in the donor history with a cancer-free interval >5 years	May be acceptable in exceptional circumstances e.g. where the recipient faces an imminent threat to life.
	Unacceptable risk	Invasive cancer of the uterus or cervix diagnosed at procurement or in the donor history with a cancer-free interval <5 years	None
	Unknown	Invasive cancer of the uterus or cervix reported in the donor history with incomplete or no follow-up documentation available	None

#### 2.4.7 Haematological cancers

Current haematological malignancy poses an unacceptable risk to organ donation.

A recent donor history of treated leukaemia, lymphoma or plasmacytoma and <5 years recurrence-free survival is also an unacceptable risk to donation.<sup>275</sup> In the context of donors with a history of treated acute leukaemia or lymphoma and 5 or more years of recurrence-free survival, including childhood leukaemia and Hodgkin's lymphoma survivors, seek expert advice from a haematologist on likely transmission risk.

Utilisation of donors with a history of low-grade haematological malignancies and other clonal haematological disorders has been proposed for certain recipients.<sup>276</sup> These include monoclonal gammopathy of uncertain significance (MGUS) and myeloproliferative neoplasms (MPN) – including polycythaemia vera, essential thrombocythaemia and monoclonal B cell lymphocytosis – all of which have a long natural median survival<sup>277,278</sup> and are becoming more common among donors as the donor population ages. MGUS are found in approximately 4% of the population older than 50 and are usually benign and asymptomatic,<sup>279</sup> hence are likely to be present in many organ donors without consequence for recipients. There have, however been reported

instances of donor-derived lymphoproliferative disorders in recipients of solid organ transplants from donors with MGUS,<sup>280</sup> hence the risk associated with such donors is not negligible. Donors with a known history of MGUS may be acceptable in certain circumstances, following advice from a haematologist. There are no data on transmission risk and the outcomes of transplantation from donors with MPN. Given that the goal of MPN treatment is usually symptom control rather than cure, even in treated patients there remains the potential for clonogenic stem cells to be transmitted with donor organs. It is not known how a transmitted MPN would behave in the immunosuppressed recipient, hence transplantation of organs from donors with a history of MPN is not recommended.

## 2.4.8 Suspicion of malignancy transmission in an organ recipient

### 2.4.8.1 Actions in the case of suspected or confirmed donor-transmitted malignancy

The potential for donor-derived malignancy may be identified at any one of three points on the donation pathway:

1. Before organ retrieval (during donor assessment and workup)
2. At organ retrieval (e.g. neoplasia discovered during retrieval surgery)
3. After the transplantation of at least one organ.

When malignancy is detected in the *donor* during workup, surgery, pretransplant organ preparation, or in the immediate post-transplant period, this is an urgent issue requiring immediate notification of all affected transplant units, DonateLife and eye and tissue banks.

In cases where organs have already been transplanted and histology reveals a malignancy (e.g. incidental cancer in a lung lobe discarded due to size reduction), a full donor autopsy should be requested whenever possible to obtain detailed information about tumour origin and dissemination. This will not be necessary in cases of small primary renal cell carcinoma found in one kidney, which would not preclude the transplantation of other organs.

Early diagnosis of donor-transmitted malignancy (within 6 weeks of transplantation) is associated with better survival outcomes. Analysis of the UK transplant registry found that 20% of recipients with a donor-derived cancer of the transplanted organ died as a direct result of cancer; however, where the donor transmitted cancer was detected early, there were no deaths related to the donor transmitted cancer.<sup>153</sup>

Where the possibility of a donor-derived cancer is identified in a recipient at some time after transplantation, DonateLife and Organ Donation New Zealand need to be informed as soon as possible and the origin of the cancer investigated.

Optimal recipient management in the event of a donor transmitted malignancy will depend on the type of tumour, the organ transplanted, the time from transplantation to diagnosis and the patient's immunosuppression regimen. How to proceed will be a joint decision of physician and recipient.

**Table 2.11:** Actions in the event of confirmed diagnosis of donor malignancy

Point in pathway	Diagnosed how	Actions
1 Before organ retrieval	Malignancy identified during donor assessment and workup	<p>If donors are accepted despite malignant neoplasia:</p> <ul style="list-style-type: none"> <li>• Detailed histological reports, staging and imaging studies as well as all information and actual diagnostic findings are to be documented on the donor information form;</li> <li>• Oncologist advice can be sought (may lead to recommendation for further tests, autopsy etc.);</li> <li>• Transplant centres may take decision to accept the organs;</li> <li>• Obtain informed consent from the recipient/their family prior to transplantation;</li> <li>• Carry out careful follow-up, bearing in mind the possibility of transmission;</li> <li>• Report any possible transmission as per local and national reporting requirements.</li> </ul>
2 At organ retrieval and before transplantation	Neoplasia incidentally found during organ retrieval surgery	<p>Immediately perform frozen section for preliminary diagnosis, subsequent work-up to be done for definite diagnosis;</p> <ul style="list-style-type: none"> <li>• Immediately alert all relevant transplant units;</li> <li>• Transplant units may take decision to accept the organs;</li> <li>• Oncologist advice can be sought (may lead to recommendation for further tests, autopsy, etc.);</li> <li>• Obtain informed consent from the recipient prior to transplantation;</li> <li>• Carry out careful follow-up, bearing in mind the possibility of transmission;</li> <li>• Report any possible transmission as per local and national reporting requirements.</li> </ul>
3 After transplantation of at least one organ	<p>a) Frozen section misinterpreted as benign, final diagnosis malignant, or</p> <p>b) neoplasia incidentally found during pre-transplant preparation of the organ in the recipient centre (other organs already transplanted), or</p> <p>c) donor autopsy results available after procurement and transplantation of organs indicate neoplasia, or</p> <p>d) diagnosis in recipient at any time after transplantation.</p>	<ul style="list-style-type: none"> <li>• Immediately alert donation agency, relevant transplant units, eye and/or tissue banks;</li> <li>• Report any possible transmission as per local and national reporting requirements;</li> <li>• Oncologist advice can be sought; include consideration of donor autopsy to identify origin and extent of the primary tumour (not necessary in case of solitary, completely resected small renal cell carcinoma pT1a)</li> <li>• Joint decision of physician and recipient about further action (removal, therapy) on the basis of a risk–benefit analysis;</li> <li>• Carry out strict follow-up.</li> </ul>

## 2.5 Risks related to other donor conditions

In addition to the risks of donor-derived infection and malignancy, other pre-existing conditions in the donor may be transmitted via organ donation, including some genetic diseases, allergies, and autoimmune diseases. It is critical that any such conditions are thoroughly characterised and conveyed to transplant units as they may influence general donor medical suitability, the suitability for transplantation of specific organs, or require transplant recipients to take particular preventative measures or receive specific treatments.

### 2.5.1 Inherited or congenital disorders

There are inherited and genetic diseases which can be transmitted to recipients, depending on the organ transplanted.<sup>1281</sup> Other genetic diseases may significantly compromise the function of the organ to be transplanted or cause connective tissue disorders, haematopoietic disorders, or predisposition for malignancy. The possibility of an underlying inherited or congenital disorder should be considered in donors with coagulation disturbance (see below), haemochromatosis, mitochondrial deficiency or mental disorder not related to infection, poisoning or malignancy. Presence of an inherited or congenital disorder in the donor must be defined as clearly as possible and communicated to the transplant programs. ALL known gene abnormalities should be communicated and considered in terms of risk of their transmission and degree of organ damage. If the transplant programs are uncertain about how to proceed, then specialist advice should be sought.

While it is beyond the scope of these guidelines to consider all potential inherited or congenital diseases that may affect the donation decision, some key examples are considered below.

#### Ornithine transcarbamylase (OTC) deficiency

OTC deficiency is an example of a latent genetic disorder which may cause cerebral oedema leading to brain death. The onset of such an event can occur in childhood or later in life and may be precipitated by high protein consumption or unusual exercise. Hyperammonaemia is a key feature and should be measured in any patient with cerebral oedema without a clear cause. Transplantation of the liver from a donor with OTC deficiency carries a high risk of recipient fatality through cerebral oedema and is absolutely contraindicated, though other organs may be safely transplanted.<sup>282,283,284</sup>

#### Alpha-1-antitrypsin deficiency

Recipients of livers from donors with Alpha-1-antitrypsin deficiency are very likely to develop cirrhosis or fibrosis within months to years of transplantation, necessitating re-transplantation. Organ donation is possible, excluding liver and lung donation in the case of emphysematous patients.<sup>285</sup>

#### Marfan syndrome and related conditions

Due to the impact of Marfan syndrome on vessel walls and the potential for arterial anastomosis failure, organ donation is generally not recommended from donors with this syndrome.<sup>286</sup> Donation of the heart, heart valves, and tissues is absolutely contraindicated, while the utilisation of other organs would require careful consideration. A diagnosis of Marfan syndrome or any other known genetic collagen vascular disorders must be communicated to the transplant programs to allow for careful surgical decision making.

### 2.5.2 Coagulation disorders

Donation of non-liver organs may be considered from donors with inherited coagulation disorders. Liver transplantation is unlikely to be acceptable, although this depends on the nature of the gene defect and the individual risk-benefit assessment given the transplant urgency and likelihood other offers for a particular recipient. In the case of a donor with antithrombin III (ATIII), protein C, protein S or Factor V Leiden deficiency, the defect will be transmitted and the risk of serious thrombotic events in the recipient is increased.<sup>287</sup> If liver transplantation is to go ahead, recipients must be willing and able to receive anti-coagulation therapy after transplantation. Any severe form of inherited bleeding disorder such as haemophilia A, B or von Willebrand disease would generally contraindicate liver donation.

Autoimmune-related bleeding or pro-coagulant disorders may also influence suitability of organs for transplantation. Liver transplantation is absolutely contraindicated if high levels of factor VIII inhibitor are detected in the donor prior to organ procurement.<sup>288</sup> A person dying as a result of catastrophic clot arising from anti-phospholipid syndrome would generally be unsuitable due to the risk of thrombosis in donor organs. However, a history of anti-phospholipid syndrome in itself would not contraindicate donation with decision making guided by the severity of the disease.

### 2.5.3 Allergy and anaphylaxis

Where a potential donor has died from anaphylactic allergy to a known allergen, or has a well-known history of serious allergic reactions, this information needs to be communicated to transplant programs and the recipient informed. Passive transfer of type 1 hypersensitivity reaction from donor to recipient has been reported following liver, lung, intestinal, kidney and heart transplantation.<sup>289,290,291,292,293,294</sup> Although the exact mechanism of this transfer is unknown, the risk of allergy transfer is higher the more lymphoid material that is transplanted, and is therefore greatest in the case of liver, lung, pancreas and intestinal transplantation.<sup>295</sup>

Recipients of organs from donors with a history of allergy and/or anaphylaxis may experience reactions to the same allergens for at least the first 3-6 months post-transplant and must be taught how to avoid such allergen exposure – especially food allergies such as peanut allergy – when the donor history includes anaphylactic reactions.<sup>296</sup>

### 2.5.4 Autoimmune disease

Donor history of autoimmune or chronic systemic diseases should be conveyed in detail to the transplant programs, as organ function can be affected and may influence suitability for transplantation. Organs from donors with autoimmune diseases can be used for transplantation after exclusion of significant organ damage and/or infections associated with immunosuppressive treatment of autoimmune disorders.

Certain autoimmune diseases may be transmitted by organ transplantation, such as immune haemolytic anaemia and autoimmune thrombocytopenia, via the transfer of passenger lymphocytes from the donor to the recipient. This usually occurs in the context of liver or lung transplantation, given the greater number of lymphocytes transferred with these organs, but has also been observed in kidney transplantation.<sup>297,298</sup> In many cases this occurs without symptoms, since immunosuppression is also part of the treatment of autoimmune disease. In some cases, however, post-transplant immune-mediated haemolysis can occur, leading to anaemia in the recipient. The potential for immune-mediated haemolysis in the recipient does not preclude organ donation, although the presence of known erythrocyte antibodies in the donor (such as ABO O donor to A or B blood group recipients) indicates prospective monitoring of recipients would be reasonable.

### 2.5.5 Poisoning

Poisoning is generally not a contraindication to organ donation – people who have died with, or as a result of, drug toxicity or poisoning can become donors. Depending on the agent, organ function can be affected, which may limit the organs which are suitable for transplantation. The decision about whether to proceed depends on whether the organ being considered is functioning adequately, and assessment should be on an organ-by-organ basis. Most drugs and toxins will have been metabolised and excreted prior to organ donation and therefore residual toxicity to the recipient is not routinely a concern.

In the case of some poisoning agents – pesticides in particular – there may be a risk of delayed organ failure, primarily affecting the liver.<sup>299</sup> If the poisoning agent is unusual or if there is uncertainty regarding the impact on organ function, seek toxicology advice.

## 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 the kidneys 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

## 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 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>300</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.

## 2.8 Vigilance and Surveillance

The *Australian Vigilance and Surveillance Framework for Organ Donation for Transplantation* was endorsed by the Australian Health Ministers' Advisory Council in 2015. This framework provides a national system for the collection, collation and analysis of adverse outcome data, with the goal of identifying areas for national practice improvement to optimise the overall safety of organ donation and transplantation within Australia.

The National Vigilance and Surveillance system works in parallel with the existing jurisdictional clinical incident management systems. The clinical management and investigation of serious adverse events and reactions (SAERs) remains the responsibility of the hospital and jurisdictions in which the incident occurs. States and territories continue to be responsible for local reporting processes including communication with associated clinicians and patients, investigation of the incident; and the response to an incident including feedback, local policy and clinical practice review. While cases of donor derived disease transmission are rare, the immediate reporting and investigation of any post-transplant infection in the recipient and the notification of the donation agency and other recipients from the same donor is imperative to prevent/minimise harm to those exposed.

A key component of the Organ and Tissue Authority (OTA) National Vigilance and Surveillance System is the Vigilance and Surveillance Expert Advisory Committee (VSEAC). VSEAC is a multi-disciplinary committee that reviews, assesses, and grades all reported SAERs. The collation and analysis of adverse event data informs the advice VSEAC provides to OTA regarding identified risks, emerging trends, and recommendations for clinical practice improvements in the sector.

Further information can be obtained by emailing [saen@donatelife.gov.au](mailto:saen@donatelife.gov.au).

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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 2.2 (SOP001/2021)*. 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 and Intestinal Transplant Registry (ANZLITR) and the Australian and New Zealand Islet and Pancreas Transplant Registry (ANZIPTTR), record and report on organ donation and transplantation activities and outcomes within Australia and New Zealand.

Through these registries,<sup>1,2</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.

### References

- 1 <http://www.anzdata.org.au>
- 2 <http://www.anzlitr.org>

# 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 87.5%; 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. This compares with an average survival of less than two years for eligible patients who do not receive a heart transplant.<sup>1</sup>

Current Australian estimates are that 30 000 patients are diagnosed with incident heart failure annually and that close to 500 000 people are living with long-standing chronic heart failure (CHF).<sup>2</sup> Between 2006 and 2011, deaths from CHF in Australia rose by 20%.<sup>3</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>4</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 2017, 124 heart transplants were performed across Australia and New Zealand. 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 25:1. For this reason, heart transplantation is offered only to patients who have:<sup>5,6</sup>

- End-stage heart disease
- Exhausted all alternative treatment options, and
- An expected survival benefit, 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>7</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>7</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 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 ( $\text{VO}_2$  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 renin-angiotensin-aldosterone system inhibitors (ARNI, ACEI or ARB), 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>8</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>9</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>7</sup>

- Advanced CHF symptoms (NYHA 3 or 4) refractory to optimal treatment
- Severe left ventricular systolic or diastolic 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 30% of heart transplants are performed in patients who are supported with a VAD. 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. 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>10</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 73 years of age. 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>11</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>5,6</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 post-transplant survival, or preclude active rehabilitation after transplantation.<sup>5,6,12</sup>

Major exclusion criteria for heart transplantation are as follows:

Active malignancy:<sup>5,13</sup> An active malignancy, other than non-melanoma skin cancers, is usually a 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>14</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>5,14</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>14</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>15-17</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>15</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>17</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>18</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>19,20</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 been gained 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>19</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>21,22</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>23-26</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>25</sup>

Active substance abuse:<sup>26,27</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>27</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>28</sup>

Irreversible degeneration/damage of other organ systems:<sup>5,6</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>29-31</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>11,12</sup> hyperbilirubinaemia >50 mmol/L,<sup>11</sup> intractable ascites with hypoalbuminaemia,<sup>32</sup> and fixed pulmonary hypertension with transpulmonary gradient (TPG) >15 mmHg or pulmonary vascular resistance (PVR) >4 Woods Units after pulmonary vasodilator challenge.<sup>11</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>11,12,32</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>33,34</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>34,35</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>35</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>36</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>11</sup> The results of heart retransplantation for acute rejection and early graft failure are extremely poor.<sup>11,37</sup> These patients should generally not be considered for retransplantation. On the other hand, 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>11</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>38</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>39</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>40</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>40</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 the onset of systemic hypotension [systolic blood pressure <90 mmHg] to the 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>40</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>41</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). For paediatric heart donors, refer to Chapter 11 for information on acceptability and allocation criteria. 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>42</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>43</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 SOP001/2021 V2.2].

#### 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: Matching criteria for heart donation. 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>44</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>45</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>29-31</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>22,46-48</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>49,50</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 anaemia 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, initial reports from several centres suggest that heart transplantation from hepatitis C, NAT negative donors is associated with very low risk of transmission of hepatitis C infection.<sup>51</sup> Heart transplantation from hepatitis C seropositive, NAT positive donors results in recipient hepatitis C infection, however this can be prevented by pre-emptive direct anti-viral therapy or cured by direct anti-viral therapy following virus detection in the recipient.<sup>52</sup> In the meantime, the use of donor hearts from hepatitis C positive donors should only be considered for wait-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>53,54</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>55</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>38,39</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 quality of life benefits from transplantation mean that some patients may still wish to receive a kidney transplant even if it might not increase their life expectancy.

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 donor numbers and characteristics, transplant outcomes, tissue typing technology, and improved allocation practices.

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.

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 the allocation of deceased donor kidneys to recipients who are very well HLA-matched—particularly highly sensitised patients (those with many HLA-antibodies) for who it is much harder to find an immunologically compatible donor. All kidney donors are therefore first considered against all patients listed in on the Kidney Transplant waiting list (TWL) program in OrganMatch. If a national match is found, according to the criteria for national allocation (see Section 5.4.2), donor kidneys are offered to the transplant unit of the waitlisted patient. 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 the state allocation algorithm (see Section 5.4.2).

### 5.1 Recipient eligibility criteria

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, 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 and 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 2019, the number of patients receiving maintenance dialysis in Australia was 13 931, with 3229 new patients commencing renal replacement therapy in that year.<sup>7,8</sup> Compared to 966 actively wait-listed patients at 31 December 2018, there were 866 kidney transplants from deceased donors in 2019.<sup>9</sup> In New Zealand there were 2868 patients on maintenance dialysis at 31 December 2019, with 656 new patients commencing renal replacement therapy in that year.<sup>7,8</sup> There were 130 kidney transplants from deceased donors in New Zealand in 2019.<sup>10</sup> 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 approximately 90%.<sup>10</sup>

Receiving a transplant has inherent risks associated with surgery and immunosuppression that need to be weighed up against the possible benefits. Patients need to be well informed by their clinical teams and accept their own individual transplant-related risks prior to listing.

Prior to 2018, it was an Australian requirement that patients have an 80% likelihood of survival at five years post-transplant to be eligible for deceased donor kidney wait-listing. This is no longer an absolute requirement.

Eligibility for deceased donor kidney transplant wait-listing in Australia now requires that potential kidney transplant candidates have a high likelihood of significant benefit from kidney transplantation. Any significant risk of death post-transplant, complications (e.g. from heart disease, vascular disease, cancer, infection) or general frailty would be a contraindication to kidney transplantation. This risk-benefit assessment is a clinical decision best made by a local multidisciplinary team experienced in managing both dialysis and transplant patients.

In New Zealand, an estimated 80% likelihood of survival at five years post-transplantation remains an eligibility requirement for deceased donor kidney transplantation. While this may be difficult to determine, New Zealand units use an algorithm to estimate survival probability.<sup>11</sup> These calculation tools are also used by other centres around the world to estimate an individual's post-transplant survival based on various factors.<sup>12</sup> These types of tools are increasingly being used to inform the decision-making process regarding eligibility for deceased donor kidney transplantation.

To ensure 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>11,12</sup> In several international programs, donor kidneys with greater estimated survival are preferentially allocated to recipients predicted to have a longer life-expectancy after transplantation; donor kidneys with shorter estimated survival are preferentially allocated to recipients predicted to have a shorter life expectancy. Acceptance of a kidney with shorted estimated survival is often with the expectation of a shorter waiting time. The goal of so-called “survival matching” is to optimise graft survival from a wide range of donors, while giving a wide range of people on dialysis the opportunity to benefit from transplantation. As of May 2021, the principle of “survival matching” has been introduced to the kidney matching algorithms in Australia. This is likely to be developed further in the future.

### 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 post-transplant patient and allograft survival. Factors that may influence graft survival include primary causes of end stage kidney disease that are likely to recur after transplantation (therefore resulting in premature graft failure), infection risk and concerns regarding non-adherence with immunosuppression.
- Age: although advanced age in the absence of significant medical comorbidity is not a contraindication to kidney transplantation, only 2.5% of the dialysis patients in Australia aged over 65 were on the waiting list for kidney transplantation at 31 December 2019 due to the high rates of comorbidities in this population.<sup>7,9</sup> A small number of patients over the age of 70 with limited comorbidities have been transplanted successfully.

### 5.1.2 Exclusion criteria

Criteria that are considered relative or absolute contraindications for deceased donor kidney transplantation wait-listing include:

- In Australia, if the perioperative and post-transplant risks outweigh the likelihood of deriving significant benefit from transplantation, and in New Zealand if there is a 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, infection risk and malignancies.<sup>13–18</sup>
- Cardiovascular disease: severe, non-correctable cardiovascular disease would be an absolute exclusion criteria. Lesser degrees of disease would also potentially contribute to a lower anticipated post-transplant survival, and hence would be considered a relative contraindication.<sup>19,20</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 post-transplant survival; such vascular complications would be a relative consideration.<sup>21,22</sup>
- Infection: uncontrolled infection is a contraindication to transplantation. Patients may be listed and transplanted once the infection has been adequately treated.

- **Malignancy:** active malignancies—other than non-melanoma skin cancers—are an absolute contraindication to kidney transplantation. However, patients with a history of malignancy deemed to be cured, 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 or other appropriate specialist (e.g. Urologist).
- **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 the risk of complications and survival after transplantation. These include but are not limited to, 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.

### 5.1.3 Assessment and acceptance

Patients referred for kidney transplantation (from kidney/dialysis units) should be initially assessed by the transplanting hospital team, with regular review of patients after listing to ensure ongoing medical, psychological and surgical suitability. Initial and subsequent patient assessments and decisions regarding acceptance onto the waiting list in OrganMatch and continued eligibility for listing should involve a transplant nurse, physician and surgeon. Only the Director of a transplant unit (or their delegate) has the authority to add or remove patients from the 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 recipients have received two or more kidney transplants. Only 1 – 2% of recipients receive a third or subsequent kidney transplant.

## 5.2 Waiting list management

The waiting list is comprised of patients who have been assessed by a transplant physician and surgeon and determined to be suitable to undergo kidney transplantation. Patients must be enrolled in the Kidney TWL program in OrganMatch in order to be matched with deceased organ donors. 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 (e.g. patients under 18 years of age; see Section 5.2.4). Once a patient is accepted onto the waiting list and enrolled in OrganMatch, blood samples are sent to the state tissue-typing laboratory. The status of transplant waiting list candidates is made “ready” when tissue-typing, HLA antibody screening and histocompatibility assessment (5.2.6) is complete. Once a patient’s status is “ready” in OrganMatch the patient can be matched with deceased organ donors. The total time from referral to a transplant unit 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 completed thoroughly than quickly. When calculating waiting time, periods of acute or temporary dialysis prior to the date that long-term dialysis was commenced do not contribute to waiting time.

In New Zealand, waiting time is calculated from the date of first activation on the waiting list or first dialysis, whichever comes later. Periods of suspension of active listing are still counted towards waiting time. Although waiting time does not accumulate pre-dialysis, patients can still be listed and pre-emptively transplanted if allocated a kidney based on the algorithm.

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 or return to dialysis (New Zealand) following failure of the previous transplant, whichever is later. Sometimes, a kidney transplant will fail very early or never function at all. When a deceased donor kidney transplant fails very early, as a result of technical issues or the poor quality of the donor kidney, it may be possible for the patient to retain their original waiting time credit (This would not apply in the case of graft loss due to non-adherence to treatment).

In Australia, if a kidney transplant fails within the first 12 months, the recipient is able to retain their original accrued waiting time credit when/if they are re-listed for a subsequent transplant. This makes allowance for kidney transplants that are performed but never functioned very well or had technical issues. Approval for reinstatement of waiting time in these circumstances needs to be obtained from the relevant state-based renal transplant advisory committee.

Live donor kidney recipients in whom the graft fails within the first 12 months post-transplant may be able to retain their previously accrued waiting time, if approved by the relevant state or national transplant advisory committees. This removes the risk of the possible loss of accrued waiting time as a disincentive to proceed with a live donor. The number of live donor kidney transplants that are lost in the first year are very low.

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.

### 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 a face-to-face assessment. It is expected that to remain on the waiting list a patient should continue to fulfil the same inclusion criteria as at 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's enrolment status to be changed to "onhold". On hold status is temporary. If a patient is no longer suitable for transplant, the enrolment must be ended in OrganMatch. For example, the development of un-correctable substantial cardiac disease would mean that a waitlisted person is no longer suitable and so their enrolment in OrganMatch would be ended. If however a patient had a treatable infection, such as peritonitis, their status would simply change to "on hold" until the infection resolved, provided no other changes occur that affect eligibility. 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. In OrganMatch a patient needs to be flagged with a State urgency index.

#### 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 2016), and have special needs with respect to physical and psychological development that are best met by transplantation.<sup>23,24</sup> In Australia, patients who are under the age of 18 years and have commenced dialysis are eligible for paediatric prioritisation under the National Interstate Exchange and State-based protocols. Once the age of 18 years old is obtained, the prioritisation ceases. Special application to state advisory committees can be made to extend this status. If this is the case, the patient's enrolment in OrganMatch is required to be updated.

Given this prioritisation, a range of kidneys of varying HLA-match and varying quality may therefore be offered. Transplant units need to weigh up the immunological and organ-quality implications of these offers. In some paediatric units both immunological exclusions (eplet based) and quality-based exclusions (e.g. setting an upper limit for donor age or donor co-morbidity) are being set for individual patients, and this approach is strongly advised. This will tend to increase the waiting time in favour of a kidney with a better immunological match and survival match (see “Emerging Issues”— section 5.7).

In New Zealand, patients under the age of 15 at the time of allocation receive paediatric prioritisation.

#### 5.2.5 Australian and New Zealand Paired Kidney Exchange (ANZKX) Priority

If the intended recipient of a kidney from a living donor matched through the Australian and New Zealand Paired Kidney Exchange (ANZKX)<sup>25</sup> is unable to receive that kidney but their co-registered living donor has already donated, the “orphan recipient” will be eligible for priority listing from the national deceased donor organ pool in their country of residence.

If the orphaned recipient is in Australia and pre-emptive (i.e. has not yet started dialysis) then an exception will be made so that these patients can be prioritised to receive a kidney from the deceased donor pool once approved by RTAC.<sup>26</sup> In OrganMatch, these patients are listed with National Urgency status.

If the orphaned recipient is in New Zealand, prioritisation for a deceased donor kidney will be discussed and approved by the New Zealand National Renal Transplant Leadership Team.

This ability to priority list ANZKX recipients in case of unforeseen circumstances safeguards the live donors and recipients participating in the ANZKX program. As of November 2020, with over 350 successful transplants through the AKX, NZKE and ANZKX programs, the need for this priority listing has not yet arisen.<sup>27</sup>

#### 5.2.6 Histocompatibility Assessment

Each recipient must undergo a series of tests performed at the state Tissue Typing laboratories. This includes the following:

- HLA Typing using molecular technique such as Next generation sequencing (NGS) at the following HLA loci – A , B, C, DRB1, DQB1, DQA1, DPB1, DPA1
- HLA antibody screening using Luminex single antigen beads

These tests will be used in the histocompatibility assessment by the Tissue Typing labs and in consultation with the clinical unit to assign Unacceptable antigens. These HLA antigens are then used as antigens for exclusion in the Kidney matching algorithm as they are deemed high risk to transplant patients across.



## 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>28,29</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>30,31</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 deceased donors undergo a detailed general assessment of medical suitability, which includes kidney function assessment through the patient's past and current medical history and medical investigations. In some cases, a kidney biopsy of the donor kidney is performed, which can be useful particularly in the case of donors who are older or have a history of diabetes, hypertension and vascular disease.<sup>32</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 (dual). This is to ensure that at least one patient can be transplanted with a successful outcome.<sup>32</sup>

For information on kidney donation from paediatric donors, see Chapter 11.

### 5.3.2 Donor-related risk

The quality of kidneys retrieved from deceased donors can vary significantly. Donor age may be anywhere from neonate to 75 years or above. In 2019, the mean age of deceased donors was 48.7 years in Australia and 47.4 years in New Zealand.<sup>33</sup> Donors aged over 65 years accounted for 17.5% and 17.6% of all deceased donors in Australia and New Zealand respectively.<sup>33</sup> Kidney function can also vary depending on the existence of any underlying disease processes in the donor (e.g. hypertension, diabetes or vascular disease). 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>28,29</sup>

The concept of a "Kidney Donor Risk Index" (or KDRI) has been developed in order to rank the quality of each donor kidney.<sup>34</sup> The KDRI is converted to a Kidney Donor Profile Index (KDPI) by remapping onto a percentage scale. Kidneys with a low KDPI 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 are donor age, donor kidney function, presence of diabetes or hypertension, cause of death, and donation pathway (brain death or circulatory death).

Within OrganMatch it is now possible for a patient with their nephrologist to indicate a specific maximum level of KDPI (KDPI max) that they are willing to accept.

It is important to note that in estimating kidney quality 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 states (e.g. Queensland and Victoria) use a consent form that is discussed with the patient and signed prior to listing, in order to better communicate the various risks and expectations of the transplant process.

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 transmission if there are factors in the donor history that increase their risk, even though screening tests may be negative
- Anatomical problems that may have been identified in the donor kidney
- Greater than usual immunological barriers 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 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 and New Zealand Paired Kidney Exchange Program, hepatitis C positive donors, increased viral risk donors (IVRD) and donors 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>11,35,36</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.

### 5.4.1 Principles

The principle intention of the allocation processes is to ensure all deceased donor kidneys are allocated to a recipient by a process that is transparent, equitable and standardised. Currently this is done according to the following criteria:

- Blood group compatible (e.g. A to A) and blood group acceptable (e.g. O to B) See Appendix C for ABO selection rules
- Waiting time (see Section 5.2.1)
- HLA matching (tissue typing to determine the level of immunological compatibility between a donor and recipient)
- HLA-antibody detection (which can identify unacceptable HLA antigens, and be used to preclude 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 equitable flow of kidneys between states and territories.

### 5.4.2 Australian Allocation Algorithms

An overview of the Australian allocation process is shown in Figure 5.1. The specific algorithms for national and state-based allocation protocols are transparent and available to all potential recipients (see Appendix C).

The first step of the allocation process is HLA Typing of donor kidneys to establish whether there is a recipient in any Australian state or territory who would receive a particular advantage or benefit from a specific kidney, based on a combination of their HLA-matching and unacceptable antigens. For these reasons, a proportion of kidneys are allocated based on immunological match according to the national allocation algorithm. In these situations, the kidney(s) may therefore be transported interstate. If not matched at the national level, the kidney(s) will be allocated according to the state algorithm of the state in which they were donated.

The national and state kidney allocation algorithms are complex and are continuously monitored and reviewed. 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.

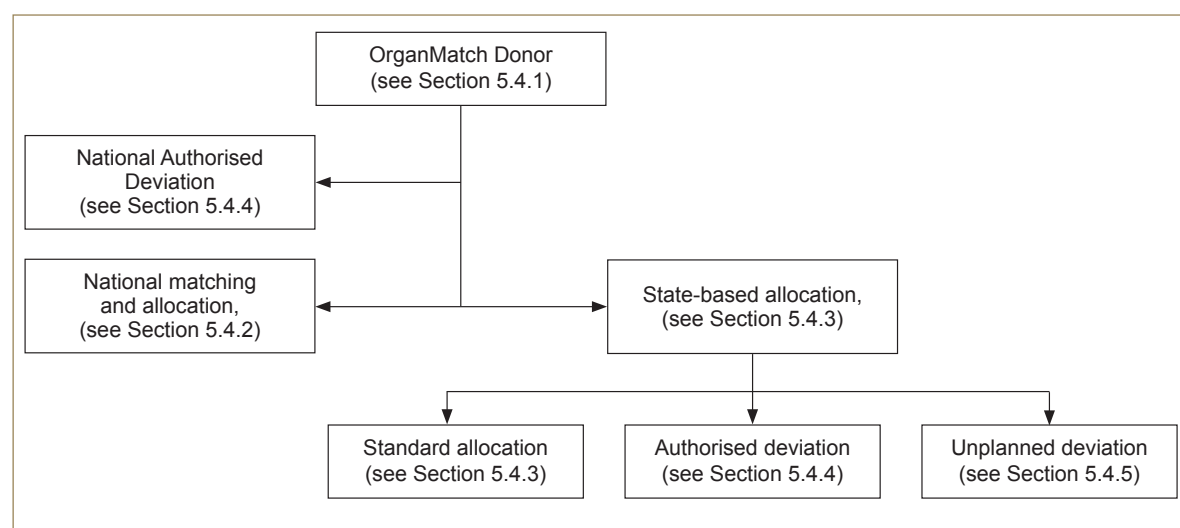
The updated algorithm, to be implemented in May 2021, gives preference to the highly sensitised waitlisted candidates, and so will likely initially result in an increased percentage of donor kidneys being allocated via the national algorithm.

For younger recipients who have longer life expectancies and thus may need more than one transplant in their lifetime, a good immunological match (if it is available) is considered more important than in older recipients, as this will help to minimise the formation of HLA antibodies that may lead to difficulties in finding a compatible subsequent donor 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.

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

The state algorithms are primarily based on waiting time and immunological matching, although to lesser degree than the national allocation (Appendix C). It is important to note that the majority of recipients overall do not receive highly immunologically-matched kidney as this is usually not possible. However, excellent graft and patient outcomes are still achieved

**Figure 5.1:** Flow diagram representing an overview of the pathway by which kidney allocation proceeds after initial matching within OrganMatch.



From a practical viewpoint, state-based allocation helps to minimise cold ischaemic time and allows for a more efficient use of local donation, laboratory, and retrieval team resources. There is good evidence that shorter ischaemic times improve transplant outcomes, especially for kidneys of lower quality. 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 to achieve the best use of these organs. 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>14,37</sup> Some of these state-based scenarios are described below in Section 5.4.4 (dual organ allocation) and Section 5.4.5.

#### 5.4.4 Authorised deviations in allocation

Kidney allocation algorithms allow 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>38</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 to a kidney-alone recipient. If, however, there are two highly-sensitised (and hence more difficult to match) kidney-alone recipients who have a very good immunological match (Level 1 or 2 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.

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.

Increased Viral Risk Donor (IVRD) Program: donors with recent increased infectious risk behaviours (defined in Section 2.3.1) proceeding to donation within the eclipse periods for detection of HIV, HBV and HCV by nucleic acid testing (NAT) (see Table 2.3) may be allocated to well informed and consenting recipients. Recipients that consent to transplantation from an increased viral risk donor accept the small but increased risk, compared to standard-risk donors, that HIV, HBV and HCV transmission may occur, due to undetectable levels of virus at the time of testing and/or false-negative results.

Dual organ allocation (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’ or ‘enbloc’ 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. This may also occur with the use of very small paediatric donors (for details see Chapter 11). 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 is fully informed of the risks and benefits of dual allocation.

Exceptional circumstances arising in the Australian and New Zealand Paired Kidney Exchange (ANZKX) Program:

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

- 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 of a problem such as 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 in the country that the kidney is located in at the point it is orphaned. Kidneys in transit between countries will be allocated in the country of arrival. Under some circumstances input from RTAC/ANZKX Clinical Oversight Subcommittee (RACOS) might be sought if required. In Australia, the allocation of the kidney will take into account the current location of the kidney, whether there are any potential recipients at level 1-3 on the National Allocation formula and the logistics of transporting the kidney, as described in the ANZKX National Protocol. In New Zealand, the kidney will be allocated according to New Zealand's National Kidney Allocation Scheme (NKAS).
- Orphaned recipient—this is a situation where a living donor kidney allocated to a recipient in the ANZKX program is surgically removed but is unusable, damaged, lost, or unable to be implanted into the intended paired recipient, even though the co-registered living donor for that recipient has already successfully donated to the other recipient in the paired exchange. This also includes the situation in which a kidney is damaged, the damage is identified by the recipient transplant surgeon prior to implantation and the kidney fails early after transplant. New Zealand and Australia will be responsible for the subsequent allocation of a kidney to an orphaned recipient enrolled in their country. In Australia, the ‘orphaned recipient’ will receive priority listing on the transplant waiting list (Level 3-4 interstate exchange) for a suitable kidney from the national deceased donor organ pool. In the case of a very highly sensitised recipient (very high calculated panel reactive antibody level) who is likely to be difficult to match, the degree of prioritisation can be altered following discussion with RTAC. Given that pre-emptive recipients are not on the deceased donor wait list in OrganMatch, approval will be sought from RTAC to allow orphaned pre-emptive recipients to be made active on the transplant waiting list and receive priority allocation. In New Zealand, prioritisation for orphaned recipients is defined in the NKAS algorithm.<sup>39</sup>

These agreements have been made with the approval of the Organ and Tissue Authority, New Zealand's National Renal Transplant Leadership Team, and RTAC endorsement. (For more information on the ANZKX, see the following link: <https://donatelife.gov.au/ANZKX>)

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. Requests for multiple organ retrieval are made via each state's transplant advisory committee. The organs in these cases are usually allocated within the donor state (see also Section 5.6).

#### 5.4.5 Unplanned (exceptional) 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 are followed as far as possible and, if not, that the reasons for deviations are 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 ischaemic time: if there is a prolonged cold ischaemic 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 needs 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, who understands the additional risks of possible cancer transmission and surgical complications.<sup>40</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, very rarely, someone who is close to needing dialysis but has not yet commenced and is deemed suitable to receive the organ.

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

In rare cases, when a kidney is required to be removed from an otherwise healthy individual with a kidney-specific disorder (eg. a small tumor) and the kidney is otherwise, the patient may indicate a wish to donate that 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 according to the state-based allocation algorithm. 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. These patients are flagged in OrganMatch as “willing to accept TRK”

Non-directed altruistic donors (NDAD) are living donors who come forward wishing to donate a kidney but without an identified recipient. NDAD are fully assessed medically, surgically and psychologically as per standard protocols.

In Australia, if they are deemed suitable their donated kidney will be allocated according to the policy of the relevant state transplant advisory committee. This is either initially to a recipient at National Allocation Level 1-3 on the transplant waiting list and then, if there is no such recipient, through the ANZKX program or directly through the ANZKX program. If allocated through the ANZKX program, a chain of transplants will be performed with one donor kidney remaining at the end of the chain. This kidney is then allocated by OrganMatch to an Australian recipient on the deceased donor transplant waiting list as per ANZKX guidelines. This recipient on the transplant waiting list should be within the state of the NDAD if possible.

In New Zealand, the National Renal Transplant Leadership Team encourages units to consider entering suitable NDAD into the ANZKX. If NDAD donate directly, they are allocated according to the NKAS. If NDAD donate into the kidney exchange, the kidney at the end of the chain is allocated as a NDAD within the NKAS.

## 5.5 Allocation: New Zealand

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

Kidneys must be offered to recipients according to the rules specified under the New Zealand Kidney Allocation Scheme. For details, visit:

<https://www.health.govt.nz/about-ministry/leadership-ministry/expert-groups/national-renal-transplant-service/nrts-papers-and-reports>

## 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.

Some patients may be considered for multi-organ transplantation prior to reaching end-stage kidney disease, but will have significantly reduced kidney function to warrant a combined transplant.

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 or have started to be incorporated into the updated and future Australian kidney allocation protocols in the near future.

The latest version of the Australian kidney matching algorithm (KAv2) addresses to varying degrees the following issues which were previously flagged as emerging issues (in guideline version 1.5).

### 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. 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. KAv2, provides increased priority matching for potential recipients that are highly sensitized.

## 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>11,12</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 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

Kidney transplantation is one way that patients 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. The KAv2, has made a first small step in this direction, by initially preferentially allocating well matched kidney donor offers to waitlisted candidates with relatively longer estimated post transplant survival.

Future version of the Australian Kidney allocation system will look to more extensively include these and potentially other factors to optimise the utility and equity of the scarce resource of donor organs, in order to maximise outcomes for transplant recipients.

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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 2017, five-year survival among liver transplant recipients in Australia and New Zealand was 78%, while waiting list mortality was approximately 2%.<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. Minimal listing criteria are therefore 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 – 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 limited 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: Calculation of MELD, PELD and HCC MELD scores<sup>a</sup>).

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: Calculation of MELD, PELD and HCC MELD scores<sup>a</sup>)<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. tumour not >6.5 cm in diameter and total diameter of all tumours not more than 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 would be an 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—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;<sup>8</sup> 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.

There has been a gradual refinement of diagnostic radiological features of HCC that includes multiphase CT, dynamic contrast enhanced MRI and advanced techniques in MRI such as diffusion weighted imaging and the use of hepatocyte-specific contrast agents.<sup>17</sup> Other tumour markers such as Golgi glycoprotein 73 (GP73) 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 guiding liver allocation 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 work out how to prioritise such patients on their own individual 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. This can happen 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 usually 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

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**Category 1**

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.

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**Category 2**

When a donor liver becomes available, discussion occurs between the urgent listing unit and the local retrieving unit to determine optimal allocation

**Category 2a** 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.

**Category 2b** 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.

**Category 2c** 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.

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## 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 (see Chapter 2).

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 CT scanning or 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).



## Use of HCV infected donor livers into HCV negative recipients

The use of HCV-positive liver donors for HCV-positive recipients has been accepted practice.<sup>21</sup> With the recent introduction of direct-acting anti-viral (DAA) therapies for HCV, yielding cure rates of greater than 95%,<sup>22,23</sup> transplantation with a liver from an HCV-NAT positive donor might now also be considered for HCV-negative recipients who are at high risk of dying on the waiting list or delisting due to progression of liver failure or tumour.<sup>i</sup> However, an HCV-NAT positive donor will transmit HCV infection to the recipient, who should be treated with DAAs in the early post-transplant period.<sup>20</sup>

Issues that need to be considered when using HCV-NAT positive livers in HCV-negative recipients:

### 1. Possible chronic damage in HCV positive livers

Chronic HCV infection in many patients is a mild illness and HCV-positive livers are currently used in HCV-NAT positive recipients. The possibility of an HCV-positive donor liver having chronic damage from the infection requires evaluation by an experienced donor surgeon and will require frozen section biopsies.

### 2. Donor hepatitis C genotype

Pan genomic direct acting anti-viral drugs are so effective that HCV genotype has become less important in the allocation and possible use of an HCV-NAT positive donor liver.

### 3. Increased donor HIV risk

The circumstances of death in a donor actively infected with HCV may carry a small risk of transmitting HIV infection. However, this risk is mitigated by NAT testing and a good donor social history.

### 4. Monitoring of HCV dynamics post-transplant

Transplantation of an untreated HCV-NAT positive recipient will result in re-infection of an HCV-negative allograft within the first 24 hours post-transplant,<sup>24</sup> and maximum replication of virus occurs somewhere between one and three months post-transplant. Recurrence of HCV is universal. The infection is more aggressive and can result in liver failure within 6-12 months.

Viral replication is accelerated by immunosuppression, and therefore monitoring of HCV loads in the weeks after transplantation is routine.

The genotype of a previously infected HCV-positive recipient should be checked following transplantation with an HCV-NAT positive donor liver.

### 5. Commencing Directly Acting Antivirals (DAA) post-transplant

The Gastroenterological Society of Australia has recently published a consensus statement on the management of HCV after liver transplantation, recommending that, when possible, treatment should be initiated early after transplantation to prevent fibrosis progression. The decision to treat actively infected patients on the waiting list should be made on a case by case basis and can be commenced pre- or post-transplantation. The treatment regimen and the duration of treatment should be based on current recommendations for the treatment of compensated and decompensated cirrhotic patients.<sup>20</sup>

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i The types of recipients that might be considered for transplantation with a liver from an HCV-NAT positive donor include:

- 1 Patients with Fulminant Hepatic Failure
- 2 Patients with severe end-stage liver disease largely based on MELD score although other features of liver disease (such as encephalopathy, Hepatorenal syndrome) may justify use in patients who have been on the waiting list for a period of time without receiving donor organ.
- 3 Patients with low MELD scores and hepatocellular cancer where there is progression of the hepatocellular cancer ( but still within transplant criteria).The use of such hepatitis C positive donors may minimise progression of HCC in this situation and withdrawal of patients from the waiting list
- 4 Possible expansion to all recipients would be considered following a review of Australia and New Zealand and or international data as it becomes available (certainly within the first 12 months following introduction). ANZ data on all cases would be reported to the ANZ Liver Transplant Registry)

## 6. Legal issues

The risks and complications of an HCV positive organ and post-transplant anti-viral therapy need to be discussed with potential recipients to ensure informed consent is obtained. Clinicians should refer to their own jurisdictional governance and legal authorities for advice where there is a lack of clarity or policy direction in relation to informed consent.

### Summary

Transplanting HCV-NAT positive livers into HCV-negative recipients has risks that need to be explicitly discussed during the consent process with potential recipients, in particular:

- underestimation of liver fibrosis in the donor liver, and
- the very small possibility of transmitting other infections such as HIV if the donor death occurs during the window period for this infection e.g. recent intravenous drug use.

Given the above, it seems reasonable that an HCV-NAT positive donor liver with minimal fibrosis could be transplanted safely into a consenting HCV-negative recipient with the plan to treat with DAAs as soon as practical post-transplant. The predicted cure rate of HCV infection with DAAs is currently greater than 95%, however the risk of transplanting HCV-NAT positive donor livers into HCV-negative recipients is low but not zero. Therefore, at the present time, such donor livers can be considered for transplantation into recipients where the risk of not receiving that transplant is greater than the risk of waiting longer for another donor liver offer.

### Technical considerations

There is emerging use of very small liver donors, including neonatal donors. For advice on paediatric liver donation and allocation, see Chapter 11.

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 lessor relevance in liver transplantation and hence tissue cross-matching is not routinely 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 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.

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<sup>ii</sup>
- 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.

ii 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 splitting may be deferred.

### 6.5.3 Paediatric donor liver allocation

Paediatric organ donors comprise approximately 5% of all organ donors in Australia and New Zealand, however there is a consensus amongst the liver transplant units and the public in Australia and New Zealand that the allocation of paediatric grafts involves considerations that are separate from the adult 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. To do otherwise would potentially deny the possibility of finding an ideal donor for an older child (for whom it can be 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. For detailed recommendations on paediatric liver donation and allocation, see Chapter 11.

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 necessary to consider the list of all children waiting for liver transplantation in Australia and New Zealand to achieve the goal of allocating paediatric donor livers to paediatric recipients. There is in effect a defacto paediatric national wait list for children activated for liver transplantation.

Paediatric donor livers will only be considered for adult recipients in only two circumstances. If the donor is not accepted or not suitable for a paediatric recipient within Australia or New Zealand or in the occasional situation of a very sick dying potential adult recipient. Use of a paediatric donor liver in this later circumstance will be discussed and only proceed if there is a consensus.

### 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, when no suitable local recipient can be identified, the liver will be offered on to other units around Australia and New Zealand for allocation under an agreed rotation.

## 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 been transplanted into 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>21</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, with an occasional 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. However, survival for current hepatitis B-infected recipients treated with the newer antiviral drugs exceeds survival among recipients transplanted for many other indications.<sup>1</sup>

A similar shift in practice and patient outcomes is now being observed for patients with active HCV infection, as a consequence of the recent development of highly effective antiviral agents for HCV infection. Previously, patients undergoing liver transplantation for HCV would universally infect their transplanted liver. If the transplanted liver failed, then re-transplantation was usually not offered because subsequent second and third grafts had an even higher failure rate due to rapid recurrence of HCV-related liver disease. With the introduction of effective therapy to eradicate HCV infection, such patients are no longer at risk of losing their graft from HCV recurrence, and retransplantation is not an issue.

The incidence of HCC is forecast to continue to rise for the next two decades, translating into increased demand for liver transplantation. There is a possibility that HCC patients might place such a demand on the waiting list in the future that transplantation opportunities for other patient groups would be compromised. The specific difficulty is how to prioritise 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 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 more dynamic 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 is 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>1,3-7</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<sub>2</sub> >50 mmHg and/or PO<sub>2</sub> <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 up to 70 years	Paediatric donors as small as 8kg may be suitable lung donors (see Chapter 11)
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 and for small paediatric lung donors
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 minor 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.

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.

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

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.

**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>20,21</sup>

### 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>20,23-25</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. For allocation of lungs from paediatric donors, see Chapter 11.

## 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 5.1.2)
- 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 µmol/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
- Creatinine clearance <75 mL/min/1.73 m<sup>2</sup>
- Serum creatinine >130 µmol/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	>25 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: Donor information required and donor suitability criteria for solid pancreas donation and Table 8.2: Donor information required and donor suitability criteria for islet cell donation. 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 (in the case of paediatric donors, only DBD donors are suitable for pancreas donation – see Chapter 11). Suitability criteria for pancreas donation from DCDs are given in Table 8.3: Extended suitability criteria for pancreas donation after circulatory death<sup>24,27</sup>.

**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 is 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: Causes of intestinal failure.

**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	Aganglionosis	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 initial 52 patients 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 2018

Ninety-four patients have been referred to Melbourne since the intestinal transplantation service was established in 2010, including 65 adults (mean age 40 years) and 29 children (mean age 6 years). Sixty-seven percent 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).

Seven patients (7%) have so far died prior to transplantation, while awaiting transplantation or during the assessment period. Causes of death included sepsis and intracranial bleed.

Seven patients (four adults, three children) have undergone intestinal multivisceral transplantation (in all but one cases combined with liver transplantation). All achieved enteral autonomy. Patients are eight months to eight years post-transplantation. There has been one death due to respiratory failure with a functioning graft at three months post-transplant.

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

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 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.

Donors and recipients need to be size-matched because of the limited abdominal space. Donors should be between 50% and 100% of recipient weight. 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 at the Melbourne unit in the near future. Only DBD paediatric donors are suitable for intestinal donation (see Chapter 11).

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>

\* “Ability to form a therapeutic alliance” refers to 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: Patient assessments required prior to listing for hand transplantation.

**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)
- 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: Recipient inclusion and exclusion criteria specified under Brigham and Women's Hospital protocols for face transplantation,<sup>4</sup> adapted for the Australian context., 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: Inclusion and exclusion criteria for hand donation. 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 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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# Part C

## Special donor groups

# 11 Paediatric donors

## 11.1 Paediatric donor eligibility

All children who die in intensive care should be considered for potential organ donation.

The overall rate of organ donation in children is similar to that in adults; however, this rate declines below two years of age.<sup>1</sup> This is due to a combination of factors – primarily medical unsuitability and age and weight limits for procurement and transplantation.

Clarity regarding donor eligibility criteria and allocation protocols is critical to maximizing donation opportunities. Particularly in the context of paediatric donation, confidence that a potential donor has a good likelihood of being suitable for transplantation is an important factor in initiating the donation conversation. Work to optimize donor identification in paediatric and neonatal intensive care units is ongoing, and criteria continue to be refined regarding suitability for transplantation of organs from paediatric donors, particularly from the smallest of these donors.

The recommendations below reflect local and international experience and current evidence with respect to paediatric donation and transplantation. However, it is acknowledged that there is a spectrum of experience with respect to the transplantation of organs from small paediatric donors and not all units will feel it is appropriate to consider all donors according to the criteria below. In order to facilitate the pathway for donation and allocation of these organs, transplant units should develop their own protocols for acceptance of paediatric donors, guided by the recommendations below as well as local expertise and other relevant considerations.

## 11.2 Paediatric kidney donation and allocation

For donors aged greater than 5 years or greater than 20kg, kidney allocation should proceed as for adult donors. For donors >10kg to 20kg, or aged >1 to 5 years, standard allocation also applies, although kidneys should be offered en-bloc first, then subsequently as single kidneys.<sup>2,3</sup>

Donors >5kg to 10kg or >3 to 12 months constitute a broad category with varying implications for the complexity of retrieval and transplant surgery, particularly in the case of the smallest donors. Availability of appropriate surgical expertise will influence the utilization of such donors. Ideally, these organs should be managed in centres with specialist experience in small grafts, where clear protocols exist on how to manage them. Centres should pre-emptively discuss their readiness and capacity to transplant small organs. Centres willing to transplant very small organs may also nominate one or more of their senior transplant physicians and surgeons to act as local experts to provide pre-allocation advice to donation staff.

Donor history should be reviewed at the time of pre-allocation discussion and subsequent organ offer, considering possible indications of inherited paediatric renal disease and/or complications of neonatal/paediatric ICU management. Given the relative lack of experience with procurement and transplantation of very small organs, donor history and any potential risk factors should be documented and post-transplant outcomes carefully monitored. Regular audit of transplant outcomes associated with the donor criteria below will be important to assess their utility and validity and to build evidence-based criteria for the allocation of very small kidneys.

In addition to routine donor information, offers of very small paediatric donors should be accompanied with the following documented data:

- antenatal factors: normal antenatal morphology scan, absence of oligohydramnios, absence of history of transmissible infection;
- gestational age at birth and/or reduced size for gestational age;
- renal ultrasound with details of kidney/ ureter/ bladder anatomy and kidney size percentile for age;
- presence of extra-renal congenital anomalies or syndrome with likelihood of systemic impact affecting the kidneys
- renal function – creatinine with normal range for age and gestation
- acute illness factors: history of central/ umbilical vascular catheterization +/- thrombosis.

**Table 11.1:** Recommendations for paediatric kidney donation (SK: single kidney, EB: en-bloc)

Age and Size Range	Single kidney (SK) or en-bloc (EB)	Allocation
>20kg or >5yo	SK	Standard allocation
>10-20kg or >1-5yo	EB first, then SK in certain cases	Standard allocation with default to offer as EB. Recipient transplanting unit has discretion to opt for SK, in which case second kidney to be offered on as SK.
>5-10kg or >3-12mth	EB	Allocation proceeds only after pre-allocation discussion with local experts. Referral should be accompanied by standardized paediatric-specific donor variables.
<5kg or ≤3mo	EB	For allocation to dedicated centres, identified as such to the donation sector, with specific protocols and relevant expertise to accept these donors.

### 11.3 Paediatric liver and intestinal donation and allocation

Paediatric liver transplantation requires appropriate size matching. For very small infants requiring liver transplantation, a suitable donor may therefore include a very small paediatric donor. The lower size limit of potential donors includes neonatal donors.

**Table 11.2:** Recommendations for paediatric liver and/ or intestinal donation

Age and Size Range	Allocation
DBD – No lower limit for age or weight.	Liver donation: Refer to local liver transplant unit first, if no suitable recipient, refer to other units on rotation. Preferential allocation of a donor liver to recipients requiring combined liver and intestinal transplant, as guided by TSANZ organ allocation guidelines.  Intestinal donation: All referrals to Victorian Liver Transplant Unit.
DCD – only donors >3mth age will be considered for liver donation.	
DCD donors are not suitable for intestinal donation.	

Universally, a paediatric donor is referred to a paediatric recipient wherever possible. As per the Guidelines, if a donor is aged 18 or under, the organ should go to an appropriate paediatric recipient. This is the case for whole liver or for both lobes of a split liver when the potential donor is less than 18 years of age. If there are no suitable paediatric recipients, it is then offered on national rotation for paediatric recipients. The only caveat being that if there is a very sick adult within the offering unit it may be used for that recipient.

## 11.4 Paediatric lung donation and allocation

The recipient criteria is set out by the Nationally Funded Centre (NFC) for Paediatric Lung and Heart-Lung Transplantation and advises lung transplantation for children  $\geq 4$  years and  $>10$ kg. Reflecting that children this small may have restrictive lung disease and a small chest cavity, smaller paediatric donors may be suitable as per recommendations in Table 11.3.

**Table 11.3:** Recommendations for paediatric lung donation and allocation

Age and Size Range	Allocation
$\leq 16$ yo or $<120$ cm (and in both cases $>8$ kg)	Allocation to Paediatric Lung Transplant NFC (Alfred Health), both DCD and DBD

## 11.5 Paediatric heart donation and allocation

Infants and children can derive significant benefit from heart transplantation, with a median post-transplant survival of up to 25 years for infants.<sup>4</sup> Any donor weighing greater than or equal to 3 kg is deemed potentially suitable. For infants with severe heart disease, an early decision on pursuing wait-listing for cardiac transplant vs mechanical support (VAD) is often necessary. An understanding of the size of the donor pool and likely waiting time is critical in informing this decision. Accordingly, it is recommended that all potential donors  $>3$ kg be formally assessed for heart donation. Discussion with the transplant team to determine if there is a suitable recipient should only be undertaken if this is the express wish of the donor family.

**Table 11.4:** Recommendations for paediatric heart donation

Age and Size Range	Allocation
3-50kg	<p>Formal referral of all cases to a Paediatric Heart Transplant NFC (Royal Children's Hospital), both DBD and DCD. If the NFC Paediatric centre can't use these organs they default back into the local state pool and national rotation.</p> <p>Paediatric donors with both heart and lungs suitable (see paediatric lung section 11.4 above) for use as a bloc should be referred to the NFC Paediatric Heart Lung Transplant Centre at the Alfred – see 11.5.1 below.</p>

### 11.5.1 Paediatric heart-lung blocs and allocation

Infants and children with a variety of medical conditions may require heart-lung transplant (2-3 cases per year). Paediatric donors suitable for these children are rare and such transplants are only performed by the NFC Paediatric Heart-Lung Transplant Centre (ie recipients under age 16) at the Alfred. The prioritisation and allocation of all these smaller donor organs must be considered at the time of referral as a bloc.

**Table 11.5:** Recommendation for paediatric heart-lung donation

Age and Size Range	Allocation
age $\leq 16$ and $<50$ kg	Formal referral of all DBD donor heart-lung blocs fitting these criteria to the NFC Heart-lung Transplant centre at Alfred. If the NFC Paediatric centre can't use these organs, then the lungs default back into the local state pool and national rotation and the heart is passed to the NFC Paediatric Heart Transplant Centre (see 11.5 above).



## 11.6 Paediatric pancreas donation and allocation

Paediatric DBD donors >25kg are suitable for pancreatic donation. These should initially be offered for solid organ donation and, if not allocated, then offered for islet donation.

Paediatric DCD donors are not currently suitable for pancreas donation.

**Table 11.6:** Recommendations for paediatric pancreas donation

Age and Size Range	Allocation
>25kg	DBD suitable for solid organ or islet donation.

## References

- 1 Corkery-Lavender T, Millar J, Cavazzoni E & Gelbart B. Patterns of organ donation in children in Australia and New Zealand. *Crit Care Resusc*, 2017; 19:296-302
- 2 Singh A, Stablein D and Tejani A. Risk factors for vascular thrombosis in pediatric renal transplantation: A special report of the North American Pediatric Renal Transplant Cooperative Study. *Transplantation*, 1997; 63(9): 1263-1267.
- 3 Foss A, Gunther A, Line PD, et al. Long-term clinical outcome of paediatric kidneys transplanted to adults. *Nephrol Dial Transplant*, 2008;23(2):726-729.
- 4 Rossano JW et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Twenty-second pediatric heart transplantation report – 2019; Focus theme: Donor and recipient size match. *J Heart Lung Transplant*, 2019 Oct;38(10):1028-1041

# 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 group 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.

By 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 Donation and Transplantation (the Ethical Guidelines). The revisions to the Consensus Statement were conducted in parallel with the development of the Ethical Guidelines, and as a consequence were informed by the content of this document. The former 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.

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

## Development

The Clinical Guidelines are 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 incorporate 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, under the leadership of the respective Advisory Committee Chairs.

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.

Targeted consultation on Version 1.0 of the Clinical Guidelines occurred between August 1 and September 15, 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 publicly available.

**Table B2:** Contributors to the content development of the TSANZ Clinical Guidelines for Organ Transplantation from Deceased Donors (Version 1.0, 2016)

TSANZ	Steven Chadban, Sarah White, Iman Ali
OTA	Eva Mehakovic, Helen Opdam
Cardiac Advisory Committee	Peter Bergin, Enzo de Angelis, Lawrence Dembo, Paul Jansz, George Javorsky, Robert Larbalestier, Peter Macdonald, Jo Maddicks-Law, Peter Ruysgrok, Robert Weintraub, Peter Wicks
Renal Transplant Advisory Committee	Allocation subcommittee: Scott Campbell, Philip Clayton, Nick Cross, Rhonda Holdsworth, Ashley Irish, John Kanellis, Fiona Mackie, Carl Pedersen, Graeme Russ, Christine Russell, Kate Wyburn General committee members: Greg Bennett, Steven Chadban, Jeremy Chapman, Toby Coates, Tina Coco, Luke Datson, Ian Dittmer, Luc Delriviere, Paolo Ferrari, David Goodman, Anthony Griffin, Julie Haynes, Frank Ierino, Mathew Jose, Lloyd D'Orsogna, Christine Russell, Narelle Watson
Liver and Intestinal Transplant Advisory Committee	Jonathan Fawcett, 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
Lung Advisory Committee	Daniel Chambers, Helen Gibbs, Allan Glanville, Emily Granger, Michelle Harkness, Jamie Hobson, Peter Hopkins, Robert Larbalestier, Sharon Lawrence, Trish Leisfield, Bronwyn Levvy, Monique Malal, David McGiffin, Tanya McWilliams, Michael Musk, Steve Peuschel, Greg Snell, Glen Westall
Pancreas and Islet Advisory Committee	Jeremy Chapman, Toby Coates, David Goodman, Wayne Hawthorne, Kathy Kable, Tom Loudovaris, Bill Mulley, Stephen Munn, Philip O'Connell, Helen Pillmore, Henry Pleass, Paul Robertson, Allan Saunders, Pat Siciliano, Angela Webster
Vascularised Composite Allotransplantation Working Committee	Tim Bennett, Jamie Burt, Robyn Langham, Karen Dwyer
Other contributors	Katrina Bramstedt, Brooke Chapman, Peter de Cruz, Adam Testro, Karen Waller

**Table B3:** List of organisations invited to submit comments on the draft Clinical Guidelines, 2<sup>nd</sup> September 2015 to 6<sup>th</sup> October 2015

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

## Version Updates

To maintain clinical relevance and community acceptability, eligibility criteria and allocation protocols must undergo periodic revision to account for evolving national and international evidence, clinical best practice, and trends in donor availability and acceptability criteria. The Clinical Guidelines are therefore regularly reviewed by the TSANZ Advisory Committees, with updates made on an *ad hoc* basis to reflect changes in clinical practice.

Updates to the Clinical Guidelines were made in May 2017 (Version 1.1) and December 2018 (Version 1.2). In May 2019, Version 1.3 of the Clinical Guidelines was released, with major changes to Chapter 2: Organ donor eligibility. These changes were made to provide more detailed guidance with respect to testing for donor transmitted infectious disease, and to incorporate recent clinical developments affecting practice in relation to donor screening, organ utilisation and recipient management. In July 2020, Version 1.4 of the Clinical Guidelines was released, with the addition of a new chapter on paediatric donor organ allocation (Chapter 11). In April 2021, Version 1.5 of the Clinical Guidelines made changes relating to; Human T-lymphotropic virus-1; allergy transmission and other donor-associated conditions, COVID-19 and the Australia and New Zealand Kidney Paired Exchange (ANZKX). In May 2021, Version 1.6 incorporates the revised kidney algorithm results following a review in Chapter 5 and Appendix C. In September 2021, Version 1.7 includes revised information for Chapter 2, Malignancy and Paediatric updates for section 6.5.3 and 11.3, 11.4, 11.5 and 11.5.1.

**Table B4:** Contributors to updates to the TSANZ Clinical Guidelines for Organ Transplantation from Deceased Donors

Version	Update Description	Working Group
Version 1.3 May 2019	Revised guidance on risk of infectious disease transmission from donors to recipients	Stephen Alexander, Peter Boan, Toby Coates, Michael Fink, Helen Opdam, William Rawlinson, Nicholas Shackel, Vicky Sheppard, and Sarah White.
Version 1.4 July 2020	New guidance on allocation of organs from paediatric donors	Joshua Kausman, John Kanellis, Ben Gelbart, Ian Michell, Henry Pleass, Robert Jones, Winita Hardikar, Elena Cavazzoni, Nicolette de Rooy, Alex Hodgson, Amanda Robertson
Version 1.5 April 2021	Updated advice on HTLV, allergy transmissions and other donor-associated conditions, COVID-19 and ANZKX	<ul style="list-style-type: none"> <li>— HTLV: Peter Boan, Jeremy Chapman, Helen Opdam, William Rawlinson and Sarah White</li> <li>— Donor Allergies: Jeremy Chapman, David Gottlieb, Helen Opdam and Sarah White</li> <li>— COVID-19: Peter Boan, Jeremy Chapman and Helen Opdam</li> <li>— ANZKX: Jo Burton, Linda Cantwell, Nick Cross, Ian Dittmer, Emma van Hardeveld, Judy Harrison, Peter Hughes and Stella McGinn</li> </ul>
Version 1.6 May 2021	Revision of the Deceased Donor Kidney Allocation Algorithm	Phil Clayton, Nicholas Larkins, Narelle Watson, Germaine Wong, Kate Wyburn
Version 1.7 September 2021	<p>Revised guidance on risk of donor-derived malignancy</p> <p>Revised advice on paediatric donor allocation, sections 6.5.3, 11.3, 11.4, 11.5, 11.5.1</p>	<ul style="list-style-type: none"> <li>— Donor-derived malignancy: Damien Bolton, Jonathan Cebon, Jeremy Chapman, Michael Crawford, Diona Damian, Melissa Goodwin, Peter Macdonald, John McCall, Miranda Paraskeva, Helen Opdam, William Silvester, Madeleine Strach, John Thompson, Kathy Tucker, Claire Vajdic, Angela Webster, Andrew Weickhardt, Sarah White, Germaine Wong, Tracey Ying</li> <li>— Paediatric updates: Nicholas Larkins, Joshua Kausman, Robert Jones, Robert Larbalestier, Robert Weintraub, Greg Snell</li> </ul>
Version 1.8 December 2021	Revised advice on COVID-19	Peter Boan, Steve Chadban, Tina Marinelli, Helen Opdam, Helen Pilmore, Kate Wyburn
Version 1.9 May 2022	Updated advice on organ donation and transplantation from donors with the diagnosis of COVID-19	Peter Boan, Steve Chadban, Tina Marinelli, Helen Opdam, Helen Pilmore, Kate Wyburn

# Appendix C

## Kidney allocation algorithms

### National Allocation formula

Match level	Description	Criteria	Base score
1	Very Highly sensitised ABO Compatible	<b>1a</b> mPRA $\geq 99.7$	99 700 000
		<b>1b</b> mPRA $\geq 99$	99 000 000
		<b>1c</b> mPRA $\geq 98$	98 000 000
		<b>1d</b> mPRA $\geq 97$	97 000 000
		<b>1e</b> mPRA $\geq 96$	96 000 000
		<b>1f</b> mPRA $\geq 95$	95 000 000
National Urgent	ABO Compatible	Recipient National urgency $>0$	90 000 000
2	EPTS restriction	<b>2a</b> 0 mismatches HLA-A or HLA-B and EPTS $\leq 25$	89 000 000
	HLA matching	<b>2b</b> 1 mismatch HLA-A or HLA-B and EPTS $\leq 25$	88 000 000
	Prioritises Low EPTS recipients	<b>2c</b> 2 mismatch HLA -A or HLA-B and EPTS $\leq 25$	87 000 000
	Matched at HLA DRB1	<b>2d</b> 0 mismatches HLA -A or HLA-B and EPTS $\leq 60$	86 000 000
3	ABO Matched		
	KDPI max value is applied from this level down		
	HLA matching	<b>3a</b> 0 mismatch at HLA A or HLA B or HLA DRB1 and mPRA $>80$	79 000 000
	Highly Sensitised	<b>3b</b> 1 mismatch at HLA A or HLA B or HLA DRB1 and mPRA $>80$	78 000 000
		<b>3c</b> 2 mismatches at HLA A or HLA B or HLA DRB1 and mPRA $>80$	77 000 000
		<b>3d</b> Matched at HLA DRB1 1 mismatch HLA A or HLA B And mPRA $\leq 80$ And Centre credit difference $\leq -3$	76 000 000
	HLA Matching	<b>3e</b> Matched at HLA DRB1 2 mismatch HLA A or HLA B And mPRA $\leq 80$ Centre credit difference $\leq -6$	75 000 000
	Centre credit difference	<b>3f</b> mPRA $>80$ Centre credit difference $\leq -9$	74 000 000
		<b>3g</b> Centre credit difference $< -20$	73 000 000



Other parameters	Bonus points added
<b>Paediatric</b>	250 000
<b>Donor centre = patient centre</b>	50
<b>Recipient Centre credit</b>	1000 + recipient centre credit
<b>Recipient and Donor are HLA DRB1 homozygote</b>	500 000 ( except level 3G)
<b>Waiting time (on dialysis)</b>	Number of months x 1

## State Allocation

- Allocation initially matched with restriction applied (EPTS-KDPI <=50) then unrestricted matching is applied
- KPDI max at clinician's discretion.

Level	Description	Details	Base Score
State Urgent	State Urgency Index >0	Urgency index added to base score	60 000 000

Level	Description	Details	Restricted base score	Unrestricted base score
State HLA	HLA mismatches A/B/DRB1	<b>1a</b> 0 0 0	49 000 000	39 000 000
		<b>1b</b> 1 0 0 or 0 1 0	48 000 000	38 000 000
		<b>1c</b> 1 1 0	47 000 000	37 000 000
		<b>1d</b> 0 0 1	46 000 000	36 000 000
		<b>1e</b> 2 0 0 or 0 2 0	45 000 000	35 000 000
		<b>1f</b> 1 0 1 or 0 1 1	44 000 000	34 000 000
		<b>1g</b> 2 1 0 or 1 2 0	43 000 000	33 000 000
State Waiting	Months on dialysis	Number of months x 1	40 000 000	30 000 000

### Additional scores

- Paediatric bonus of 100 000 for restricted algorithms – state HLA and state waiting
- Recipient and donor are HLA DRB1 homozygous bonus 500 000 to state HLA matching algorithms only.

In the event that a more than one patient has the same score, the ranking is randomised.

## Interstate Utilisation Algorithm

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 interstate Utilisation t is run. This list incorporates patients from across the country, to ensure that the kidneys do not go to waste.

Level	Description	Details	Restricted base score	Unrestricted base score
State HLA	HLA mismatches A/B/DRB1	<b>1a</b> 0 0 0	19 000 000	9 000 000
		<b>1b</b> 1 0 0 or 0 1 0	18 000 000	8 000 000
		<b>1c</b> 1 1 0	17 000 000	7 000 000
		<b>1d</b> 0 0 1	16 000 000	6 000 000
		<b>1e</b> 2 0 0 or 0 2 0	15 000 000	5 000 000
		<b>1f</b> 1 0 1 or 0 1 1	14 000 000	4 000 000
		<b>1g</b> 2 1 0 or 1 2 0	13 000 000	3 000 000
State Waiting	Months on dialysis	Number of months x 1	10 000 000	0

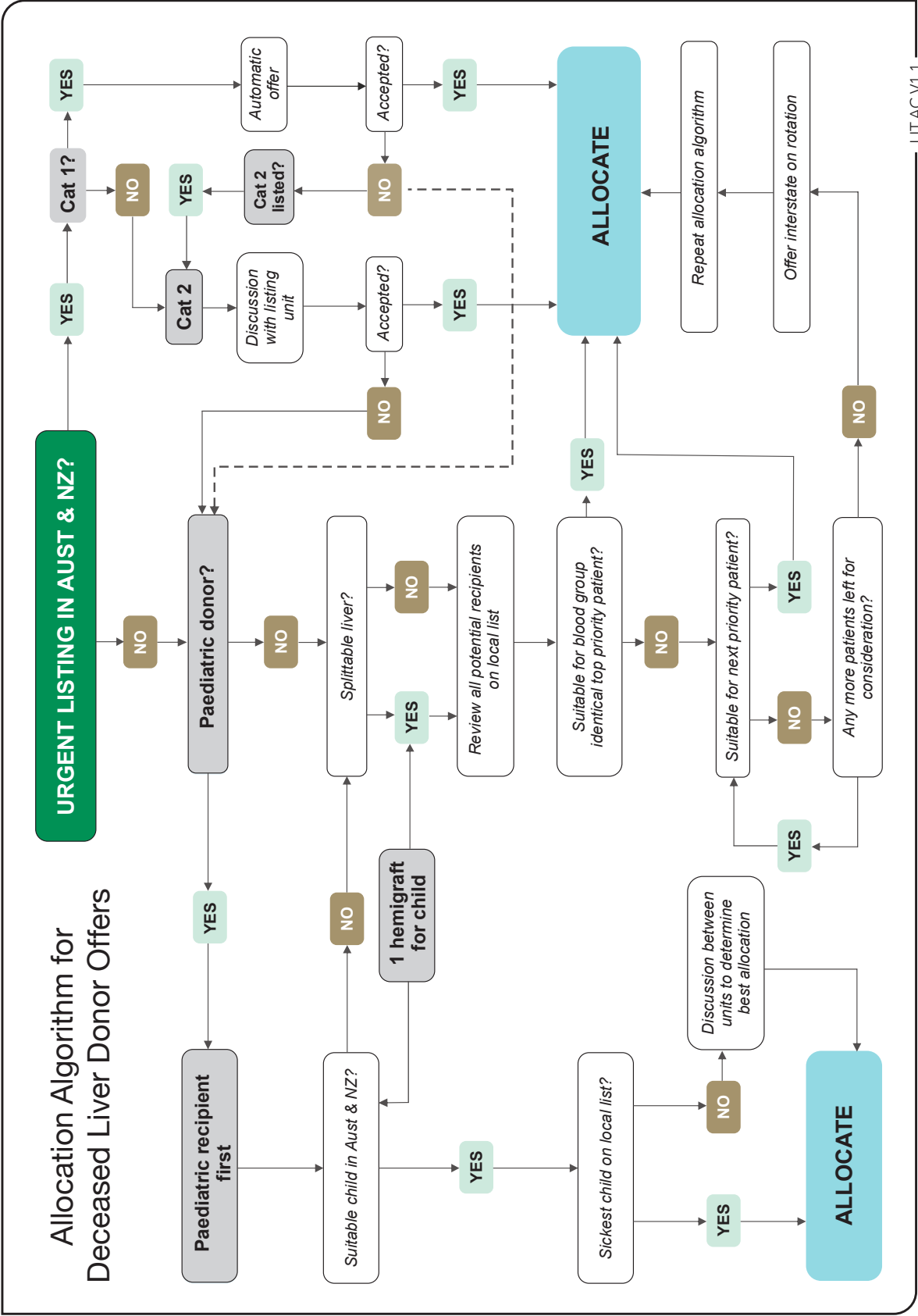
## ABO selection rules

The ABO selection rules determine the acceptable organ matches, as shown:

Algorithm	Level	Donor ABO type	Patient ABO type
National	Level 1	A	A
		A	AB
		B	B
		B	AB
		AB	AB
		O	O
		O	A
		O	B
		O	AB
National	Level 2 and Level 3	A	A
		B	B
		AB	AB
		O	O
State	NSW	A	A
	WA	A	AB
	VIC	B	B
	SA	B	AB
		AB	AB
		O	O
State	QLD	A	A
		A	AB
		B	B
		B	AB
		AB	AB
		O	O
		O	B

# Appendix D

Liver donor allocation flow diagram



LIT AC V1.1

# 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 DonateLife 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 Transplant Advisory Committee (LTAC) and be listed as a standing agenda item at LTAC 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 well established. 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 transplantation of organs 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 Sydney
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
	St Vincent's Hospital Sydney
VIC	The Alfred Hospital
	Austin Hospital
	Monash Medical Centre
	Royal Children's Hospital
	Monash Children's Hospital
	The Royal Melbourne Hospital
	St Vincent's Hospital Melbourne
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
	Sir Charles Gairdner Hospital
NZ	Auckland City Hospital
	Wellington Hospital
	Christchurch Hospital

#### Lung transplantation units

NSW	St Vincent's Hospital Sydney
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 Hospital Melbourne
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	St Vincent's Hospital Melbourne
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# Appendix I

## Summary of recommendations for infectious disease screening in deceased donors

Abbreviated infectious disease screening recommendations by pathogen. The recommendations below should be used in conjunction with the detailed explanations of these recommendations provided in Chapter 2.

Pathogen	Distribution/ endemic areas/high-risk groups	Screening recommendations	Utilisation
<b>Viruses</b>			
Coronavirus (SARS- CoV-2)	Worldwide	All donors should be tested for SARS-CoV-2 on a nasopharyngeal swab ideally within 24 hours of planned donation (no greater than 48 hours from actual donation). In addition, lung donors should be tested on a sample from the lower respiratory tract.	All donors should be tested for SARS-CoV-2 on a nasopharyngeal swab ideally within 24 hours of donation (no greater than 48 hours from actual donation). In addition, lung donors should be tested on a sample from the lower respiratory tract. Lung and small bowel organs from donors with a positive PCR for SARS-CoV-2 from upper or lower respiratory tract sampling are not suitable for transplantation. Organs other than lung and small bowel from donors with a positive PCR for SARS-CoV-2 may be suitable for transplantation if no evidence of severe COVID-19 or complications relating to the allograft. All donors should be screened for recent SARS-CoV-2 exposure within the preceding 7 days and if deemed a "close contact" suitability for transplantation should be assessed on a case-by-case basis.
Cytomegalovirus (CMV)	Worldwide; >50% prevalence in the Australian adult population	Anti-CMV (IgG) recommended for all donors, with prospective results preferable where possible	Accept, irrespective of CMV serostatus. If donor is CMV+ve, suitable prophylaxis and post-transplant monitoring of the recipient are required
Epstein-Barr virus (EBV)	Worldwide; >90% prevalence in the Australian adult population	Anti-EBV (IgG) recommended for all donors, with prospective results preferable where possible	Accept, irrespective of EBV serostatus. If donor is seropositive and recipient is seronegative, post-transplant virological monitoring is suggested
Hepatitis B virus (HBV)	Worldwide, with high prevalence (>50% HBcAb +ve) in Asia, South Pacific, sub-Saharan Africa and the Middle East	HBsAg, HBcAb, HBsAb should be performed for all donors, with results required prior to transplantation proceeding; HBV-NAT is recommended for all donors, with results required prospectively wherever logistically feasible.	HBV-NAT +ve OR HBsAg +ve: Organs may be transplanted in HBV+ve recipients, or in exceptional circumstances in HBV-ve recipients after specialist advice. If proceeding, also test for HDV. HBcAb+ve/HBsAg-ve: Transmission is unlikely for non-liver organs. Livers may be transplanted in HBV+ve or vaccinated recipients with the provision of HBV prophylaxis

Pathogen	Distribution/ endemic areas/high-risk groups	Screening recommendations	Utilisation
Hepatitis C virus (HCV)	Worldwide, with prevalence >3% in many African and Middle Eastern countries (Egypt >15%) Highest prevalence in ANZ among IDU and the prison population.	Anti-HCV should be performed for all donors, with results required prior to transplantation proceeding; HCV-NAT is recommended for all donors, with results required prospectively wherever logistically feasible.	HCV-NAT +ve: Organs may be transplanted into actively infected recipients, and may also be suitable for transplantation into HCV –ve recipients in specific circumstances. Anti-HCV +ve/HCV-NAT –ve: Represents spontaneous clearance of the virus or successful treatment. Transplantation should be considered for all recipients.
Hepatitis D virus (HDV)	High prevalence though with wide local/ regional variation in the Mediterranean, Eastern Europe, Middle East, Pakistan, central and northern Asia, western and central Africa, Amazonian basin, Pacific Islands and Vietnam	In the event of an HBsAg +ve or HBV-NAT +ve donor, the HDV status of the donor should be determined, including HDV RNA and HDV antibody assays.	Where there is a risk of HDV transmission, transplantation should be discussed with an infectious diseases physician or hepatologist prior to proceeding.
Herpes simplex virus (HSV)	Worldwide; seroprevalence of 76% (HSV-1) and 12% (HSV-2) in Australian adults	Screening not required where antiviral prophylaxis is routinely administered.	Organs can be accepted from donors with latent herpes family infections. Organs from donors with acute herpes viraemia should only be considered with the administration of HSV-active antiviral treatment to the recipient.
Human herpes virus-8 (HHV-8) or Kaposi's sarcoma herpes virus	Variable; high prevalence in the Mediterranean, parts of Africa and parts of China	Routine screening is not recommended	-
Human immunodeficiency virus (HIV)	Worldwide, with highest prevalence in sub-Saharan Africa, Russia, Ukraine, Estonia, Thailand, Papua-New Guinea, Belize, Surinam, Guyana and some Caribbean regions.	All donors should be screened for HIV using an HIV Ag/Ab combination assay, with results required prior to transplantation proceeding; HIV-NAT is recommended for all donors, with results required prospectively wherever logistically feasible.	Use of organ from an HIV +ve donor is generally contraindicated except in exceptional circumstances.
Human T-lymphotrophic virus-1 (HTLV-1)	Regions of high endemicity in sub-populations of Japan, sub-Saharan Africa, the Caribbean, South America, the Middle East, and Aboriginal people of central Australia.	HTLV-1/2 screening using serology is recommended for all organ donors, with prospective results preferable where possible.	Organs should not be utilized from donors confirmed to have HTLV-1/2. Screening tests can produce false positive results and if timely confirmatory testing is not possible, it is recommended that an infectious diseases physician or microbiologist advise on whether the results predict genuine HTLV infection, which is influenced by the strength of the test (e.g. signal to cut-off ratio) and the pre-test probability of infection. If a donor is retrospectively confirmed to be infected with HTLV-1 and organs are transplanted, monitoring of recipients for infection/disease is recommended.

Pathogen	Distribution/ endemic areas/high-risk groups	Screening recommendations	Utilisation
Influenza	Worldwide; influenza season in ANZ from June to August, affecting 5-10% of the population	If influenza-like illness in the donor is suspected, influenza-specific NAT should be performed (although prospective results are not essential).	The presence of influenza is not a contraindication to the transplantation of non-lung organs. Utilisation of lungs should be considered on a case-by-case basis. Post-transplant influenza treatment for 5-10 days is suggested for all recipients of organs from a donor infected with influenza.
West Nile virus	Variable; seasonal epidemics during late summer in Africa, parts of Europe, the Middle East, North America and west Asia.	Screening of asymptomatic donors is not recommended. Targeted testing using serology and NAT is recommended for donors with compatible symptoms and recent history of travel (<4 weeks) to an endemic country or region with an ongoing outbreak.	If a donor is suspected or known to be infected with WNV, an infectious disease specialist should be consulted for advice on testing requirements and whether it is safe to proceed with donation.
Zika virus	Widespread; outbreaks possible wherever there are mosquito vectors, a suitable climate, and intense movement of people.	Screening of asymptomatic donors for Zika virus is not recommended. Zika serology should only be used as a diagnostic test in donors with compatible symptoms and epidemiological risk factors (i.e. history of travel to an endemic area <4 weeks previous).	In the event that a donor tests positive for Zika virus infection, seek advice from an infectious diseases specialist.
<b>Bacteria and other</b>			
Multidrug resistant (MDR) bacteria	Worldwide; risk factors include prolonged ICU stay, prior hospitalization in a foreign country, vasopressor use, need for cardiopulmonary resuscitation, traumatic injury	No requirement for enhanced microbiological screening over and above standard ICU practice	Organs from donors with positive cultures for MDR bacteria may be considered for transplantation with close recipient follow-up. Transplantation should be carefully considered in the event the organ to be transplanted is itself colonized or the donor is bacteraemic. Discuss with an infectious disease specialist and, if donation proceeds, provide a full treatment course to the recipient.
<i>Mycobacterium tuberculosis</i>	Worldwide; majority of cases in ANZ occur in the overseas born population, most commonly in persons born in India, China, central and south east Asia, Papua New Guinea and Africa. Other risk factors include household/ occupational contact with tuberculosis, incarceration, residence in an aged care facility, homelessness and immunosuppression	Donor testing with microscopy and PCR are recommended where infection is suspected based on epidemiological and clinical factors suggestive of active or latent infection.	Donation of organs from donors currently being treated for tuberculosis or with positive test results is not recommended other than in exceptional circumstances after discussion with an infectious diseases physician. Donors with previous active or latent tuberculosis can be considered, taking into account completeness of treatment, antibiotic sensitivities and current evidence of infection in the donor. Discussion with an infectious diseases physician close follow-up of the recipient, and consideration of tuberculosis prophylaxis for the recipient are recommended.

Pathogen	Distribution/ endemic areas/high-risk groups	Screening recommendations	Utilisation
Malaria	Any tropical country is a risk area	Donors who have spent >3 month in an endemic area should be tested for Plasmodium using NAT or serology or both.	In the event of donor-derived malaria transmission, treatment is effective if transmission is detected early. If a donor tests positive for malaria, the recipient should be tested and treated routinely for malaria
<i>Strongyloides stercoralis</i>	Developing countries and central/tropical Australia	Donors who have spent >3 months in an endemic area should be screened for <i>Strongyloides</i> (prospective results are not essential)	If the donor tests positive for <i>Strongyloides</i> , transplantation may proceed with recipients treated with ivermectin.
<i>Transmissible spongiform encephalopathies (TSE)</i>	Risk factors include family history of CJD, receiving human pituitary-derived hormones prior to 1986, notification from the department of health as being at increased risk of TSE due to risk factor exposure, death from early onset dementia, death from any obscure undiagnosed neurological disorder.	No appropriate screening test exists, exclude on the basis of donor history indicating risk of TSE	Persons at risk of TSE should be excluded from organ donation
<i>Treponema pallidum</i> (syphilis)	Worldwide	All donors should be screened for <i>T.pallidum</i> , with results available prospectively where possible. Donors should be first screened using a treponemal-specific enzyme immunoassay, with confirmation of positive results by a non-treponemal test (e.g. the rapid plasma reagin test).	If primary, latent or tertiary syphilis is detected in the donor, donation may proceed with appropriate prophylactic treatment of the recipient. A donor with secondary syphilis may be bacteraemic with the involvement of many organs, hence caution should be taken if clinical manifestations of secondary syphilis are present.
<i>Trypanosoma cruzi</i>	Mexico, Central and South America	Donors who have spent >3 months in Mexico, Central or South America at any time in their lives should be screened for <i>T.cruzi</i> using serology.	Donor with known <i>T.cruzi</i> infection should be excluded from heart donation. Infection with <i>T.cruzi</i> is not a contraindication to the donation of non-cardiac organs, although recipients require close follow-up for 24 months for the appearance of acute infection.

# Appendix J

## Further resources for assessing risk of donor-derived malignancy

**Table J1:** Guidelines and web-based resources containing information on donor-derived malignancies

Guideline/resource	Publisher	Contents	URL
NOTIFY Library		Library of documented adverse outcomes associated with the clinical use of human organs, blood, tissues and cells.	<a href="http://notifylibrary.org">notifylibrary.org</a>
Transplantation of Organs from Deceased Donors with Cancer or a History of Cancer. Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO), 2014.	UK Government Department of Health	Recommendations for patients in the UK, based on a review of the UK National Transplant Registry and a review of the literature.	<a href="http://odt.nhs.uk/pdf/transplantation_of_organ_from_deceased_donors_with_cancer_or_a_history_of_cancer.pdf">http://odt.nhs.uk/pdf/transplantation_of_organ_from_deceased_donors_with_cancer_or_a_history_of_cancer.pdf</a>
Guide to the Quality and Safety of Organs for Transplantation (7th ed.). Chapter 9: Risk of Transmission of neoplastic diseases.	European Directorate for the Quality of Medicines & Health Care, Council of Europe	Current evidence for assessment of the risk of transplanting organs from donors with a past or present history of malignancies. Grading of risk is provided for an extensive list of malignancies that may be identified in the donor history or be discovered at the time of organ procurement.	<a href="https://www.edqm.eu/en/guide-quality-and-safety-organs-transplantation">https://www.edqm.eu/en/guide-quality-and-safety-organs-transplantation</a>

**Table J2:** Key registries and databases containing information on donor-derived malignancies

Database/registry	Contents	Key references
United Network for Organ Sharing Registry	Incidence of cancer history in donors; rate of malignancy transmission from donors with a known cancer history.	Kauffman et al. Transplantation, 2000; 70(12):1747 Kauffman et al. Transplantation, 2002; 73(4):579 Kauffman et al. Transplantation, 2002; 74(3):358 Kauffman et al. Transplantation, 2007; 84(2):272
Organ Procurement and Transplantation Network/ Disease Transmission Advisory Committee	Reports of confirmed donor-transmitted malignancies	Ison et al. Am J Transplant, 2011; 11(6):1123 Nalesnik et al. Am J Transplant, 2011;11(6):1140 Green et al. Transplantation, 2015; 99(2):282
The Israel Penn International Transplant Tumor Registry	Voluntary reporting of donor malignancy resulting in transmission to one or more recipients	Feng et al. Transplantation, 2002;74(12):1657 Buell et al. Surgery, 2001;130(4):660 Buell et al. Transplantation, 2003;76(2):340 Buell et al. Transplant Proc, 2005;37(2):581
United Kingdom Transplant Registry	Reports of confirmed donor-transmitted malignancies; case series reports of outcomes of transplantation from donors with a history of cancer	Desai et al. Transplantation, 2012;94(12):1200 Desai et al. Br J Surg, 2014; 101(7):768 Watson et al. Am J Transplant, 2010; 10(6):1437
Organización Nacional de Trasplantes Registry (Spain)	Reports of confirmed donor-transmitted malignancies	Garrido et al. Transplantation, 2008;85(8 Suppl):S61
Centro Nazionale Trapianti Registry (Italy)	Incidence of cancer history in donors; outcomes of transplantation from donors with a history of cancer	Venettoni et al. Ann Transplant, 2004;9(2):15 Nanni Costa et al. Transplantation, 2008;85(8S Suppl):52 Taioli et al. Transplantation, 2007;83(1):13 Zucchini et al. Transplantation, 2008;85(8 Suppl):S57 Fiaschetti et al. Transplant Proc, 2012;44(7):1848

MALORY – MAlignancy in Organ donors and Recipient safetY (Germany)	Cohort study of 648 recipients of organs from 248 donors with a history of cancer, with recipients followed for 6 years.	Moench et al. Transplantation, 2012; 94(10S):208
Danish Registry	Data linkage study, linking organ donors from a single transplant centre in Denmark to the Danish tumour registry and examining outcomes in recipients over 27 years.	Birkeland et al. Transplantation, 2002;74(10):1409



# Appendix K

## Family history of cancer and cancer genes

Donor assessment should include a history of genetic testing identifying a cancer predisposition mutation in the donor or their first-degree blood relatives. The presence of such a mutation may indicate an increased risk of occult malignancy in the donor, or an increased risk of cancer developing in the donated organ during the lifetime of the recipient. The level of risk will vary according to the specific gene and the specific organs donated (see Table K1).

Where no specific mutation has been identified in the individual or their family, the interview should also determine if there is a family history of cancer where:

- Multiple cancers have been diagnosed at young age
- There are multiple cases of the same type of cancer or patterns indicative a cancer predisposition syndrome
- Multiple cases of rare cancers

Consideration should be given to investigation of donors with a known cancer predisposition genetic mutation for occult malignancy. The risk of occult malignancy will vary depending on the gene, the age of the donor and previous screening or risk reducing strategies. There are no data to determine the risk of malignancy in transplanted organs from donors with a cancer predisposition gene.

Further advice as to the likelihood of a genetic susceptibility syndrome and the potential risk of malignancy in donated organs may be sought from a familial cancer service. See <https://www.genetics.edu.au/genetic-services/cancer-genetics-clinics> for services in Australia/N.Z.

**Table K1:** Risk of malignancy in known mutation carriers for cancer predisposition genes and affected transplant organs

Gene	Organ at increased risk	Risk in known mutation carriers
TP53	Multiple	>90%
VHL (Von Hippel Lindau Syndrome)	Pancreas, Kidney, Adrenal	80% RCC 10-17% PNET
STK11 (Peutz-Jegher Syndrome)	Pancreas	26% adenocarcinoma
FH (Hereditary Leiomyoma RCC)	Kidney	15% RCC
FLCN (Birt Hogg Dube Syndrome)	Kidney	19% (various types)
APC (familial adenomatous polyposis)	Pancreas, gastrointestinal (stomach, duodenum, small and large bowel)	5%
Mismatch Repair (Lynch Syndrome)	Urothelial tract Pancreas	3% Increased, but <2%
CDKN2A	Pancreas, Skin (melanoma)	Increased, but <2%
BRCA2	Pancreas	Increased, but <2%

# Appendix L

## Information on Australian and New Zealand cancer registries

### Australia

Cancer is a notifiable disease in Australia under the Public Health Act or equivalent in each state and territory. As a result, operational and governance arrangements vary; however, the Australian Association of Cancer Registries encourages a standard approach to cancer data collection and management across Australia.

Each state and territory operates a cancer registry that assembles information about new cases of cancer and cancer deaths. Data are supplied to the registries from a range of sources, such as hospitals, pathology laboratories, radiotherapy centres and the registrars of births, deaths and marriages—though mandated notifiers and the breadth of data collected vary between jurisdictions (Table L1). All registries record location, morphological type, topography, diagnosis date, grade and basis of diagnosis.

The registries are “case-based” data collections: Each piece of information provided to the registry is considered in the context of other information about the same person and used to progressively create a complete picture of tumours for that person. This differs from standard event-based data collections where each episode is coded in isolation. Cases are generally identified by Name, Sex and Date of Birth. In most jurisdictions, this is regularly validated within the jurisdiction against electoral rolls to improve data accuracy and reduce duplicate entries.

The cancer registries’ responsibilities are local: they supply information for use by their state or territory for planning of services, estimation of survival rates and treatment evaluation. Cancer data are also available for use in epidemiological studies.

Arrangements exist in some jurisdictions (see Section 2.4.2.6 ) for DonateLife staff to query the state-based registry (either directly or indirectly) to obtain the history of a potential donor once appropriate consent for donation is obtained from the next of kin. However, information from the registry is limited to those cancers diagnosed or treated within that state or territory and is identified primarily by name and date of birth. In order to obtain a complete history, it is important to ascertain if the donor previously resided in a different state or territory, and/or may have been diagnosed or treated under a different name. Where the potential donor resided in another jurisdiction, contact DonateLife staff in that jurisdiction to proceed with further enquires.

The registries forward an agreed list of data elements to the Australian Institute of Health and Welfare (AIHW) annually to a national repository—the Australian Cancer Database—for national reporting and disease monitoring. National de-duplication and cross-border case resolution is undertaken annually by the AIHW in the preparation of the annual reporting database. Availability of jurisdictional data to the Australian Cancer Database is usually around 1-3 years after diagnosis. This data collection is not available for interrogation to obtain the malignancy history of a potential donor.

**Table L1:** Data providers to state and territory cancer registries

	NSW*	VIC	QLD	WA	SA	TAS	NT	ACT
Hospitals	Mandated	Mandated	Mandated	Mandated	Mandated	Mandated	Mandated	Mandated
Pathology laboratories	Mandated	Mandated 94% of pathology is available within 6 weeks	Mandated	Mandated	Mandated	Mandated	Mandated	Mandated
Radiation oncology treatment centres	Mandated	Mandated (ROV notifiers) since 2017		Mandated	Mandated	Mandated	Not mandated	Not mandated

Screening programs		Breast and cervical screening programs			Breast and HCC screening programs**	
Residential aged care facilities	Mandated		Mandated		Not mandated	Mandated
Other	Oncology outpatients Cancer care centres Haematology and bone marrow transplant services Forensic medicine Treatment information: chemo & radiotherapy episodes from 2010 onwards			Opthamologists GPs	Not mandated	

\* A lot of information is captured on the pathology report, the inpatient notification (surgical) or on the radiotherapy/chemotherapy treatment notification, which may not be explicitly listed in a data field.

\*\* Annual ascertainment with BreastScreen NT and Hepatobiliary Multi-Disciplinary Teams (HCC surveillance)

**Table L2:** Cancer-specific information available in state and territory cancer registries

Non-melanoma skin cancer								
	NSW*	VIC	QLD	WA	SA	TAS	NT	ACT
		VCR does not capture skin SCC and BCC. <sup>1</sup>		Incidental collection of head and neck coded when received.	Skin BCCs of ano-genital area <sup>2</sup>  Skin SCCs of ano-genital area <sup>2</sup> and skin of lip	Machine coded according to ICD-O3 only.	Skin BCCs of ano-genital area <sup>2</sup>  Skin SCCs of ano-genital area <sup>2</sup> and skin of lip	
Melanoma of the skin								
	NSW*	VIC	QLD	WA	SA	TAS	NT	ACT
Primary site	✓	✓	✓	✓	✓	✓	✓	✓
Subsite			✓	✓	✓	✓	✓	
Morphology	✓	✓	✓	✓	✓	✓	✓	✓
Differentiation		Grade always 9	✓	✓			✓	
Laterality	✓	✓	✓	✓	✓	✓	✓	✓
Level		✓	✓	✓	✓	✓	✓	

Ulceration	✓	✓		✓			From 2014 <sup>3</sup>	
Breslow thickness	✓	✓	✓	✓	✓	✓	✓	✓
Mitotic rate		✓					From 2014 <sup>3</sup>	
Regression	✓	✓						
Nodal status	✓	✓					From 2014 <sup>3</sup>	
Metastatic status		Stage at diagnosis from 2018 Stage 4 at diagnosis since 2016	✓	✓ (only when identified via path/ death cert)	✓ a category under the 'level of invasion'	✓	From 2014 <sup>3</sup>	
Recurrence or progression		✓	✓					
Degree of spread*	✓	TNM stage at diagnosis from 2018				✓	From 2014 <sup>3</sup>	✓
Breast cancer								
	NSW*	VIC	QLD	WA	SA	TAS	NT	ACT
Stage at Dx		✓						
Tumour size	✓	✓	✓	✓	✓	✓	✓	✓
Nodal status		✓	✓	✓	✓	✓	✓	
Tumour grade		✓	✓	✓	✓	✓	✓	
Laterality	✓	✓	✓	✓	✓	✓	✓	✓
Degree of spread*	✓					✓	✓	✓
Hormone receptor status		✓	From 2019	Oestrogen receptor status only	Oestrogen receptor status only		From 2014 – PR in notes field; ER and HER2 in specific fields	
Chemotherapy	✓							
Radiotherapy	✓	From 2017						
Colorectal cancer								
	NSW*	VIC	QLD	WA	SA	TAS	NT	ACT
Stage at Dx		✓			✓		From 2014 – If pTNM available	
Tumour size			✓		✓	✓ (resection only)	✓	
Tumour grade		✓	✓	✓	✓	✓	✓	

Degree of spread*	✓					✓	From 2014 – In notes field or in specific field if pTNM available	✓
Prostate cancer								
	NSW*	VIC	QLD	WA	SA	TAS	NT	ACT
Tumour size			✓		✓	✓		
Gleason score		✓	From 2019	✓	✓	✓	From 2014 <sup>3</sup>	
ISUP		Grade in ISUP class since 2017				From 2017	From 2014 <sup>3</sup>	
Degree of spread*	✓					✓	From 2014 <sup>3</sup>	✓
Thyroid cancer								
	NSW*	VIC	QLD	WA	SA	TAS	NT	ACT
Tumour size			✓		✓	✓	✓	
Degree of spread*	✓	Stage 4 at Dx from 2016				✓	From 2014 <sup>3</sup>	✓
Bladder cancer								
	NSW*	VIC	QLD	WA	SA	TAS	NT	ACT
Tumour size			✓		✓ but not usually reported on path	✓	✓	
Tumour behaviour		✓ urothelial cell tumours						
Tumour grade		✓	✓		✓	✓	✓	
Degree of spread*	✓	Stage 4 at Dx				✓	From 2014 <sup>3</sup>	✓

\* A lot of information is captured on the pathology report, the inpatient notification (surgical) or on the radiotherapy/chemotherapy treatment notification, which may not be explicitly listed in a data field.

<sup>1</sup> VCR is receiving some notifications (hospital and Path reports) for SCC and BCC of skin. VCR may provide incomplete data on such cases. Notifications for SCC of skin for C445, C510-C519, C600-C609, C632 (anogenital area) only.

<sup>2</sup> Anogenital area refers BCC/SCC of anus, perineum, perianal area, labia, vulva, penis, or scrotum.

<sup>3</sup> Documented in notes field. Nodal and metastatic status documented in notes field or in specific field if pTNM available.

## New Zealand

The New Zealand Cancer Registry (NZCR) captures all primary malignant tumours (invasive and in situ) first diagnosed in New Zealand, excluding squamous and basal cell skin cancers unless they arise in the skin of the

genitalia. The NZCR was originally established in 1948, with coverage increasing after the passage of the Cancer Act in 1993. As of August 2021, Organ Donation New Zealand and the NZCR are in the process of establishing a protocol for health professionals to access the registry at the time of donor evaluation.

The NZCR is “case-based”, with each piece of information provided to the registry considered in the context of other information about the same person and used to progressively create a complete picture of tumours for that person. Cases are generally identified by Name, Sex, and NHI number. In addition to the data specified in Table L3, the NZCR captures clinical notes – a text field with supplementary information on the cancer registration – from 2001 onwards. The NZCR does not collect treatment information.

**Table L3:** Cancer-specific information available in the New Zealand Cancer Registry

	Cancer type					
	Breast	Colorectal	Gynaecological	Melanoma	Prostate	Respiratory
Primary site	✓	✓	✓	✓	✓	✓
Morphology	✓	✓	✓	✓	✓	✓
Tumour grade/Differentiation	✓	✓	✓	✓	✓	✓
Laterality	✓		✓			✓
TNM stage at diagnosis	✓	✓	✓	✓	✓	✓
Tumour size	✓	✓	✓	✓	✓	✓
Nodal status	✓	✓	✓	✓	✓	✓
Metastatic status	✓	✓	✓	✓	✓	✓
Multiple tumours flag	✓	✓	✓	✓	✓	✓
Degree of spread	✓	✓	✓	✓	✓	✓
Level of direct spread		✓				
Ulceration				✓		
Breslow thickness				✓		
Mitotic rate				✓		
Hormone receptor status	✓ (ER/PR since 2001, HER2 since 2008)					
Gleason score					✓	
Resection margin	✓			✓		
Recurrence or progression						

# Appendix M

## Recommendations on the use of organs from donors with CNS tumours

**Table M1:** Recommendations on the use of organs from donors with central nervous system (CNS) tumours, by risk category. Derived from SaBTO<sup>1</sup> and the 2016 WHO classification of tumours of the central nervous system.<sup>2</sup>

### Minimal risk of transmission (<0.1%) – Likely to be acceptable for all organ types and recipients

WHO Grade I and II tumours:

- Pilocytic/ Subependymal giant cell
- Diffuse astrocytoma, IDH-mutant
- Pleomorphic xanthoastrocytoma
- Oligodendroglioma, IDH-mutant & 1p/19q-codeleted
- Oligoastrocytoma
- Subependymoma/ Myxopapillary ependymoma
- Ependymoma
- Choroid plexus/ Atypical choroid plexus papilloma
- Angiocentric glioma
- Chordoid glioma of the third ventricle
- Gangliocytoma
- Ganglioglioma
- Desmoplastic infantile astrocytoma and ganglioglioma
- Dysembryoplastic neuroepithelial tumour
- Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)
- Central/ Extraventricular neurocytoma
- Cerebellar liponeurocytoma
- Papillary glioneuronal tumour
- Rosette-forming glioneuronal tumour
- Pineocytoma
- Schwannoma
- Neurofibroma
- Perineurioma
- Meningioma/ Atypical meningioma
- Solitary fibrous tumour/Haemangiopericytoma (I, II or III)
- Haemangioblastoma
- Craniopharyngioma
- Granular cell tumour
- Pituicytoma
- Spindle cell oncocytoma of the adenohypophysis

### Low-risk of transmission (0.1% to <2%) – Likely to be acceptable for many organ types and recipients

WHO Grade III and equivalents:

- Anaplastic astrocytoma, IDH-mutant
- Anaplastic oligodendroglioma, IDH-mutant & 1p/19q-codeleted
- Ependymoma, RELA fusion-positive (II or III)
- Anaplastic ependymoma
- Choroid plexus carcinoma
- Anaplastic gangliomyoma
- Pineal parenchymal tumour of intermediate differentiation (II or III)
- Papillary tumour of the pineal region (II or III)
- Malignant peripheral sheath tumour (II, III or IV)
- Anaplastic (malignant) meningioma
- Anaplastic pleomorphic xanthoastrocytoma

### Low- to intermediate-risk of transmission<sup>a</sup> – consider on a case-by-case basis

WHO grade IV tumours and equivalents:

- Glioblastoma
- Diffuse midline glioma, H3K27 M-mutant
- Pineoblastoma
- Medulloblastoma
- Embryonal tumour with multilayered rosettes, C19MC-altered
- CNS embryonal tumour, NOS
- CNS embryonal tumour with rhabdoid features
- Medulloepithelioma
- Ependymblastoma
- Atypical teratoid/rhabdoid tumour
- Germinoma
- Immature teratoma
- Teratoma with malignant transformation
- Yolk sac tumour
- Embryonal carcinoma
- Non-gestational Choriocarcinoma

### Unacceptable risk

- Primary cerebral lymphoma
- All secondary intracranial tumours

<sup>a</sup> Best available evidence suggests that the risk of transmission from donor to recipient in the case of Grade IV CNS tumours is ≤2%

## References

- 1 Transplantation of Organs from Deceased Donors with Cancer or a History of Cancer. Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO), UK Government Department of Health, London, UK, 2014.
- 2 Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. World Health Organisation Histological Classification of Tumours of the Central Nervous System. International Agency for Research on Cancer, 2016, France