Strategies to Increase Organ Donation

James A Hedley

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Statement of originality

This is to certify that to the best of my knowledge, the content of this thesis is my own work.

This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

James A Hedley

Date: 23rd June 2023

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Authorship attribution statement

This thesis contains both published manuscripts and original chapters. I confirm that I was the primary contributor to each chapter, and that this thesis is my original work. This thesis was conducted under the supervision of A/Prof Patrick J Kelly (Sydney School of Medicine and Health, The University of Sydney), with co-supervision from Prof Angela C Webster (Sydney School of Medicine and Health, The University of Sydney) and Dr. Melanie Wyld (Sydney School of Medicine and Health, The University of Sydney).

Authors' contributions to each chapter are outlined below.

Chapter 1 is original work, authored by Hedley JA and Kelly PJ. JH designed the research and wrote the chapter. PK participated in research design and writing of the chapter.

Chapter 2 of this thesis has been previously published as:

Hedley JA, Kelly PJ, Waller KMJ, Thomson IK, De La Mata NL, Rosales BM, Wyburn K, Webster AC. Perceived Versus Verified Cancer History and Missed Opportunities for Donation in an Australian Cohort of Potential Deceased Solid Organ Donors. *Transplantation Direct*. 2022;8(2):e1252. https://doi.org/10.1097/txd.0000000000001252

JH designed the research, performed the research, performed data analysis, and wrote the paper. PK and AW participated in research design, performance of the research, and writing of the paper. NDM, BR, and KWy participated in research design and writing of the paper. KWa and IT participated in writing of the paper.

Chapter 3 of this thesis has been previously published as:

Hedley JA, Vajdic CM, Wyld M, Waller, KMJ, Kelly PJ, De La Mata N, Rosales BM, Wyburn K, Webster AC. Cancer transmissions and non-transmissions from solid organ transplantation in an Australian cohort of deceased and living organ donors. *Transplant International*. 2021;34(9). https://doi.org/10.1111/tri.13989

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Chapters 4 and 5 of this thesis describe in detail the methods of an economic evaluation that has been previously published, while **chapter 6** is the economic evaluation which has been previously published as:

Hedley JA, Kelly PJ, Wyld M, Shah K, Morton RL, Byrnes J, Rosales BM, De La Mata NL, Wyburn K, Webster AC. Cost-effectiveness of interventions to increase utilization of kidneys from deceased donors with primary brain malignancy in an Australian setting. *Transplantation Direct*. 2023;9(5):e1474. https://doi.org/10.1097/txd.0000000000001474

Chapter 7 is original work, authored by Hedley JA and Kelly PJ. JH designed the research, performed the research, performed the data analysis, and wrote the chapter. PK participated in research design and writing of the chapter.

Chapter 8 is original work, authored by Hedley JA and Kelly PJ. JH designed the research, performed the research, performed the data analysis, and wrote the chapter. PK participated in research design and writing of the chapter.

Chapter 9 is original work, authored by Hedley JA and Kelly PJ. JH wrote the chapter. PK participated in writing of the chapter.

I attest that the statements above are correct. In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

James A Hedley

Date: 23rd June 2023

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

A/Prof Patrick J Kelly

Date: 23rd June 2023

Ethics approvals

Chapters 2 and 3: The Safety and Biovigilance in Organ Donation (SAFEBOD) study used data from the NSW Biovigilance Public Health Register, which was initiated under the NSW Public Health Act 2010. Ethics approval was provided by the University of Sydney Human Research Ethics Committee (project number 2016/758).

Chapters 4, 5 and 6: The Maximising Organ Donor Utility System-wide (MODUS) study received ethics approval from the University of Sydney Human Research Ethics Committee (project number 2020/828).

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Abbreviations

95%CI	95% confidence interval
AIC	Akaike Information Criterion
AIHW	Australian Institute of Health and Welfare
ALD	Alcoholic liver disease
ANZCOTR	Australian and New Zealand Cardiothoracic Transplant Registry
ANZDATA	Australian and New Zealand Dialysis and Transplant Registry
ANZIPTR	Australian and New Zealand Islets and Pancreas Transplant Registry
ANZLITR	Australian and New Zealand Liver and Intestine Transplant Registry
ANZLKD	Australian and New Zealand Living Kidney Donor Register
ANZOD	Australian and New Zealand Organ Donor Registry
APDC	Admitted Patient Data Collection
CCR	Central Cancer Registry
CHeReL	Centre for Health Record Linkage
CHF	Chronic heart failure
CKD	Chronic kidney disease
CMV	Cytomegalovirus
CNS	Central nervous system
CODURF	Cause of Death Unit Record File
COPD	Chronic obstructive pulmonary disease
CPR	Cardio-pulmonary Transplant Registry
CVD	Cerebrovascular disease
DBD	Donation after brain death
DCD	Donation after circulatory death
EBV	Epstein-Barr virus
ECD	Expanded criteria donor
EDDC	Emergency Department Data Collection
ESOT	European Society for Organ Transplantation
GB	Gigabyte
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HIVNSD	HIV and AIDS Notifications and Surveillance Data Set

ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems Tenth Revision Australian Modification
ICD-O	International Statistical Classification of Diseases for Oncology 3rd Edition
IQR	Interquartile range
κ	Cohen's kappa
k	Thousand
KDPI	Kidney donor profile index
KRT	Kidney replacement therapy
m	Million
MODUS	Maximising Organ Donor Utility System-wide study
MoH	Ministry of Health
NCIMS	Notifiable Conditions Information Management System
NSW	New South Wales
ORCHARD	Organ Referral CHARacteristics Database
OTA	Organ and Tissue Authority
OTDS	Organ and Tissue Donation Service
PBM	Primary brain malignancy
PSA	Probabilistic sensitivity analysis
PVD	Peripheral vascular disease
QALY	Quality-adjusted life-year
RBDM	Registry of Births, Deaths, and Marriages
RRR	Relative risk ratio
SAFEBOD	SAFEty and Biovigilance in Organ Donation study
SCD	Standard criteria donor
SE	Standard error
SPK	Simultaneous pancreas and kidney transplant
TSANZ	Transplantation Society of Australia and New Zealand
VPN	Virtual private network

Publications arising from this thesis

Chapter 2

Hedley JA, Kelly PJ, Waller KMJ, Thomson IK, De La Mata NL, Rosales BM, Wyburn K, Webster AC. Perceived Versus Verified Cancer History and Missed Opportunities for Donation in an Australian Cohort of Potential Deceased Solid Organ Donors. *Transplantation Direct*. 2022;8(2):e1252. https://doi.org/10.1097/txd.0000000000001252

Chapter 3

Hedley JA, Vajdic CM, Wyld M, Waller, KMJ, Kelly PJ, De La Mata N, Rosales BM, Wyburn K, Webster AC. Cancer transmissions and non-transmissions from solid organ transplantation in an Australian cohort of deceased and living organ donors. *Transplant International*. 2021;34(9). https://doi.org/10.1111/tri.13989

Chapter 6

Hedley JA, Kelly PJ, Wyld M, Shah K, Morton RL, Byrnes J, Rosales BM, De La Mata NL, Wyburn K, Webster AC. Cost-effectiveness of interventions to increase utilization of kidneys from deceased donors with primary brain malignancy in an Australian setting. *Transplantation Direct*. 2023;9(5):e1474. https://doi.org/10.1097%2FTXD.0000000000001474

Other publications which I contributed to during my candidature, but which did not form part of this thesis, are listed in Appendix A.

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Abstract

With the increasing prevalence of kidney failure, demand for kidney transplants outpaces kidneys available for transplantation. People who die in hospital under appropriate circumstances may be considered for potential organ donation. If their family consents and they are medically suitable, they become an actual donor. Efforts to increase potential donors have not translated to more actual donors. Potential donors declined due to perceived cancer transmission risk may be suitable under donation guidelines, presenting an avenue for increasing donation.

Relying on SAFEBOD data (donors and recipients linked to health records), this thesis sought to: 1) identify missed opportunities for donation from deceased donors with perceived cancer, 2) evaluate the risk of receiving a transplant from a donor with cancer, 3) develop an economic model to assess the cost-effectiveness of strategies to increase utilisation of kidneys from deceased donors with brain cancer, and 4) explore variations to this model.

Decisions about donors' medical suitability are often made with imperfect information (e.g., cancer reported by next-of-kin but not confirmed in health records). Among those declined due to perceived cancer, 29% were verified suitable (missed opportunities). Possible interventions are: 1) decision support, 2) real-time data-linkage, and 3) more risk tolerance. Cancer transmission is rare, especially from donors with brain cancer. No brain cancer transmissions were identified in SAFEBOD, and risk estimates are based on case reports. The economic model showed transplanting more kidneys from brain cancer donors improves health outcomes and saves money. More risk tolerance (accept grade IV brain cancers: 6.4%

transmission risk) provides the most benefit, +18.6 quality-adjusted life-years (QALYs) and $2.2m savings. Findings were robust to rigorous scenario and sensitivity analyses.

Accepting more donors with brain cancer could increase donation and improve patient outcomes.

Chapter 1: Introduction

1.1 Background

People with end-stage organ failure face a high rate of mortality and experience a poor quality of life, and organ transplantation confers best outcomes [1]. However, the demand for organs for transplantation far exceeds the number of suitable organs donated [2]. Donations from deceased donors can be broadly categorised into eye, tissue (e.g., skin) and solid organs (kidneys, liver, heart, lungs, pancreas, and intestines) [3]. A deceased donor can potentially save the lives of up to seven people waiting for an organ transplant [4]. In addition to deceased donation, some people waiting for a kidney may find a suitable living donor [5]. It is also possible for a living donor to donate part of their liver, usually to a child [6].

Kidneys are the most commonly transplanted organ, comprising more than half of all solid organ transplant procedures in Australia in 2021 [7], and are therefore the primary focus of this thesis. However, over 96% of deceased donors consent to kidney donation [7], so there is considerable overlap between deceased organ donors and deceased kidney donors. Any increase in organ donation overall means an increase in kidney donation.

In Australia, recent efforts to increase the number of donor organs available for transplant have primarily focussed on increasing the number of people referred to a donation service at the time of their death [8]. However, the number of people referred who eventually proceed to donation has failed to increase proportionally [9]. The two main barriers to donation are family consent and medical suitability in line with clinical guidelines from the Transplantation Society of Australia and New Zealand (TSANZ) [10]. The Australian Organ and Tissue Authority (OTA) has run successful campaigns through their state-based DonateLife network to increase the number of deaths in hospital referred for donation from 725

(0.96%) in 2013 [11] to 1,250 (1.56%) in 2021 [3]. Recent research has also demonstrated that donors with previously contraindicated infectious diseases such as hepatitis C (HCV) and human immunodeficiency virus (HIV) may also be suitable for donation [12,13], providing another avenue for increasing the number of donor organs available for transplantation.

However, there remain further opportunities to increase the pool of available donors as many donor referrals are declined because they are perceived to have a cancer, even if their cancer is not a contraindication for donation or if it cannot be verified in other health records [9].

This thesis is a collection of published manuscripts and original chapters presenting research to 1) identify potential missed opportunities for donation from deceased donors with a perceived malignancy, 2) evaluate the absolute risk to potential recipients of accepting an organ from a donor with cancer, 3) develop an economic evaluation to assess the cost-effectiveness of strategies to increase the utilisation of kidneys from deceased donors with primary brain malignancy, and 4) explore the impact of variations to this economic model on results and conclusions of cost-effectiveness. Kidneys are the most commonly donated organ [7] and are the primary focus of this thesis. This introduction chapter will describe the clinical context for increasing organ donation and summarise the current evidence surrounding transplantation from organ donors with cancer. The specific aims of each chapter are outlined at the end of this introduction chapter.

1.2 Deceased donor referral process in Australia

In Australia, deceased organ donor referrals are managed centrally by state and territory-based donor referral services. This thesis primarily relies on organ donation and transplantation data from New South Wales (NSW), which is the largest state in Australia (8.1 million population [14]) and is demographically representative of the entire country. Therefore, description of the donor referral process will focus on NSW, but processes are generally similar across all states and territories.

People who die or will likely die in hospital under appropriate circumstances for donation (approximately 1% of all hospital deaths [10]) are identified by hospital staff and referred to the NSW Organ and Tissue Donation Service (OTDS). Death can be classified as either brain death, or circulatory death. While circulatory death is more common overall, most donor referrals arise from brain death. Historically, only donation after brain death (DBD) was permissible, but in modern clinical practice donation after circulatory death (DCD) is also acceptable.

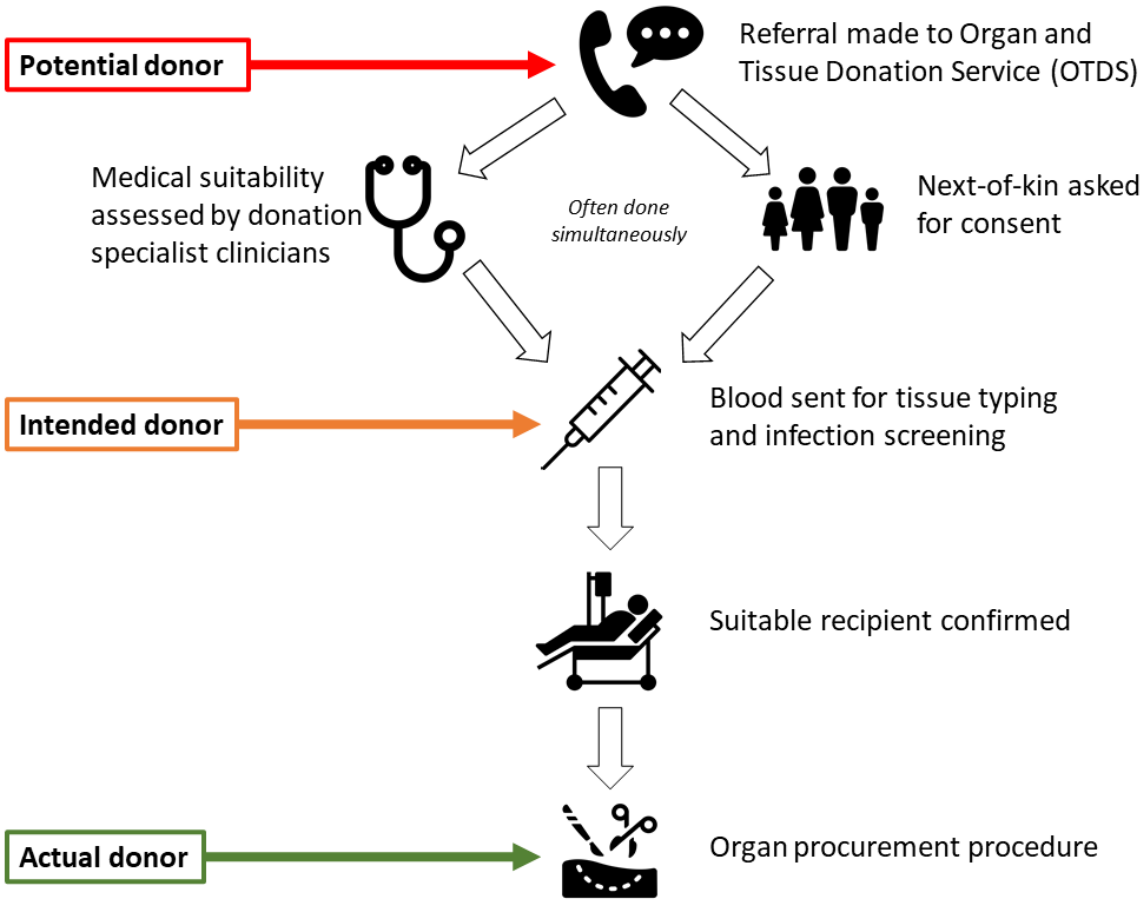
People referred at this stage are considered potential donors. Potential donors' medical history is assessed by donation specialist clinicians to determine medical suitability for donation in accordance with Transplantation Society of Australia and New Zealand (TSANZ) clinical guidelines [10]. Medical suitability discussions can be lengthy and iterative, sometimes requiring additional information to be followed-up before a decision can be made. Approximately 59% of potential donors are declined at this stage [15] due to medical contraindications including cancer, old age (there is no maximum eligible age for donation, but 98% of donors are <75 years old), or infection (e.g., hepatitis or HIV) [16].

Potential donors' family or next-of-kin must also give consent for donation to proceed. Family consent may be sought before, after, or at the same time as medical suitability discussions. While a potential donor's organ donation preferences may provide a useful reference for their family, ultimately their family has the final say in whether or not to give consent. Among the families approached, 58% provide consent for donation [3].

Once a potential donor has been deemed medically suitable and has obtained family consent to donate, their blood will be sent for tissue typing (to identify suitable recipients) and routine serological testing for infections, and they will be allocated a donor number. At this stage, they are considered an intended donor [17]. If there is suspicion of a particular infectious disease in the donor (e.g., due to a high-risk behaviour such as being an injecting drug user, or men who have sex with men), additional serological testing may also be performed at this stage to confirm any suspected infections.

Once a suitable recipient has been found, the intended donor will proceed to organ procurement and is considered an actual donor, regardless of whether any organs are retrieved or used for transplant [18]. Organ discard rates (i.e., the proportion of organs procured and not used for transplant) from in NSW 2010-2015 were 3% for kidneys, 4% for liver, 7% for heart, 2% for lungs, 6% for pancreas, and 4% across all organs [15]. In Australia, organs are only procured if a transplant recipient has been confirmed. Therefore, discard rates are much lower than in other countries such as USA, where the all-organ discard rate was 15% in 2020 [19]. The donor referral process is summarized in Figure 1.1 (adapted from Figure 1.1 in Rosales 2021 [20]).

Figure 1.1. Deceased organ donor referral process in NSW



1.3 Shortage of donor kidneys for transplantation

Globally, the demand for kidneys for transplantation far exceeds the available supply [21]. In Australia, the number of deceased donors has increased 55% from 354 in 2012 [22] to 548 in 2019 [23]. The number of kidney recipients increased 41% over the same period, from 607 in 2012 [22] to 857 in 2019 [23]. There were slight decreases in donation and transplantation activity in 2020 and 2021 due to the COVID-19 pandemic [24], but in general donations and transplantations have been trending upwards.

Despite increases in donation and transplantation activity, the number of Australians waiting for a kidney transplant has remained relatively steady over this same period,

increasing only 3.3% from 1,065 at end of 2012 [25] to 1,100 at end of 2019 [23], suggesting that the gap between supply and demand for organs is widening. Currently, there are approximately 1,396 Australians waiting for a kidney transplant [26]. Furthermore, there were 15,193 Australians receiving dialysis in 2021 who could potentially benefit from a kidney transplant, with only 1,443 (9%) listed on a deceased donor waiting list [27].

Since increasing organ donation rates was identified as a national priority in 2008 [28], efforts to identify every potential donor have resulted in a 3.5-fold increase (+256%) in the number of donor referrals to NSW OTDS, from 374 in 2010 to 1,316 in 2019 [9,16]. However, this has not translated to a proportional increase in donation, with only a 66% increase in actual donors over the same period (from 87 in 2010 to 144 in 2019). Since 2014, the national donation consent rate (i.e., the proportion of potential donors' families who consented to donation when asked) has remained relatively stable at around 60% [3,11,29-35]. It follows that the proportion of potential donors deemed medically unsuitable has increased dramatically in recent years. While an increase in potential donors declined is a necessary side-effect of efforts to identify every potential donor, it nevertheless presents a new avenue through which overall donation rates may be further increased.

Clinical guidelines recommend that potential donors with certain cancers pose a minimal (<0.1%) or low-risk (0.1-2%) of transmission and should be accepted for donation [10]. In the majority of cases where the risk of cancer transmission is known, an appropriate decision is made in line with clinical guidance. However, there remain missed opportunities for donation, where potential donors are declined due to a perceived risk of cancer transmission, despite this risk either being considered acceptable, or being incorrectly

estimated based on lack of accurate information available at time of referral [36]. The potential to increase organ donation through identifying and utilising these missed donation opportunities is the primary motivation for this thesis.

1.4 Risk of disease transmission from solid organ transplantation

During the assessment of medical suitability of donor referrals, the risk of potential disease transmission from donor to recipient must be balanced against the benefits of transplantation. Donor to recipient disease transmission is usually categorised as infectious diseases and cancer, both of which present very different biovigilance risks and considerations. Current clinical donation guidelines provide detailed recommendations for donors who pose a risk of disease transmission [10].

1.4.1 Infectious disease transmission risk

Many viral infections usually pose a relatively minor risk to recipients and can be easily treated either prophylactically or after confirmed transmission. Examples include cytomegalovirus (CMV), Epstein-Barr virus (EBV), and seasonal influenza. Although EBV can lead to post-transplant lymphoproliferative disorder, this is rare and does not contraindicate donation. The recent development of a drug therapy for HCV has also opened the possibility for donation from HCV positive donors.

For other more serious blood-borne virus infections such as HIV and hepatitis B (HBV), donation is usually not permitted. An exception to this is HBV, where donation is permitted if transmission risk is low (e.g., because the donor has a past infection that is not currently active, or the recipient has been adequately immunised) [10].

All donors are routinely screened for a range of blood-borne virus infections, regardless of whether they have any high-risk behaviours (e.g., injecting drug user, or men who have sex with men). Even if a donor is negative for a particular virus, there is still a window period in which they may have been infected without the possibility of detection via routine screening. This residual risk may be higher for those with high-risk behaviours, but recent research has demonstrated that this risk may not be as high as previously suspected [37], and that accepting such donors for transplantation may be cost-effective [38].

1.4.2 Cancer transmission risk

The risk of a donor potentially transmitting cancer to a transplant recipient presents different challenges compared to the risk of infectious disease transmission. Firstly, cancer encompasses a broad range of diseases [39] and screening for all cancers is generally not possible within the short timeframes required for organ donation. Instead, identification of cancer in a potential donor is often based on sparse medical history or family reports. Secondly, there is no prophylaxis for cancer available to recipients prior to transplantation, whereas for many infectious diseases there exist safe and effective vaccines and drug therapies. Finally, in a transplant recipient who subsequently develops cancer, it can be difficult to determine whether a recipient's cancer is truly donor-transmitted (i.e., a cancer transmitted from donor to recipient via organ transplantation) vs. the alternative possibilities that it was donor-derived (i.e., a cancer that develops in the recipient in the transplanted organ after transplantation) or *de-novo* (i.e., a newly developed cancer in the recipient unrelated to the transplanted organ). This is further complicated as transplant recipients have a much higher risk of developing *de-novo* cancer than the general population. International guidelines for imputability have been established [40,41], but often a

biopsy from the donor is required to make a definitive decision and this may not be possible if the donor was not known to have cancer at the time of donation or if the recipient's cancer is identified long after transplantation.

1.4.2.1 Non-brain cancers

In general, the presence of cancer in a potential donor means their organs will be unacceptable for transplantation, however there are some exceptions noted in donation guidelines [10]. Many *in-situ* or low-grade donor cancers present a minimal (<0.1%) or low (0.1-2%) risk of transmission and organs from these donors may be donated. Furthermore, some small kidney tumours discovered during organ retrieval may be resected and the kidneys safely transplanted [42].

1.4.2.2 Brain cancers

The cancer for which transmission risk is the lowest, and the primary focus of this thesis, is cancers of the central nervous system (CNS), or brain cancers. Apart from cerebral lymphoma, all primary non-metastatic brain cancers present a minimal, low, or intermediate risk of transmission and are not contraindications for organ donation. Although TSANZ recently updated national donation guidelines in September 2021 to incorporate the best available contemporary evidence, international reluctance to accept donors with brain cancer makes estimating the true risk of transmission challenging. For example, the risk of transmission for high-grade (grade IV) brain cancers is ultimately derived from a 2010 UK transplant registry-based study of 448 transplant recipients receiving 495 organs from 177 donors with a primary CNS tumour, in which no cases of transmission were identified [43,44]. Several systematic reviews [45-47] have identified case

reports of donor to recipient transmission of brain cancer, which are summarised in Table 1.1. Although there is a definite non-zero risk of transmission, many of these studies are more than 20 years old and the true transmission risk in modern clinical practice may be much lower than guidelines suggest.

Table 1.1. Case reports of transmission of donor brain cancer through organ transplantation

Donor					**Recipient**					**Ref.**
Year	Country	Age	Sex	Cancer	Age	Sex	Organ(s)	Transmission	Outcome	
1976*	UK	45	M	Cerebral glioma	61	M	Kidney	Yes	Malignancy identified after 1 week from perioperative biopsy, lung cancer diagnosed 5 months later, patient died 3 weeks later	48
					38	M	Kidney	No	Malignancy identified after 1 week from perioperative biopsy, kidney removed, patient alive on dialysis 1 year later	
1986-1992	USA	32	M	Glioblastoma multiforme	32	M	Kidney	Yes	Malignancy identified after 10 months, kidney removed and patient recovered	49
					23	F	Kidney	Yes	Malignancy identified after 10 months, kidney removed	
1987*	France	?	?	Medulloblastoma	?	F	Kidney, pancreas	Yes	Pancreas removed after 3 days due to arterial thrombosis. Malignancy identified in kidney after 4 months, removed, patient died 1 month later with diffuse tumour	50
					?	?	Kidney	Yes	Malignancy identified after 4 months, kidney removed, patient alive after 1 year follow-up	
					?	?	Heart	Yes	Patient died	
1988	USA	14	?	Malignant glioma	48	F	Liver	Yes	Malignancy identified after 9 months, patient died 1 month later	51
							Kidney	No	Alive with transplant after 25 months	
							Kidney	No	Alive with transplant after 25 months	
							Heart	No	Alive with transplant after 25 months	
1989	Spain	42	M	Glioblastoma multiforme	48	F	Kidney	Yes	Malignancy identified after 17 months, kidney removed, patient alive on dialysis 15 months later	52,53
					23	M	Kidney	Yes	Malignancy identified after 18 months, kidney removed, patient alive on dialysis 15 months later	
1992	Germany	48	M	Glioblastoma multiforme	28	F	Liver	Yes	Malignancy identified after 4 months, patient died 2 months later	54
1992-2006	USA	27	F	Ganglioglioma	54	M	Liver	Yes	Malignancy identified after 5 months, patient died	55

Donor					**Recipient**					**Ref.**
Year	Country	Age	Sex	Cancer	Age	Sex	Organ(s)	Transmission	Outcome	
1993*	Austria	70	M	CNS Non-Hodgkin's lymphoma	33	M	Kidney	Yes	Malignancy identified after 16 weeks, kidney removed, patient underwent chemotherapy but died 8 weeks later due to CMV pneumoina and pericarditis. Autopsy showed no signs of tumour recurrence	56
					44	F	Kidney	Yes	Malignancy identified after 18 weeks, kidney removed, patient was tumour-free for 10 months then retransplanted 3 months later with no recurrence	
1997*	Belgium	?	?	Malignant meningioma	49	M	Kidney	Yes	Malignancy identified after 1 year, kidney removed, complete remission 1 year later	57
1998*	Germany	47	F	Glioblastoma multiforme	29	?	Liver	Yes	Died with transplant after 5 months, autopsy found malignancy	58
					?	?	Kidney	No	Alive with transplant after 52 months	
					?	?	Kidney	No	Alive with transplant after 52 months	
2003*	USA	29	M	Glioblastoma multiforme	28	M	Lungs	Yes	Cancer diagnosed identified after 3 months, died 1 month later	46
					?	?	Liver	Yes	Developed metastatic glioblastoma multiforme	
					?	?	Kidney	No	Donor kidney removed, remained on dialysis	
					?	?	Kidney	No	No evidence of metastases	
					?	?	Heart	No	No evidence of metastases	

Donor					**Recipient**					**Ref.**
Year	Country	Age	Sex	Cancer	Age	Sex	Organ(s)	Transmission	Outcome	
2005	USA	47	M	Glioblastoma multiforme	57	M	Lungs	Yes	Malignancy diagnosed after 15 months, patient died 2 months later	59-61
					?	?	Heart	No	No evidence of transmission	
					?	?	Liver	No	No evidence of transmission	
					?	?	Kidney, pancreas	No	No evidence of transmission	
					?	?	Kidney	No	Kidney removed after 15 months (after cancer diagnosis in lung recipient), no evidence of transmission	
2010*	USA	1	M	Pineoblastoma	1	M	Liver, pancreas, intestine	Yes	Malignancy diagnosed after 4 months, patient died 2 months later	62

* Year of donation estimated from case report submission or publication date

? indicates age or sex not reported

1.5 Safety and Biovigilance in Organ Donation (SAFEBOD) study

The SAFEty and Biovigilance in Organ Donation (SAFEBOD) study was conceived to address potential missed opportunities for organ donation due to biovigilance concerns – specifically risk of transmission of infectious diseases or cancer [16]. The study's database, the Biovigilance Register, was established by the NSW Ministry of Health (MoH) under the NSW Public Health Act 2010 to monitor for previously unidentified cases of donor-to-recipient disease transmission. The database includes data from existing administrative datasets relating to organ donors (including deceased donor referrals, living kidney, and living liver donors), transplant recipients (including kidney, liver, heart, lung, and pancreas), and their health outcomes (including hospitalisations, infectious disease notifications, cancer diagnoses, and death records). These datasets were linked together by the NSW Centre for Health Record Linkage (CHeReL) to provide a database with organ donors linked to their recipients, and with both donors and recipients linked to their respective health records before and after donation/transplantation.

The first round of data linkage, completed in 2020, included data for a study cohort from 2010-2015 and is the main source of data for this thesis. A second round of linkage was completed in 2022 and included data for a study cohort from 2010-2020, but this data has not yet been analysed and is therefore not included in this thesis. The specific data sources included in SAFEBOD are summarised in Table 1.2, and the SAFEBOD data linkage process is summarised in Figure 1.2 (reproduced with permission from Figure 4 in Rosales et al., 2020). Overall linkage rates were excellent, with successful linkage to health records for 94.5% of potential donor referrals (ORCHARD), 99.1% of actual/intended donors (ANZOD), and 99.4% of dialysis and kidney recipients (ANZDATA). The false positive rate was set to 0.5%.

Table 1.2. Data sources included in SAFEBOD data linkage

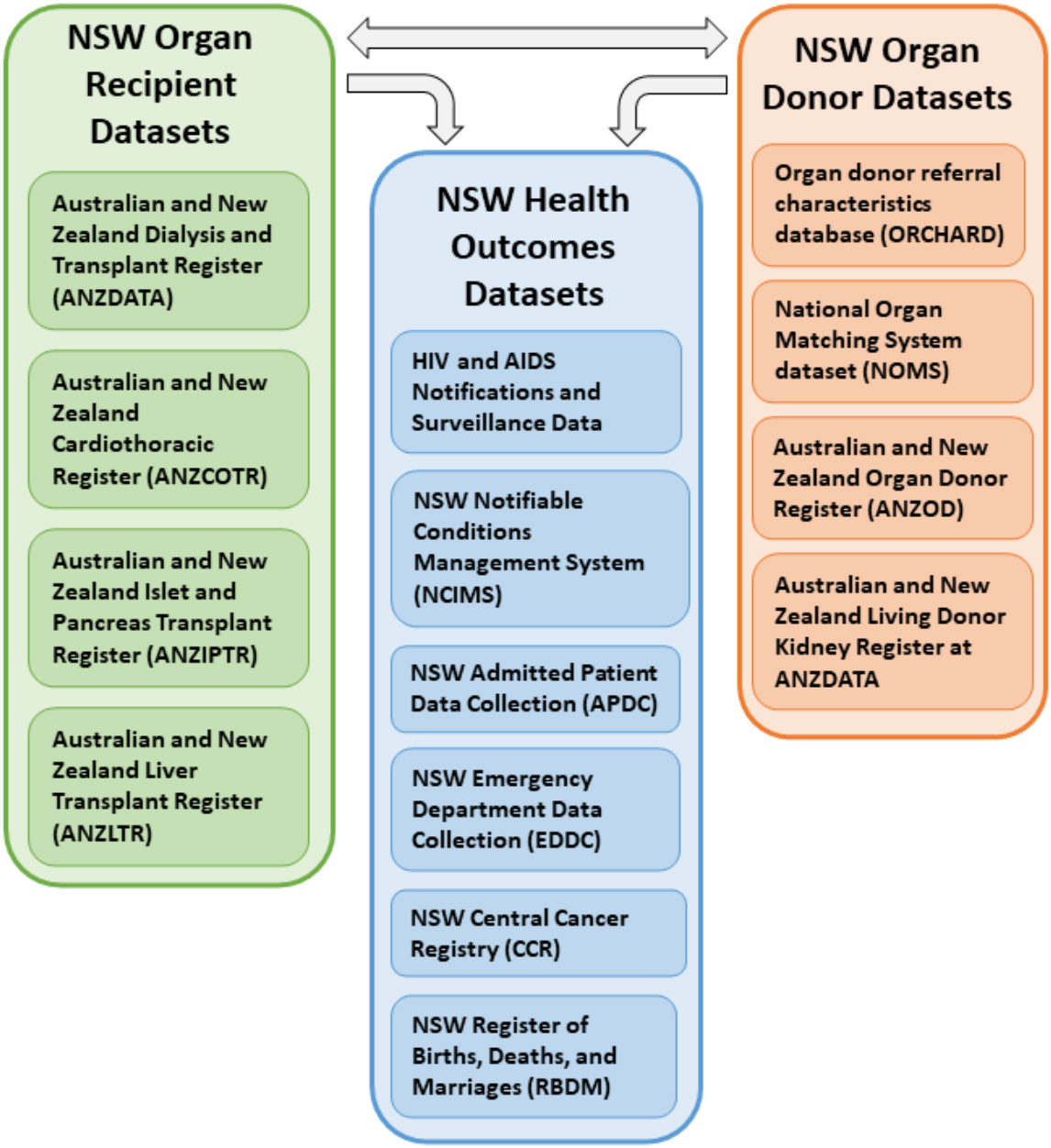
Data source	Category	Included cohort	Dates
Organ Referral CHARacteristics Database, ORCHARD	Donors	Deceased organ donor referrals	2005-2015
National Organ Matching System, NOMS[1]	Donors	Donors and recipients matched for potential transplantation	2000-2015
Australian and New Zealand Organ Donor Registry, ANZOD	Donors	Deceased organ donors	2000-2015
Australian and New Zealand Living Kidney Donor Register, ANZLKD	Donors	Living kidney donors	2004-2016
Australian and New Zealand Dialysis and Transplant Registry, ANZDATA	Recipients	Kidney transplant recipients	1970-2016
Australian and New Zealand Islet and Pancreas Transplant Registry, ANZIPTR	Recipients	Pancreas transplant recipients	2000-2015
Australian and New Zealand Cardiothoracic Transplant Registry, ANZCOTR[2]	Recipients	Heart and lung transplant recipients	2000-2015
Australian and New Zealand Liver Transplant Registry, ANZLTR[3]	Recipients	Liver transplant recipients	2000-2015
Admitted Patient Data Collection, APDC	Outcomes	Public hospital admissions	2000-2017
Inpatient Statistics Collection	Outcomes	Private hospital admissions	2000-2017
Cause of Death Unit Record File, CODURF	Outcomes	Death records	2000-2015
Emergency Department Data Collection, EDDC	Outcomes	Public hospital emergency department presentations	2005-2017
HIV and AIDS Notifications Surveillance Data Set, HIVNSD	Outcomes	HIV infection notifications	1985-2014
Notifiable Conditions Information Management System, NCIMS	Outcomes	Communicable disease notifications	1993-2016
Central Cancer Register, CCR	Outcomes	Cancer diagnoses	1972-2013
Registry of Births, Deaths, and Marriages, RBDM	Outcomes	Death records	2000-2017

1, Now known as OrganMatch

2, Now known as the Cardio-pulmonary Transplant Registry, CPR

3, Now known as the Australian and New Zealand Intestine and Liver Transplant Registry, ANZLITR

Figure 1.2. Data sources and data linkage process used in the SAFEBOD study



1.6 Thesis aims

This thesis aims to better understand potential missed opportunities for donation from deceased organ donor referrals (potential donors) who are declined for donation on the basis of cancer, and to explore how these potential donors could be better utilised to

increase the number of donor organs available for transplantation. Specifically, the aims of this thesis are to:

1) Identify potential missed opportunities for donation from deceased donors with a perceived malignancy (chapter 2),
2) Evaluate the absolute risk to potential recipients of accepting an organ from a donor with cancer (chapter 3),
3) Develop an economic evaluation to assess the cost-effectiveness of strategies to increase the utilisation of kidneys from deceased donors with primary brain malignancy (chapters 4, 5, and 6), and
4) Explore the impact of variations to this economic model on results and conclusions of cost-effectiveness (chapters 7 and 8)

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Chapter 2: Missed opportunities for donation

2.1 Preface

This chapter presents an analysis of SAFEBOD data that compares information related to cancer that was known or suspected at the time of donor referral (i.e., perceived) to information collected retrospectively from linked health records (i.e., verified). The aims of this study were to:

1) establish the accuracy of perceived information known at time of donor referral,
2) identify any missed opportunities for donation, and
3) explore potential strategies to avoid missed opportunities and increase donation

This study is published in *Transplantation Direct* [1]

2.1.1 Working with linked SAFEBOD data

This study is based on SAFEBOD data, which presented several challenges during the analysis. Linked SAFEBOD data was provided by the CHeReL as 39 separate datasets containing data at various analysis unit levels (i.e., individual records corresponded to donors, recipients, transplanted organs, cancers, hospital episodes of care, etc.). Before commencing the analysis for this study, I first created some summary datasets to make working with SAFEBOD data ('data wrangling') easier. These included a study-wide data dictionary, a list of all individuals (identified by their project-specific person number, PPN) and the datasets in which they appear, and a dataset mapping organ donors to their recipients at the individual organ level.

Another challenge was that some of the datasets were very large, such as the hospitalisations data (APDC) which included over 1 million records (rows) and had a file size

of over 1GB. Since I completed this analysis working remotely from my home, I had to use a VPN to access data which could only be stored on secure servers at the University of Sydney as per SAFEBOD ethics approval. Some datasets took several minutes to open, which required me to plan around this and adapt my workflow. For example, I found that using the Stata command 'snapshot' [2] was useful for saving a temporary version of large datasets that I could access again if I needed to revert to the original data after making changes for exploratory analysis.

2.1.2 Coding cancer information from SAFEBOD datasets

Many of the datasets included in SAFEBOD contained information about cancers in donors and recipients that was relevant to for this analysis, as well as the analysis presented in chapter 3 of this thesis. Each dataset recorded information about cancers differently. For example, cancer information in ORCHARD was included as part of medical history, which was a free-text field rather than being coded. In ANZDATA and ANZOD, cancers were classified using a coding system specific to these datasets, rather than the more universal approach of using ICD-10-AM [3] codes (which were included in APDC, EDDC, and CCR data). The possibility of multiple cancers being recorded against a single record in a dataset further complicated the analysis.

My solution to this problem was as follows. Firstly, within each SAFEBOD dataset (except for ORCHARD) I combined all available cancer information into a single text field (using Stata [2]). For example, if cancers were coded using ICD-10-AM codes, I included both the code and its corresponding description in the combined text field. Secondly, I created a Microsoft Excel [4] spreadsheet with the cancer information as a single text field from all datasets (excluding

ORCHARD), along with the dataset it came from. I then removed any replicates (e.g., if multiple people within SAFEBOD had the same type of cancer, the details of this cancer might be identical across all of their records), which resulted in a much more manageable set of only 3,722 unique records (most of which corresponded to a unique cancer). The third step was to code this cancer information in a standardised way. To do this, I created separate fields for cancer site, whether the cancer was primary or secondary, specific details about the type of cancer, whether it was malignant or benign, whether or not it had metastasized, and approximate date of diagnosis (for datasets where an exact date was not provided, e.g., RBDM which reported a diagnosis as being 'X weeks ago'). I repeated this up to 5 times, since this was the maximum number of cancers reported against a single record in any SAFEBOD dataset. To ensure that cancers were coded consistently, I followed guidelines from the SEER program [5], with oversight from one of my clinician supervisors, Prof. Angela Webster who helped with more difficult coding decisions and also checked the final set of manually coded cancers for any errors. Even after removing replicates, many unique cancer descriptions actually referred to the same cancer, with only very minor differences (e.g., presence or absence of metastases). Coding these cancers was therefore much simpler after sorting by the combined description field, since all similar records would be grouped together. One potential disadvantage of using Excel for this task is that the individual steps involved are not documented and therefore not exactly reproducible. However, the steps for *how* cancers were manually coded are not actually important, rather it is important that the final decision made for each cancer is documented. An Excel spreadsheet documents this well as it is easy to find a specific cancer and see how it was manually coded, with the additional advantage that the process to do the manual coding is much more efficient (compared to for example, writing thousands of very long lines of Stata

code, one line for each cancer). Although I believe my approach made coding these cancers as efficient as possible, it was nevertheless a very tedious and time-consuming task which took several months of my time. The fourth and final step was to link this coded cancer information back to each SAFEBOD dataset.

My approach for the ORCHARD dataset was different because cancer information was not easy to extract automatically (e.g., with Stata or R coding). Since cancer information was included in a single text field alongside all other medical history, I found it was easier to code any cancers in this dataset manually. To make this task more efficient, I sorted records by the length of their medical history (number of characters). Those with very short histories were very easy to code since they often did not have any cancer reported. For the more complicated medical histories, I used several search terms to identify as many cancers as I could. For example, a search for medical histories containing 'oma' would return many records with 'carcinoma' or 'melanoma' (but would also return some false positives, e.g., with 'coma').

2.1.3 Comparing perceived and verified cancer information

By comparing perceived and verified information to donation guidelines [6] (which have since been updated), potential donors can be dichotomised as medically suitable or unsuitable for donation. We assumed that low-risk ≤2% was an appropriate threshold (low-risk or lower was suitable, any higher risk was unsuitable). This was based on advice from clinicians about the threshold that was generally applied in practice. Low risk is also recommended by Nalesnik et. al., 2011 [22] for “use in recipients at significant risk without transplant”, while the next level of intermediate risk is “generally not recommended”.

Based on their perceived information, their verified information, and their actual donation outcome (accepted or declined), there are eight possible categorisations which are summarised in Table 2.1. This framework guided the analysis for this chapter. Importantly, the same rules were applied to both perceived and verified cancers to determine if they were suitable or not. This was done using Stata code, not human judgement, so there is minimal risk of bias. Furthermore, the manual coding was applied to cancer details, not to individual people. So if two people had the exact same cancer history reported, the relevant cancer details would have been manually coded only once, and the same decision applied to both individuals. This means that when coding cancers, no information about other potential cancers was available, hence the risk of bias is again minimal.

Table 2.1 Eight possible categorisations of potential donors based on their perceived and verified information, and their donation outcome

Perceived	Verified	Outcome	Information	Decision	Conclusion
Suitable	Suitable	Accepted	Accurate	Appropriate	Suitable donor accepted
Unsuitable	Suitable	Accepted	Inaccurate	Inappropriate	Inappropriate decision at the time, fortunately accepted a suitable donor
Suitable	Unsuitable	Accepted	Inaccurate	Appropriate	Unknown transmission risk
Unsuitable	Unsuitable	Accepted	Accurate	Inappropriate	Known transmission risk
Suitable	Suitable	Declined	Accurate	Inappropriate	Known missed opportunity
Unsuitable	Suitable	Declined	Inaccurate	Appropriate	Unknown missed opportunity
Suitable	Unsuitable	Declined	Inaccurate	Inappropriate	Inappropriate decision at the time, fortunately avoided transmission risk
Unsuitable	Unsuitable	Declined	Accurate	Appropriate	Unsuitable donor declined

2.1.4 Simulation to estimate uncertainty in number of verified suitable and unsuitable donors accepted or declined with each potential strategy

Some of the key results from this chapter are the number of verified suitable and unsuitable donors who would be accepted or declined with each potential strategy aimed at reducing missed opportunities and excess-risk donors under various risk thresholds. This is presented as absolute numbers in Table 2.S3, and as a difference in numbers compared to what was observed in Figure 2.3 and Supplementary Figure 2.S2. In all cases, these results are calculated by sampling counting the number of donors in each group, with no estimation of uncertainty. While this is helpful in making the conclusion of this analysis easier to understand, it might also be helpful to estimate a confidence interval for each result. For example, we reported that under a low-risk threshold, decision support would result in 7 additional donors (5 missed opportunities avoided + 2 additional excess-risk donors accepted), but we did not report any measure of uncertainty about this result such as a confidence interval.

To estimate confidence intervals for these results, I used a bootstrapping approach. I ran a simulation in which 1000 potential donors were randomly selected with replacement from the cohort of 472 potentially suitable donor referrals. Results for these 1000 potential donors were calculated, scaled to be comparable to the original cohort of n=472 potential donors (by multiplying each number by 472/1000), and the simulation was repeated for 1000 iterations. The mean, as well as a 95%CI (constructed using the 5^{th} and 95^{th} percentiles) were calculated for each result.

An updated version of Table 2.S3 including the bootstrapped mean and 95%CI for each cell is presented over three tables in Table 2.2, Table 2.3, and Table 2.4. The numbers used in Figure 2.S2 including the bootstrapped mean and 95%CI are presented in Table 2.5.

The point estimate for the number of missed opportunities under a low-risk threshold was 38 (29% of 132 potential donors declined due to perceived cancer transmission risk). The bootstrapped 95%CI for this estimate is 31.2 to 44.6, i.e., we can be 95% confident that there were between 31 (23%) and 45 (34%) missed opportunities. Similarly, the estimated number of excess-risk donors was 5 (1% of 340 actual donors), with 95%CI 3 (1%) to 8 (2%).

Under a low-risk threshold, decision support would result in 7 additional donors (+2.1% compared to n=340 actual donors observed), with 95%CI 4 (+1.2%) to 11 (+3.2%). This would include 5 missed opportunities avoided (n=33 missed opportunities, -13% compared to n=38 missed opportunities observed), with 95%CI 2 (-5%) to 8 (-21%). It would also include 2 additional excess-risk donors being accepted (+40% compared to n=5 excess-risk donors observed), with 95%CI 0 (+0%) to 5 (+100%).

Table 2.2 Number of verified suitable accepted or declined with each potential strategy for reducing missed opportunities and excess-risk donors under various risk thresholds, with bootstrapped mean and 95%CI (based on Table 2.S3)

	Verified suitable					
	Declined			Accepted		
Strategy	*Observed*	*Mean*	*95%CI*	*Observed*	*Mean*	*95%CI*
Minimal-risk threshold						
Actual	34	33.9	27.1-40.1	334	334.2	322.4-345.3
Decision support	32	31.9	25.5-38.7	336	336.1	324.7-347.4
Linkage to CCR	31	30.9	24.5-37.3	337	337.1	325.7-347.9
Linkage to APDC	32	31.9	25.5-38.7	336	336.1	324.7-347.4
Linkage to CCR and APDC	31	30.9	24.5-37.3	337	337.1	325.7-347.9
Reduced lag linkage to CCR and APDC	31	30.9	24.5-37.3	337	337.1	325.7-347.9
Increased risk tolerance (low-risk)	32	31.9	25.5-38.7	336	336.1	324.7-347.4
Low-risk threshold						
Actual	38	37.9	31.2-44.6	335	335.2	323.3-346.4
Decision support	33	32.9	26.7-39.6	340	340.1	329.0-351.2
Linkage to CCR	32	32.0	25.7-38.2	341	341.0	329.9-352.1
Linkage to APDC	33	32.9	26.7-39.6	340	340.1	329.0-351.2
Linkage to CCR and APDC	32	32.0	25.7-38.2	341	341.0	329.9-352.1
Reduced lag linkage to CCR and APDC	32	32.0	25.7-38.2	341	341.0	329.9-352.1
Increased risk tolerance (intermediate-risk)	32	32.0	26.0-38.7	341	341.1	329.9-352.1
Intermediate-risk threshold						
Actual	43	42.8	35.9-50.0	335	335.2	323.3-346.4
Decision support	32	32.0	26.0-38.7	346	346.0	335.1-356.8
Linkage to CCR	31	31.0	25.0-37.3	347	347.0	336.1-357.8
Linkage to APDC	32	32.0	26.0-38.7	346	346.0	335.1-356.8
Linkage to CCR and APDC	31	31.0	25.0-37.3	347	347.0	336.1-357.8
Reduced lag linkage to CCR and APDC	31	31.0	25.0-37.3	347	347.0	336.1-357.8
Increased risk tolerance (high-risk)	26	26.0	20.8-32.1	352	352.0	340.8-363.0

Table 2.3 Number of verified unsuitable donors accepted or declined with each potential strategy for reducing missed opportunities and excess-risk donors under various risk thresholds, with bootstrapped mean and 95%CI (based on Table 2.S3)

	Verified unsuitable					
	Declined			Accepted		
Strategy	*Observed*	*Mean*	*95%CI*	*Observed*	*Mean*	*95%CI*
Minimal-risk threshold						
Actual	98	98.0	87.8-108.6	6	6.0	3.3-9.0
Decision support	99	98.9	88.7-109.5	5	5.0	2.8-7.6
Linkage to CCR	99	98.9	88.7-109.0	5	5.1	2.8-7.6
Linkage to APDC	101	100.9	90.6-111.4	3	3.0	1.4-5.2
Linkage to CCR and APDC	101	100.9	90.6-111.4	3	3.1	1.4-5.2
Reduced lag linkage to CCR and APDC	104	103.9	93.5-114.2	0	0.0	-
Increased risk tolerance (low-risk)	93	92.9	82.8-102.9	11	11.0	7.1-15.1
Low-risk threshold						
Actual	94	94.0	84.0-104.3	5	5.0	2.8-8.0
Decision support	92	91.9	81.9-102.0	7	7.1	4.2-10.4
Linkage to CCR	94	93.9	83.8-103.8	5	5.1	2.8-7.6
Linkage to APDC	94	93.9	84.0-104.1	5	5.1	2.8-8.0
Linkage to CCR and APDC	96	95.9	85.7-106.2	3	3.1	1.4-5.2
Reduced lag linkage to CCR and APDC	99	99.0	88.7-109.5	0	0.0	-
Increased risk tolerance (intermediate-risk)	83	83.0	73.6-92.5	16	16.0	11.8-20.3
Intermediate-risk threshold						
Actual	89	89.0	79.3-98.6	5	5.0	2.8-8.0
Decision support	83	83.0	73.6-92.5	11	11.0	7.6-15.1
Linkage to CCR	86	86.0	76.9-95.3	8	8.0	4.7-11.3
Linkage to APDC	86	86.0	76.5-95.6	8	8.0	5.2-11.3
Linkage to CCR and APDC	88	88.0	78.8-97.7	6	6.0	3.3-9.0
Reduced lag linkage to CCR and APDC	91	91.1	81.2-101.0	3	2.9	1.4-5.2
Increased risk tolerance (high-risk)	72	72.1	62.8-80.7	22	22.0	17.0-27.8

Table 2.4 Overall number of donors accepted or declined with each potential strategy for reducing missed opportunities and excess-risk donors under various risk thresholds, with bootstrapped mean and 95%CI (based on Table 2.S3)

	Overall					
	Declined			Accepted		
Strategy	*Observed*	*Mean*	*95%CI*	*Observed*	*Mean*	*95%CI*
Minimal-risk threshold						
Actual	132	131.8	120.8-143.0	340	340.2	329.0-351.2
Decision support	131	130.8	120.4-142.1	341	341.2	329.9-351.6
Linkage to CCR	130	129.8	118.9-141.4	342	342.2	330.6-353.1
Linkage to APDC	133	132.8	122.2-144.0	339	339.2	328.0-349.8
Linkage to CCR and APDC	132	131.8	121.3-143.5	340	340.2	328.5-350.7
Reduced lag linkage to CCR and APDC	135	134.9	124.1-146.3	337	337.1	325.7-347.9
Increased risk tolerance (low-risk)	125	124.8	114.2-135.9	347	347.2	336.1-357.8
Low-risk threshold						
Actual	132	131.8	120.8-143.0	340	340.2	329.0-351.2
Decision support	125	124.8	114.2-135.9	347	347.2	336.1-357.8
Linkage to CCR	126	125.9	115.2-136.9	346	346.1	335.1-356.8
Linkage to APDC	127	126.8	116.1-137.8	345	345.2	334.2-355.9
Linkage to CCR and APDC	128	127.9	117.1-139.2	344	344.1	332.8-354.9
Reduced lag linkage to CCR and APDC	131	131.0	119.9-142.1	341	341.0	329.9-352.1
Increased risk tolerance (intermediate-risk)	115	115.0	104.3-125.6	357	357.0	346.4-367.7
Intermediate-risk threshold						
Actual	132	131.8	120.8-143.0	340	340.2	329.0-351.2
Decision support	115	115.0	104.3-125.6	357	357.0	346.4-367.7
Linkage to CCR	117	117.0	106.4-127.4	355	355.0	344.6-365.6
Linkage to APDC	118	118.0	107.6-128.4	354	354.0	343.6-364.4
Linkage to CCR and APDC	119	119.0	108.6-129.8	353	353.0	342.2-363.4
Reduced lag linkage to CCR and APDC	122	122.1	111.4-132.9	350	349.9	339.1-360.6
Increased risk tolerance (high-risk)	98	98.1	88.3-108.1	374	373.9	363.9-383.7

Table 2.5 Change in number of verified suitable and unsuitable donors with each potential strategy to reduce missed opportunities and excess-risk donors – sensitivity analyses under varying risk tolerance thresholds with bootstrapped mean and 95%CI

	Verified suitable			**Verified unsuitable**			**Overall**		
Strategy	*Observed*	*Mean*	*95%CI*	*Observed*	*Mean*	*95%CI*	*Observed*	*Mean*	*95%CI*
Minimal-risk threshold	*n=34 missed opportunities*			*n=6 excess risk donors*			*n=340 actual donors*		
Decision support	+2	+2.0	+0.5, +3.8	-1	-1.0	-3.3, +1.4	+1	+1.0	-1.9, +4.2
Linkage to CCR	+3	+2.9	+1.2, +5.2	-1	-0.9	-4.2, +2.8	+2	+2.0	-1.9, +5.7
Linkage to APDC	+2	+2.0	+0.5, +3.8	-3	-3.0	-5.2, -0.9	-1	-1.0	-3.8, +1.4
Linkage to CCR and APDC	+3	+2.9	+1.2, +5.2	-3	-2.9	-6.1, 0.0	0	+0.0	-3.8, +3.3
Reduced lag linkage to CCR and APDC	+3	+2.9	+1.2, +5.2	-6	-6.0	-9.0, -3.3	-3	-3.1	-6.6, +0.5
Increased risk tolerance (low-risk)	+2	+2.0	+0.5, +3.8	+5	+5.0	+2.4, +8.0	+7	+7.0	+3.8, +10.4
Low-risk threshold	*n=38 missed opportunities*			*n=5 excess risk donors*			*n=340 actual donors*		
Decision support	+5	+4.9	+2.4, +7.6	+2	+2.1	0.0, +4.7	+7	+7.0	+3.8, +10.4
Linkage to CCR	+6	+5.9	+3.3, +8.5	0	+0.1	-3.3, +3.3	+6	+5.9	+1.4, +9.9
Linkage to APDC	+5	+4.9	+2.4, +7.6	0	+0.1	-1.4, +1.4	+5	+5.0	+1.9, +8.0
Linkage to CCR and APDC	+6	+5.9	+3.3, +8.5	-2	-1.9	-5.2, +0.9	+4	+3.9	-0.5, +7.6
Reduced lag linkage to CCR and APDC	+6	+5.9	+3.3, +8.5	-5	-5.0	-8.0, -2.8	+1	+0.9	-3.3, +4.7
Increased risk tolerance (intermediate-risk)	+6	+5.9	+3.3, +8.7	+11	+11.0	+7.1, +15.1	+17	+16.9	+12.3, +21.7
Intermediate-risk threshold	*n=43 missed opportunities*			*n=5 excess risk donors*			*n=340 actual donors*		
Decision support	+11	+10.8	+7.1, +14.6	+6	+6.0	+2.8, +9.4	+17	+16.9	+12.3, +21.7
Linkage to CCR	+12	+11.8	+8.5, +15.6	+3	+3.0	-0.7, +7.1	+15	+14.8	+9.4, +20.3
Linkage to APDC	+11	+10.8	+7.1, +14.6	+3	+3.0	+0.9, +5.7	+14	+13.9	+9.4, +18.4
Linkage to CCR and APDC	+12	+11.8	+8.5, +15.6	+1	+1.0	-2.8, +4.7	+13	+12.8	+7.6, +17.9
Reduced lag linkage to CCR and APDC	+12	+11.8	+8.5, +15.6	-2	-2.1	-5.7, +1.4	+10	+9.7	+4.7, +15.1
Increased risk tolerance (high-risk)	+17	+16.8	+12.3, +21.2	+17	+17.0	+12.3, +21.7	+34	+33.8	+26.9, +40.6

2.1.5 References

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2.2 Abstract

Background: There is imperative to maximise donation opportunities given ongoing organ shortages, but donor suitability assessments can be challenging.

Methods: We analysed an Australian cohort of potential deceased donors 2010-2013 to explore misclassification of cancer risk and potential strategies for improvement (decision support, real-time data-linkage to existing datasets, and increasing risk tolerance). Cancer history perceived at referral was compared with verified cancer history in linked health records. Transmission risks were based on clinical guidelines. Potential donors declined due to cancer but verified low-risk were missed opportunities; those accepted but verified high-risk were excess-risk donors.

Results: Among 472 potentially suitable donor referrals, 132 (28%) were declined due to perceived transmission risk, and 340 (72%) donated. Assuming a low-risk threshold, there were 38/132 (29%) missed opportunities and 5/340 (1%) excess-risk donors. With decision support there would have been five (13%) fewer missed opportunities and two (40%) more excess-risk donors, with real-time data-linkage six (16%) fewer missed opportunities and two (40%) fewer excess-risk donors, and with increased risk tolerance six (16%) fewer missed opportunities and 11 (220%) more excess-risk donors.

Conclusions: Potential donors' cancer history is typically incomplete at referral. There are missed opportunities where decision support or more accurate cancer history could safely increase organ donors.

2.3 Introduction

Organ donation rates in Australia have increased from 12.1 donors per million population in 2008[1] to 21.6 in 2019[2]. However, Australia still lags behind other nations such as the UK (23.1), USA (32.0), and Spain (46.9, highest globally)[3]. Despite increases in donation resulting from efforts to identify all potential deceased donors[4], this exceeds the incremental gain in actual donors[5] suggesting potential donors are underutilised. Due to ongoing organ shortages[6] and the well-known benefits of transplantation, it is imperative that all avenues to increase organ donation are explored.

Potential deceased donors are managed centrally by the Organ and Tissue Donation Service (OTDS) in New South Wales (NSW), which is the most populous state in Australia (8.1 million[7]) and is demographically representative of the entire country. Those with family consent and no medical preclusions proceed to organ procurement and are considered an actual donor, regardless of whether any organs are used for transplant[8]. Organs are only procured if a transplant recipient has been confirmed, hence the organ discard rate is much lower than in other jurisdictions such as the USA[9].

Potential donors are medically unsuitable if their organs are inadequate quality for donation, or there is a risk of transmission of infection or cancer from donor to recipient. The Transplantation Society of Australia and New Zealand (TSANZ) guidelines aide clinicians in assessing donor suitability, including estimating the risk of cancer transmission by cancer type (not contraindicated, minimal-risk (<0.1%), low-risk (0.1-2%), intermediate-risk (2-10%), high-risk (>10%), or contraindicated)[10]. However, the decision about which level of risk is acceptable for donation is left to individual clinicians.

Decisions are based on available medical information (e.g., the referring hospital or history from relatives), which is recorded in OTDS donor referral logs. Verifying perceived cancers with pathology reports is often impossible in the short timeframes required. Misclassification of risk can lead to missed opportunities, or unrecognised excess-risk donors with potential for transmissions. In the USA, 25% of deceased organ donors with a reported cancer history could not be verified in cancer registries[11]. Furthermore, studies from Denmark and Italy found that 1% of donors had cancer that was undetected until after transplantation[12,13]. Despite evidence that cancer information scarcity leads to inconsistent and potentially harmful donation decisions, no studies have evaluated the impact of potential solutions.

Firstly, we aimed to establish the accuracy of health information known at the time of donation decisions, by comparing the perceived cancer diagnoses in donor logs with verified diagnoses from linked health records. Secondly, we aimed to identify any missed donor opportunities (suitable donors who were declined) and excess-risk donors (unsuitable donors who were accepted). Finally, we aimed to evaluate potential strategies to avoid missed donor opportunities through support in following clinical guidelines, improving quality of available information, and varying risk tolerance thresholds.

2.4 Methods

2.4.1 Study cohort

We conducted an observational cohort study using data from the NSW Biovigilance Public Health Register (SAFEBOD)[14]. Briefly, SAFEBOD linked all potential and actual donors to their administrative health records including the NSW Central Cancer Registry (CCR) and NSW

Admitted Patient Data Collection (APDC). The register was initiated under the NSW Public Health Act 2010 and received ethics approval from the University of Sydney Human Research Ethics Committee (project number 2016/758). Records were linked probabilistically, and linkage was completed in 2018 by the Centre for Health Record Linkage[15]. SAFEBOD has previously been used to identify missed donation opportunities relating to blood borne viruses [16], and to identify transplants resulting in cancer transmission and non-transmission[17].

The study population included all potential donors referred to the NSW OTDS for deceased solid organ donation from 1st January 2010 to 31st December 2013, as this was the only period in SAFEBOD with complete data for potential donors (2010-2015), and linked cancer records (1972-2013) due to a 5-year lag in availability of data from the CCR. We excluded potential donors with a non-NSW postcode since the CCR only includes cancers diagnosed in NSW residents, even if the diagnosis occurs interstate. We also excluded those without family consent and those medically unsuitable for reasons other than cancer since they would not have donated regardless of their perceived cancer history. Those remaining were considered potentially suitable for donation. The investigators had access to the full SAFEBOD dataset from which the study population was selected.

2.4.2 Perceived and verified cancers

We compared information known at time of donation decisions (perceived) with information gleaned from case records in SAFEBOD (verified). Perceived cancers included malignancies or potential malignancies reported in the OTDS donor referral logs, which records transcribed conversations about medical suitability. We supplemented this with

cancer details reported for intended and actual donors in the Australian and New Zealand Organ Donor Registry (ANZOD), since these would have been known at time of referral. All in-situ and malignant cancers (except for non-melanoma skin cancer) must be notified to the CCR under mandate. Therefore, verified cancers were those notified to the CCR, as well as non-melanoma skin cancers reported as malignant or potentially malignant in any linked SAFEBOD dataset (other than OTDS referral logs or ANZOD).

For all cancers we assigned a site based on International Statistical Classification of Diseases for Oncology 3rd Edition (ICD-O)[18] code reported in the CCR. If unavailable, we used the International Statistical Classification of Diseases and Related Health Problems Tenth Revision Australian Modification (ICD-10-AM)[19] code reported in the APDC. If neither ICD-O nor ICD-10-AM were available, two co-authors (JH and AW) manually assigned a site based on tumour description (AW is a clinician and provided clinical input to cancer coding). Malignancy and metastases were based on the CCR if available, otherwise ICD-10-AM code from the APDC, or otherwise ascertained from tumour descriptions by two co-authors (JH and AW). Diagnosis and last treatment dates were based on earliest and most recent reported date across all SAFEBOD datasets. Tumour size and type were based on the most detailed description available in any SAFEBOD dataset.

2.4.3 Cancer transmission risk

TSANZ clinical guidelines for organ transplantation from deceased donors[10] (henceforth TSANZ guidelines) assist clinicians in estimating the risk of cancer transmission based on tumour details (primary site, malignancy, metastases, diagnosis date, last treatment date, size, and type). Guidelines are similar in the UK[20] and Europe[21], with risk estimates based on

expert consensus and limited observational studies[22,23]. Despite the poor quality of evidence to support transmission risk estimates in international guidelines, these estimates are the best available. More importantly, these guidelines form the basis for decisions to accept or decline potential donors and are therefore more relevant than the 'true' transmission risk for identifying missed opportunities for donation.

We applied the TSANZ guidelines to each potential donor in our cohort to categorize their risk of transmission as: not contraindicated, minimal-risk (<0.1%), low-risk (0.1-2%), intermediate-risk (2-10%), high-risk (>10%), or contraindicated. We performed this step twice, once based on perceived cancer history only, and again based on verified cancer history.

We dichotomized potential donors as suitable or unsuitable for donation based on transmission risk. There is no established risk tolerance threshold recommended in the TSANZ guidelines, and clinicians' views differ about what level of transmission risk is acceptable. This means some perceived low-risk potential donors may be declined, while some perceived high-risk potential donors may be accepted. For this study, we assumed that low-risk ≤2% was an appropriate threshold. Perceived suitable means that we have retrospectively deemed potential donors as suitable based on our assumed risk tolerance threshold and the information that was known at time of referral. If the consulting clinician had a different risk tolerance threshold than our assumption, then a potential donor we deemed perceived suitable may have been declined (or a potential donor we deemed perceived unsuitable may have been accepted). Verified suitable means that we have retrospectively deemed a potential donor as suitable based on our assumed risk tolerance

threshold and information from all linked SAFEBOD datasets (including the CCR which was only available five years after referral). We explored alternative thresholds (minimal-risk <0.1% and intermediate-risk ≤10%) in sensitivity analyses.

We compared agreement between perceived and verified cancers as proportions, by primary cancer site. We also compared agreement between perceived and verified transmission risks, and between perceived and verified suitability, as proportions and using Cohen's kappa (κ).

2.4.4 Missed opportunities and excess-risk donors

A missed opportunity was any potential donor who was verified suitable but did not donate. They may have been declined because they were perceived unsuitable (e.g., due to inaccurate information available at referral), or they may have been declined despite being perceived suitable (e.g., if the consulting clinician had a lower risk tolerance than we assumed). Conversely, an excess-risk donor was any actual donor who was verified unsuitable. They may have been accepted because they were perceived suitable (e.g., due to insufficient information available at referral), or they may have been accepted despite being perceived unsuitable (e.g., if the consulting clinician had a higher risk tolerance than we assumed).

We considered three potential strategies to improve utilisation of missed opportunities: decision support, real-time data-linkage, and increased risk tolerance. Decision support encompassed any intervention that would assist clinicians to follow the TSANZ guidelines consistently, bringing individuals' risk tolerance in line with our assumed low-risk threshold. How this could be implemented is beyond the scope of this study but could potentially be

provided through an app where details of a potential donor's cancer are entered, and a recommendation is returned. Real-time data-linkage would allow clinicians to search potential donors' cancer history in existing health databases, specifically the CCR and APDC. We assumed this would be in addition to decision support, since we were unable to assess how any strategy would affect decisions if clinicians applied their own individual risk thresholds. Again, how this might be implemented is beyond the scope of this study but could potentially involve providing OTDS staff with remote access to NSW health datasets. Increased risk tolerance would involve applying a higher risk threshold for determining perceived suitability (i.e., instead of a low-risk threshold we would use an intermediate-risk threshold). The threshold for verified suitability would remain the same (i.e., low-risk ≤2%) to ensure the definition of a missed opportunity and an excess-risk donor is unchanged to allow for direct comparison with other strategies. This was also assumed to be in addition to decision support.

For each potential strategy we constructed a counterfactual scenario where perceived suitability could differ but verified suitability remained the same (since it is based on the best information available retrospectively). Decisions would be reversed if perceived suitability changed; some declined potential donors may instead be accepted, while some actual donors may instead be declined. Ideally each strategy would always result in positive changes, however appropriate decisions might also inadvertently be reversed. For example, a potential donor perceived to be low-risk may have been declined because the consulting clinician had a very low risk tolerance. Under decision support this decision would be reversed, and the potential donor would instead be accepted. However, if they were verified to be high-risk then this would be a negative outcome resulting in an additional

excess-risk donor. To account for this, we evaluated each strategy by comparing changes in the number of missed opportunities (fewer is better), as well as changes in the number of excess-risk donors (fewer is better).

2.5 Results

2.5.1 Study cohort

There were 1,706 potential donors referred for solid organ donation in NSW from 2010-2013, and 1,694 (>99%) were NSW residents. Among these, 1,222 (72%) would not have proceeded to donation regardless of their cancer history including 494 (40%) due to lack of family consent, 149 (12%) due to medical reasons other than cancer, and 579 (47%) due to both lack of consent and medical reasons other than cancer. Therefore, 472 (28%) were potentially suitable donor referrals and included in our study cohort. Of these, 340 (72%) became actual donors while 132 (28%) were declined for donation due to their perceived cancer transmission risk. The potential donors included in our study cohort, and their donation outcomes, are presented in Figure 2.1.

2.5.2 Verification of perceived cancers

Among 472 potentially suitable donor referrals, 156 (33%) were perceived to have history of at least one cancer. There were 175 perceived cancers in total, and 106 (61%) were verified in linked health records. The most common perceived cancers were blood (n=26), brain/central nervous system (n=19), breast (n=19), colorectal (n=16), and melanoma (n=15). The number of perceived cancers by primary site and their verification is presented in Figure 2.2, and the number of verified cancers by primary site are presented in Supplementary Figure 2.S1.

There were 397 (84%) potentially suitable donor referrals with agreement between perceived and verified cancer transmission risk (κ=0.72), and 432 (91%) with agreement between perceived and verified suitability (κ=0.77). Agreement under sensitivity analysis scenarios is summarised in Supplementary Table 2.S1.

Of the 156 potentially suitable donor referrals with at least one perceived cancer, 132 (85%) were declined and 24 (15%) donated. Only 93 (60%) had their entire cancer history verified, and 100 (64%) had at least one perceived cancer verified. The 132 declines were due to perceived cancer transmission risk, as reported in a dedicated field for reason for decline in the OTDS donor referral logs. Compared to the 24 with perceived cancer who were accepted for donation, those who were declined were of a similar age (median 61 vs. 63, p=0.5), similar sex (female 45% vs. 38%, p=0.5), had fewer other comorbidities (mean 0.8 vs. 1.9, p<0.001). Therefore, it is unlikely there was any other systematic reason that these potential donors were declined, so we would expect that if it weren't for their perceived cancer, they would have been accepted. The characteristics of potential donors with at least one perceived cancer and their donation outcomes are summarised in Table 2.6.

2.5.3 Missed opportunities and excess-risk donors

Among 132 potential donors declined due to perceived cancer transmission risk, 38 (29%) were verified suitable (i.e., missed opportunities). Among 340 actual donors, five (1%) were verified unsuitable (i.e., excess-risk donors). Perceived and verified risk of all potentially suitable donor referrals is summarised in Table 2.7, and the primary site of cancers among missed opportunities is summarised in Supplementary Table 2.S2.

Decision support would result in five more suitable donors being accepted, which is five (13%) fewer missed opportunities (n=33 missed opportunities, 13% reduction from n=38). Unfortunately, this would also result in two more unsuitable donors being accepted, which is two (40%) more excess-risk donors (n=7 excess-risk donors, 40% increase from n=5). There would be seven (2.1%) more donors overall (n=347 donors, 2.1% increase from n=340).

In conjunction with decision support, real-time linkage to the CCR and APDC would result in six (16%) fewer missed opportunities, two (40%) fewer excess-risk donors, and four (1.2%) more donors overall. Incrementally (i.e., in addition to decision support) this would mean one (3%) fewer missed opportunity, four (57%) fewer excess-risk donors, and three (0.9%) fewer donors overall.

In conjunction with decision support, increased risk tolerance would result in six (16%) fewer missed opportunities, 11 (220%) more excess-risk donors, and 17 (5.0%) more donors overall. The 11 excess-risk donors include five verified intermediate-risk who may be considered suitable under an increased risk tolerance threshold. Excluding those verified intermediate-risk, there would be six (120%) more excess-risk donors. Incrementally (i.e., in addition to decision support) this would mean one (1%) fewer missed opportunity, nine (129%) more excess-risk donors (including five intermediate-risk who may be considered suitable), and 10 (2.9%) more donors overall. The impact of each strategy is summarised in Figure 2.3, and the impact under alternative risk thresholds explored in sensitivity analyses are presented in Supplementary Figure 2.S2 and Supplementary Table 2.S3. The calculations

used to determine the impact of each strategy are shown in further detail in Supplementary Tables 2.S4-2.S7.

2.6 Discussion

We analysed an observational cohort of potentially suitable deceased donor referrals from NSW during 2010-2013 and found that information available at referral relating to potential donors' cancer history was lacking. Despite this, perceived cancer transmission risk was mostly accurate. Nevertheless, more than a quarter of those declined for donation because of a perceived cancer transmission risk were verified as suitable using linked health records and were classified as missed opportunities. Decision support could marginally reduce missed opportunities but would also increase the number of excess-risk donors. While it is unclear whether the benefits of increasing donation outweigh the costs of increasing transmission risk, this trade-off could be mitigated with real-time data-linkage to existing health datasets which would reduce both missed opportunities and excess-risk donors.

These findings demonstrate that relatively simple interventions to utilise potential donors with a history of cancer more efficiently could provide small improvements in terms of the quantity and suitability of donors. A single donor provides an average of 3.3 organs[24], so even a small increase in the annual donation rate translates to a very real and meaningful difference for the 1,700 people waiting for an organ transplant[25]. Strategies to avoid missed opportunities among potential donors with cancer may be worthwhile pursuing in conjunction with other efforts such as increasing family consent rates. Indeed, our study highlights the broader point that information available at referral relating to other diseases

could also be verified to potentially increase the pool of available organs, for example infectious diseases such as HIV, and hepatitis B and C[16].

Our findings are likely relevant to other jurisdictions within Australia due to similarities in organ donation systems. It may be challenging to identify missed opportunities in other countries that do not collate donor referral information. However, many regions such as the UK, Canada, and the USA maintain a working transplant registry and could link to population-based cancer registries to verify cancers. Any potential increase in donation rates may suggest previous missed opportunities.

To our knowledge no studies have examined the impact of decision support or real-time data-linkage to potential donor's health records, despite calls for this to be implemented[26]. In 2019 the NSW OTDS began linkage to the cancer registry, but we currently have insufficient data to determine the effectiveness of this measure. Furthermore, TSANZ guidelines are currently under review and will include changes to estimated transmission risks, revising some cancers to a lower risk category which will likely increase donation[27].

A major strength of this study is the use of comprehensive linked data from SAFEBOD. Including many health datasets means it is unlikely any transmissible cancers diagnosed or treated whilst resident in NSW have been missed. Although some non-melanoma skin cancers diagnosed or treated in private clinics may not be reported in SAFEBOD, these are not contraindicated for donation[10] and would therefore have little impact on our findings. Despite only including potential donors from NSW, it remains possible that some who

moved to NSW had previous cancer diagnoses interstate which would not be verified in SAFEBOD, hence accuracy of perceived information may be underestimated.

Although SAFEBOD includes the CCR records from 1972, these only extend until 2013 despite the linkage for SAFEBOD being completed in 2018 (i.e., a 5-year lag). It is possible that cancers diagnosed before 1972 have been missed, but unlikely that these would be relevant to determining transmission risk without a more recent recurrence reported in other SAFEBOD datasets (e.g., APDC). Restricting our study period to the end of 2013 limits the relevance of our findings to current practice, however due to the lag in CCR data availability this delay was unavoidable. Attitudes to cancer transmission risk are unlikely to have changed significantly over time, so we would expect to find a similar number of missed opportunities if more recent data were available. Based on our findings, we expect that the introduction of linkage to the cancer registry by the NSW OTDS in 2019, without any additional decision support, has had only a small impact overall. Although electronic medical records were introduced across Australia in 2019, these have not been widely used until very recently and are therefore unlikely to have impacted donation practices[28].

A limitation of our study is that potential donors reported as declined due to perceived cancer may have been declined for multiple reasons, so they may not have been accepted even in the absence of a perceived cancer. Considering that those declined due to perceived cancer are of a similar age and have fewer comorbidities than those who were accepted despite a perceived cancer suggests that these potential donors may have been accepted had they not had a perceived cancer. Furthermore, we have assumed that clinicians' decisions to accept or decline a potential donor are based on the donor's characteristics and

medical history alone. In practice, other factors may also influence this decision, such as which organ is being considered, or the recipient's age. We lacked data on individual organ offers to transplanting centres, hence we could only account for donor-level factors in our analysis. It is possible that some of the missed opportunities we identified may have been because a potential donor was declined without considering all potential recipients.

We have demonstrated that missed opportunities could be better utilised to slightly increase donation without necessarily compromising recipients' safety, however bigger increases inherently involve a trade-off between increasing donation and reducing cancer transmission risk. Future work using SAFEBOD will focus on identifying cases of donor to recipient transmissions to provide further evidence to evaluate the costs and benefits of our proposed strategies for increasing donation and to support policy decisions.

2.7 Conclusions

Information about potential donors' cancer history available at referral is lacking, however overall perceived cancer risk is nevertheless relatively accurate. Despite this, there are a substantial number of missed opportunities where decision support and more accurate cancer history would have resulted in more donations, without necessarily compromising safety.

2.8 Acknowledgements

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2.10 Tables

Table 2.6: Characteristics of potentially suitable donor referrals with at least one perceived cancer

	Declined for donation						Accepted for donation						Overall		
	Verified unsuitable		Verified suitable		Total		Verified unsuitable		Verified suitable		Total				
Characteristics			*Missed opportunities*				*Excess-risk donors*								P-value[†]
N (row %)	94	(60)	38	(24)	132	(85)	5	(3)	19	(12)	24	(15)	156	(100)	
Age, median (IQR)	61.5	(50-71)	67	(51-71)	63	(51-72)	61	(60-62)	61	(54-64)	61	(56-63.5)	62	(52-71)	0.5
Female	41	(44)	19	(50)	60	(45)	3	(60)	6	(32)	9	(38)	69	(44)	0.5
Comorbidities, mean (SD)	0.8	(0.96)	0.9	(1.11)	0.8	(1.00)	1.2	(1.10)	2.1	(1.15)	1.9	(1.18)	1.0	(1.10)	<0.001
Hypertension	17	(18)	9	(24)	26	(20)	0	(0)	9	(47)	9	(38)	35	(22)	
Hyperlipidaemia	4	(4)	1	(3)	5	(4)	2	(40)	9	(47)	11	(46)	16	(10)	
Chronic liver disease	0	(0)	0	(0)	0	(0)	0	(0)	1	(5)	1	(4)	1	(<1)	
Chronic kidney disease	4	(4)	2	(5)	6	(5)	1	(20)	2	(11)	3	(13)	9	(6)	
Diabetes (T1 or T2)	5	(5)	5	(13)	10	(8)	0	(0)	5	(26)	5	(21)	15	(10)	
Respiratory disease	10	(11)	3	(8)	13	(10)	1	(20)	5	(26)	6	(25)	19	(12)	
Infection	11	(12)	7	(18)	18	(14)	0	(0)	1	(5)	1	(4)	19	(12)	
Ischaemic heart disease	20	(21)	7	(18)	27	(20)	2	(40)	8	(42)	10	(42)	37	(24)	
Perceived risk															<0.001
Not contraindicated	2	(2)	2	(5)	4	(3)	3	(60)	16	(84)	19	(79)	23	(15)	
Minimal risk (<0.1%)	0	(0)	0	(0)	0	(0)	0	(0)	2	(11)	2	(8)	2	(1)	
Low risk (0.1-2%)	1	(1)	3	(8)	4	(3)	1	(20)	1	(5)	2	(8)	6	(4)	
Intermediate risk (2-10%)	9	(10)	1	(3)	10	(8)	0	(0)	0	(0)	0	(0)	10	(6)	
High risk (>10%)	11	(12)	6	(16)	17	(13)	0	(0)	0	(0)	0	(0)	17	(11)	
Contraindicated	71	(76)	26	(68)	97	(73)	1	(20)	0	(0)	1	(4)	98	(63)	

[†]P-values calculated using Wilcoxon rank-sum test for age, comorbidities and perceived risk, and Fisher's exact test for sex

Table 2.7: Perceived and verified cancer transmission risk for potentially suitable donor referrals with transmission risks estimated using TSANZ guidelines

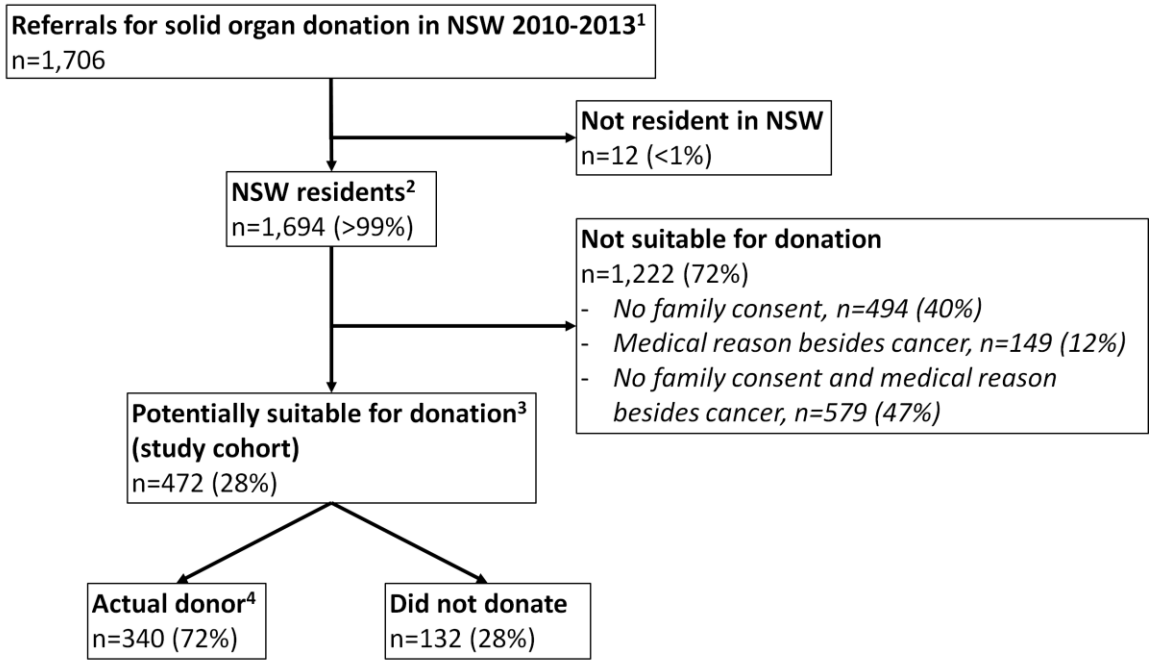
			Verified risk					
Perceived risk	None	Not contraindicated	Minimal-risk (<0.1%)	Low-risk (0.1-2%)	Intermediate-risk (2-10%)	High-risk (>10%)	Contraindicated	Total
Declined for donation								
None	0	0	0	0	0	0	0	0
Not contraindicated	0	2	0	0	0	0	2	4
Minimal-risk (<0.1%)	0	0	0	0	0	0	0	0
Low-risk (0.1-2%)	0	0	0	3	0	0	1	4
Intermediate-risk (2-10%)	0	1	0	0	5	0	4	10
High-risk (>10%)	0	6	0	0	0	6	5	17
Contraindicated	0	25	0	1	0	0	71	97
Total	0	34	0	4	5	6	83	132
Actual donors								
None	283	24	0	0	0	0	0	307
Not contraindicated	0	25	0	0	0	0	3	28
Minimal-risk (<0.1%)	0	2	0	0	0	0	0	2
Low-risk (0.1-2%)	0	0	0	1	0	0	1	2
Intermediate-risk (2-10%)	0	0	0	0	0	0	0	0
High-risk (>10%)	0	0	0	0	0	0	0	0
Contraindicated	0	0	0	0	0	0	1[†]	1
Total	283	51	0	1	0	0	5	340

Agreement between perceived and verified transmission risk
Potential appropriate decision to decline/accept for donation
Potential missed opportunity
Potential excess-risk donor

[†]One potential donor with a malignant melanoma (perceived and verified) was accepted for donation

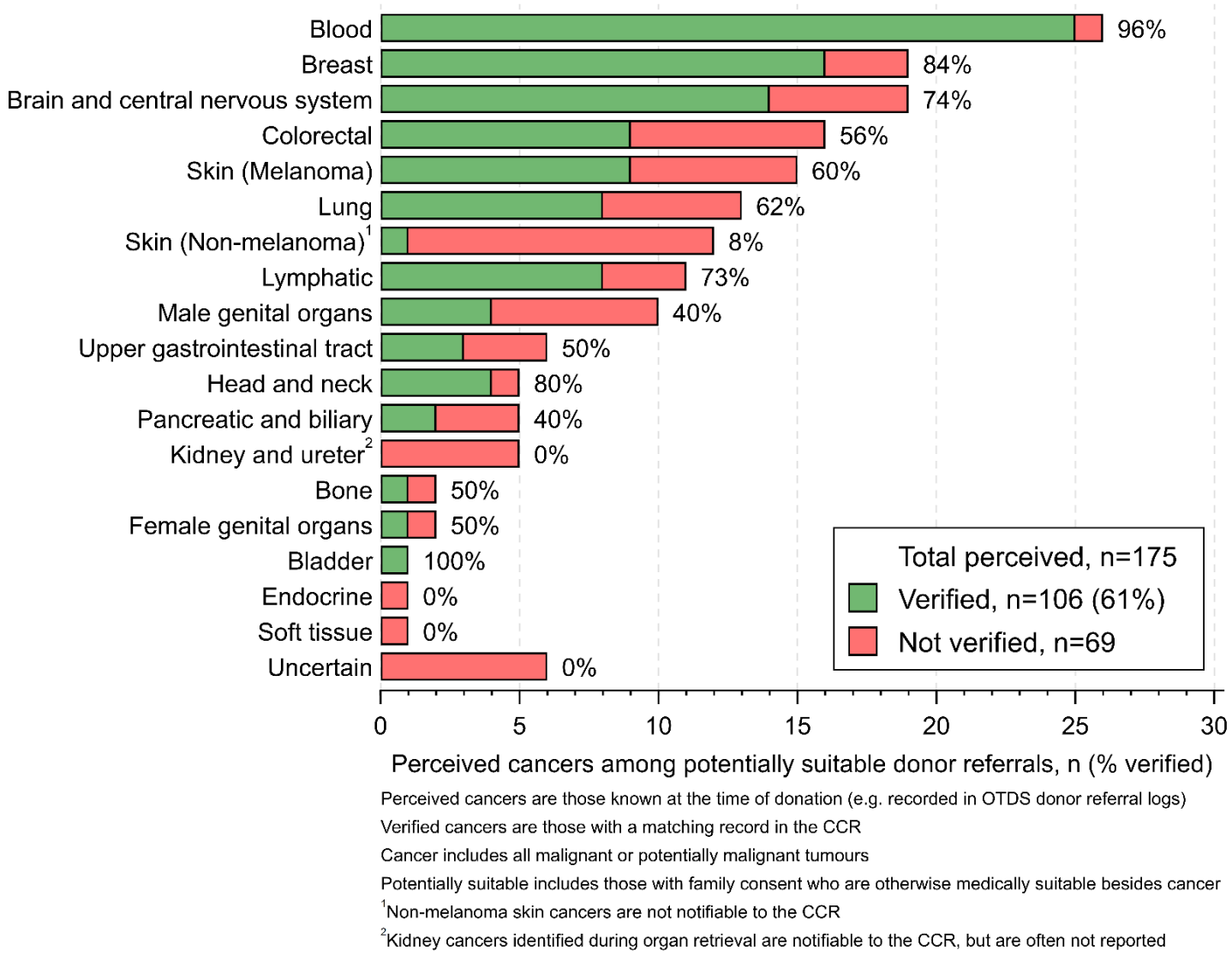
2.11 Figures

Figure 2.1: Flowchart of donation outcomes for potential solid organ donor referrals in NSW



[1] *Includes three people who recovered after referral (i.e. medically unsuitable), and were later referred again*
[2] *Based on postcode, and includes postcodes that cross a NSW border*
[3] *Donor referrals who potentially could have donated if we ignore their cancer history. Includes all actual donors, and those declined because of their perceived cancer transmission risk*
[4] *Includes 20 donors (6%) with no organs used for transplant*

Figure 2.2: Perceived cancers and their verification from linked cancer registry records, by primary site



Perceived cancers are those known at the time of donation (e.g. recorded in OTDS donor referral logs)

Verified cancers are those with a matching record in the CCR

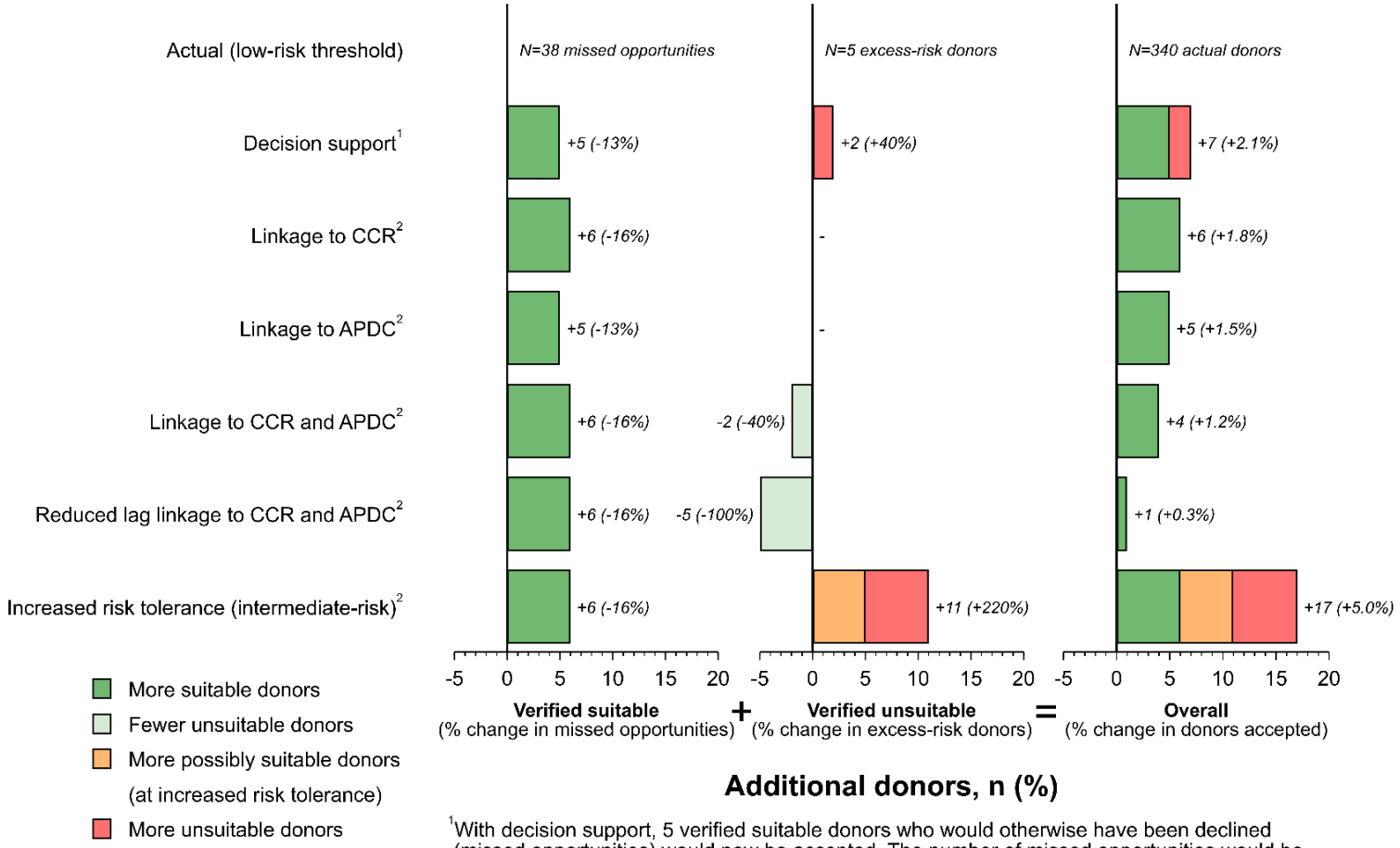
Cancer includes all malignant or potentially malignant tumours

Potentially suitable includes those with family consent who are otherwise medically suitable besides cancer

[1]Non-melanoma skin cancers are not notifiable to the CCR

[2]Kidney cancers identified during organ retrieval are notifiable to the CCR, but are often not reported

Figure 2.3: Change in number of verified suitable and unsuitable donors with each potential strategy to reduce missed opportunities and excess-risk donors, under a low-risk threshold



[1]With decision support, 5 verified suitable donors who would otherwise have been declined (missed opportunities) would now be accepted. The number of missed opportunities would be reduced from 38 to 33, which is a 13% reduction. Furthermore, 2 verified unsuitable donors who would otherwise have been declined would now be accepted (excess-risk donors). The number of excess-risk donors would increase from 5 to 7, which is a 40% increase. Overall, the number of donors would increase from 340 to 347, which is a 2.1% increase.

[2]Linkage and increased risk tolerance are in conjunction with decision support

2.12 Supplementary material

Supplementary Table 2.S1: Agreement in cancer transmission risk and suitability for donation stratified by risk tolerance threshold

	Agreement in risk			Agreement in suitability								
				Minimal-risk threshold			*Low-risk threshold*			*Intermediate-risk threshold*		
Strategy	n	%	κ	n	%	κ	n	%	κ	n	%	κ
Actual	397	84	0.72	435	92	0.79	432	92	0.77	429	91	0.74
Linkage to CCR	400	85	0.73	436	92	0.80	435	92	0.79	433	92	0.76
Linkage to APDC	423	90	0.82	437	93	0.80	434	92	0.78	432	92	0.76
Linkage to CCR and APDC	425	90	0.83	438	93	0.81	437	93	0.80	435	92	0.78
Reduced lag linkage to CCR and APDC	430	91	0.85	441	93	0.83	440	93	0.82	438	93	0.80

Supplementary Table 2.S2: Primary site of cancers among missed opportunities for donation under minimal-risk, low-risk, and intermediate-risk thresholds

Primary site	Perceived risk	Verified risk	Risk threshold under which cancer would be a missed opportunity	N[†]
Prostate	Low-risk (0.1-2%)	Not contraindicated	Minimal-risk, low-risk, or intermediate-risk	3
Brain	Intermediate-risk (2-10%)	Not contraindicated	Minimal-risk, low-risk, or intermediate-risk	1
Colorectal	High-risk (>10%)	Not contraindicated	Minimal-risk, low-risk, or intermediate-risk	3
Lung	High-risk (>10%)	Not contraindicated	Minimal-risk, low-risk, or intermediate-risk	3
Leukaemia	Contraindicated	Not contraindicated	Minimal-risk, low-risk, or intermediate-risk	8
Breast	Contraindicated	Not contraindicated	Minimal-risk, low-risk, or intermediate-risk	6
Bone marrow	Contraindicated	Not contraindicated	Minimal-risk, low-risk, or intermediate-risk	3
Lymphatic	Contraindicated	Not contraindicated	Minimal-risk, low-risk, or intermediate-risk	2
Pancreas	Contraindicated	Not contraindicated	Minimal-risk, low-risk, or intermediate-risk	2
Bladder	Contraindicated	Not contraindicated	Minimal-risk, low-risk, or intermediate-risk	1
Blood	Contraindicated	Not contraindicated	Minimal-risk, low-risk, or intermediate-risk	1
Bone	Contraindicated	Not contraindicated	Minimal-risk, low-risk, or intermediate-risk	1
Lung	Contraindicated	Not contraindicated	Minimal-risk, low-risk, or intermediate-risk	1
Oesophagus	Contraindicated	Not contraindicated	Minimal-risk, low-risk, or intermediate-risk	1
Stomach	Contraindicated	Not contraindicated	Minimal-risk, low-risk, or intermediate-risk	1
Uterus	Contraindicated	Not contraindicated	Minimal-risk, low-risk, or intermediate-risk	1
Prostate	None (no cancer recorded)	Low-risk (0.1-2%)	Low-risk or intermediate-risk	3
Brain	Low-risk (0.1-2%)	Low-risk (0.1-2%)	Low-risk or intermediate-risk	1
Brain	Intermediate-risk (2-10%)	Intermediate-risk (2-10%)	Intermediate-risk	5

[†] There were 47 cancers among 43 missed opportunities for donation under an intermediate-risk threshold

Supplementary Table 2.S3: Number of verified suitable and unsuitable donors accepted or declined with each potential strategy for reducing missed opportunities and excess-risk donors under various risk thresholds

	Verified suitable		Verified unsuitable		Overall	
Strategy[†]	Declined[‡]	Accepted	Declined	Accepted[§]	Declined	Accepted
Minimal-risk threshold						
Actual	34	334	98	6	132	340
Decision support	32	336	99	5	131	341
Linkage to CCR	31	337	99	5	130	342
Linkage to APDC	32	336	101	3	133	339
Linkage to CCR and APDC	31	337	101	3	132	340
Reduced lag linkage to CCR and APDC	31	337	104	0	135	337
Increased risk tolerance (low-risk)	32	336	93	11	125	347
Low-risk threshold						
Actual	38	335	94	5	132	340
Decision support	33	340	92	7	125	347
Linkage to CCR	32	341	94	5	126	346
Linkage to APDC	33	340	94	5	127	345
Linkage to CCR and APDC	32	341	96	3	128	344
Reduced lag linkage to CCR and APDC	32	341	99	0	131	341
Increased risk tolerance (intermediate-risk)	32	341	83	16	115	357
Intermediate-risk threshold						
Actual	43	335	89	5	132	340
Decision support	32	346	83	11	115	357
Linkage to CCR	31	347	86	8	117	355
Linkage to APDC	32	346	86	8	118	354
Linkage to CCR and APDC	31	347	88	6	119	353
Reduced lag linkage to CCR and APDC	31	347	91	3	122	350
Increased risk tolerance (high-risk)	26	352	72	22	98	374

[†] Linkage and increased risk tolerance are in conjunction with decision support

[‡] Missed opportunities

[§] Excess-risk donors

Supplementary Table 2.S4: Calculation of number of accepted donors, declined donors, missed opportunities, and excess-risk donors - Actual

		Verified risk					
Perceived risk	None	Not contraindicated	Minimal risk (<0.1%)	Low risk (0.1-2%)	Intermediate risk (2-10%)	High risk (>10%)	Contraindicated
Declined for donation							
None	0	0	0	0	0	0	0
Not contraindicated	0	2	0	0	0	0	2
Minimal risk (<0.1%)	0	0	0	0	0	0	0
Low risk (0.1-2%)	0	0	0	3	0	0	1
Intermediate risk (2-10%)	0	1	0	0	5	0	4
High risk (>10%)	0	6	0	0	0	6	5
Contraindicated	0	25	0	1	0	0	71
Actual donors							
None	283	24	0	0	0	0	0
Not contraindicated	0	25	0	0	0	0	3
Minimal risk (<0.1%)	0	2	0	0	0	0	0
Low risk (0.1-2%)	0	0	0	1	0	0	1
Intermediate risk (2-10%)	0	0	0	0	0	0	0
High risk (>10%)	0	0	0	0	0	0	0
Contraindicated	0	0	0	0	0	0	1

38 **94** **335** **5**

This table is identical to Table 2.7, but with highlighting and bordering to demonstrate how the number of missed opportunities and excess-risk donors are calculated

Declined for donation: 38 verified suitable (missed opportunities) + 94 verified unsuitable (appropriate declines) = 132 declined for donation

Accepted for donation: 335 verified suitable (appropriate accepts) + 5 verified unsuitable (excess-risk donors) = 340 accepted for donation

Missed opportunities: 38 verified suitable but declined for donation

Excess-risk donors: 5 verified unsuitable but accepted for donation

Supplementary Table 2.S5: Calculation of number of accepted donors, declined donors, missed opportunities, and excess-risk donors – Decision support

			Verified risk				
Perceived risk	None	Not contraindicated	Minimal risk (<0.1%)	Low risk (0.1-2%)	Intermediate risk (2-10%)	High risk (>10%)	Contraindicated
Actual declines							
None	0	0	0	0	0	0	0
Not contraindicated	0	2	0	0	0	0	2
Minimal risk (<0.1%)	0	0	0	0	0	0	0
Low risk (0.1-2%)	0	0	0	3	0	0	1
Intermediate risk (2-10%)	0	1	0	0	5	0	4
High risk (>10%)	0	6	0	0	0	6	5
Contraindicated	0	25	0	1	0	0	71
Actual donors							
None	283	24	0	0	0	0	0
Not contraindicated	0	25	0	0	0	0	3
Minimal risk (<0.1%)	0	2	0	0	0	0	0
Low risk (0.1-2%)	0	0	0	1	0	0	1
Intermediate risk (2-10%)	0	0	0	0	0	0	0
High risk (>10%)	0	0	0	0	0	0	0
Contraindicated	0	0	0	0	0	0	1

5 **3** **33** **91** **335** **4** **0** **1**

With decision support, all potential donors perceived > low-risk would be declined, and all those perceived ≤ low-risk would be accepted

Declined for donation: 33 missed opportunities unchanged + 91 appropriate declines unchanged + 0 verified suitable donors declined + 1 excess-risk donor declined = 125 declined for donation

Accepted for donation: 5 missed opportunities accepted + 3 appropriate declines now accepted + 335 appropriate accepts unchanged + 4 excess-risk donors unchanged = 347 accepted for donation

Missed opportunities: 33 missed opportunities unchanged + 0 verified suitable donors declined = 33 missed opportunities. Excludes 5 actual missed opportunities now accepted for donation

Excess-risk donors: 3 appropriate declines now accepted + 4 excess-risk donors unchanged = 7 excess-risk donors. Excludes 1 actual excess-risk donor now declined for donation

Supplementary Table 2.S6: Calculation of number of accepted donors, declined donors, missed opportunities, and excess-risk donors – Real-time data-linkage to the CCR and APDC

			Verified risk				
Perceived risk	None	Not contraindicated	Minimal risk (<0.1%)	Low risk (0.1-2%)	Intermediate risk (2-10%)	High risk (>10%)	Contraindicated
Actual declines							
None	0	0	0	0	0	0	0
Not contraindicated	0	3	0	0	0	0	2
Minimal risk (<0.1%)	0	0	0	0	0	0	0
Low risk (0.1-2%)	0	0	0	3	0	0	0
Intermediate risk (2-10%)	0	1	0	0	5	0	3
High risk (>10%)	0	6	0	0	0	6	4
Contraindicated	0	24	0	1	0	0	74
Actual donors							
None	283	3	0	0	0	0	0
Not contraindicated	0	46	0	0	0	0	1
Minimal risk (<0.1%)	0	2	0	0	0	0	0
Low risk (0.1-2%)	0	0	0	1	0	0	0
Intermediate risk (2-10%)	0	0	0	0	0	0	0
High risk (>10%)	0	0	0	0	0	0	0
Contraindicated	0	0	0	0	0	0	4

6 **2** **32** **92** **335** **1** **0** **4**

With real-time data-linkage to the CCR and APDC, potential donors' perceived risk would change based on new information available at time of referral

Declined for donation: 32 missed opportunities + 92 appropriate declines + 0 verified suitable donors declined + 4 excess-risk donors declined = 128 declined for donation

Accepted for donation: 6 missed opportunities accepted + 2 appropriate declines now accepted + 335 appropriate accepts + 1 excess-risk donor = 344 accepted for donation

Missed opportunities: 32 missed opportunities + 0 verified suitable donors declined = 32 missed opportunities. Excludes 6 actual missed opportunities now accepted for donation

Excess-risk donors: 2 appropriate declines now accepted + 1 excess-risk donor = 3 excess-risk donors. Excludes 4 actual excess-risk donors now declined for donation

Supplementary Table 2.S7: Calculation of number of accepted donors, declined donors, missed opportunities, and excess-risk donors – Increased risk tolerance

			Verified risk				
Perceived risk	None	Not contraindicated	Minimal risk (<0.1%)	Low risk (0.1-2%)	Intermediate risk (2-10%)	High risk (>10%)	Contraindicated
Actual declines							
None	0	0	0	0	0	0	0
Not contraindicated	0	2	0	0	0	0	2
Minimal risk (<0.1%)	0	0	0	0	0	0	0
Low risk (0.1-2%)	0	0	0	3	0	0	1
Intermediate risk (2-10%)	0	1	0	0	5	0	4
High risk (>10%)	0	6	0	0	0	6	5
Contraindicated	0	25	0	1	0	0	71
Actual donors							
None	283	24	0	0	0	0	0
Not contraindicated	0	25	0	0	0	0	3
Minimal risk (<0.1%)	0	2	0	0	0	0	0
Low risk (0.1-2%)	0	0	0	1	0	0	1
Intermediate risk (2-10%)	0	0	0	0	0	0	0
High risk (>10%)	0	0	0	0	0	0	0
Contraindicated	0	0	0	0	0	0	1

6 **5** **7** **32** **82** **335** **0** **4** **0** **1**

With increased risk tolerance, all potential donors perceived > intermediate-risk would be declined, and all those perceived ≤ intermediate-risk would be accepted

Declined for donation: 32 missed opportunities + 82 appropriate declines + 0 verified suitable donors declined + 1 excess-risk donor declined = 115 declined for donation

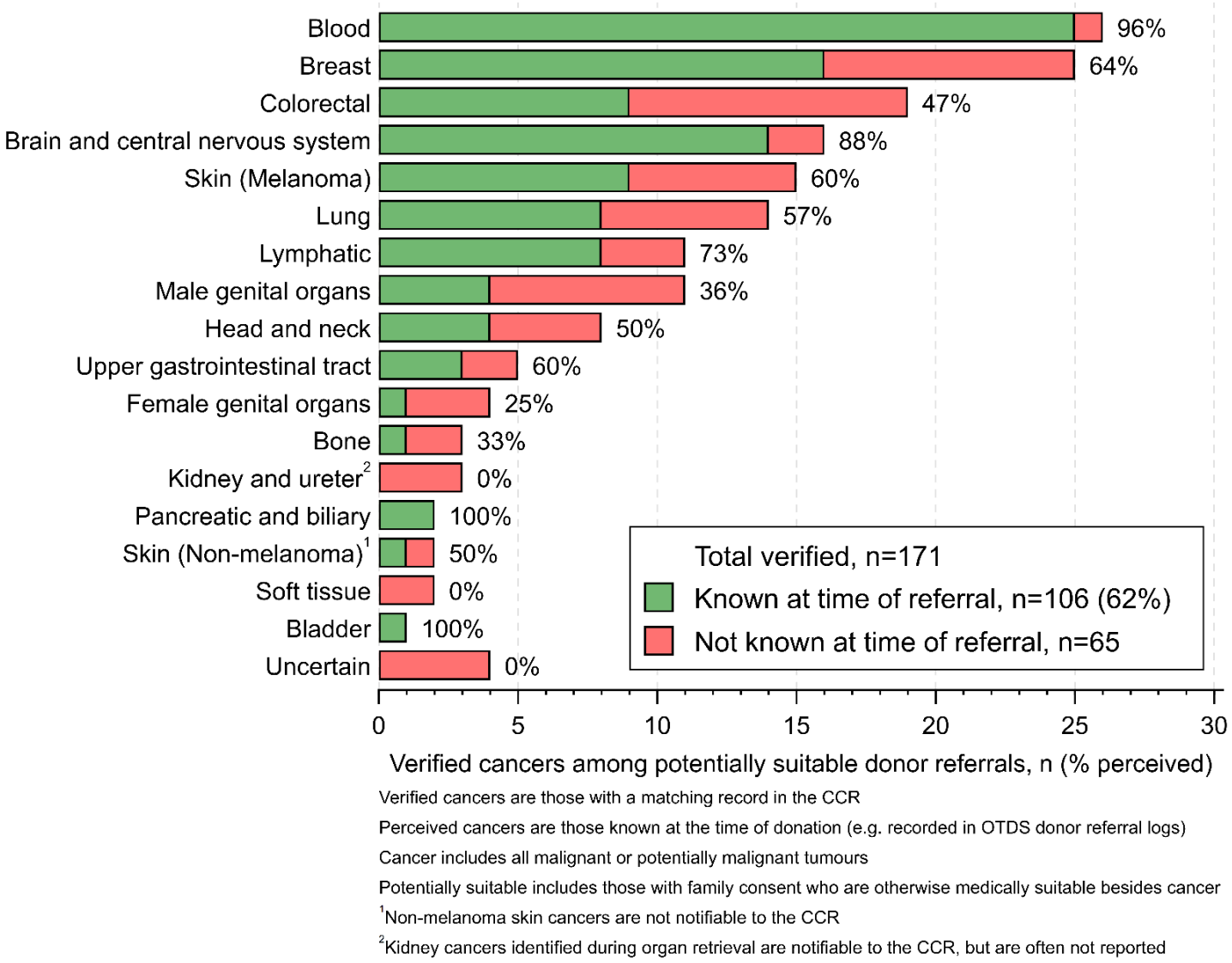
Accepted for donation: 6 missed opportunities accepted + 5 intermediate-risk declines now accepted + 7 appropriate declines now accepted + 335 appropriate accepts + 0 intermediate-risk donors + 4 excess-risk donors = 357 accepted for donation

Missed opportunities: 32 missed opportunities + 0 verified suitable donors declined = 32 missed opportunities. Excludes 6 actual missed opportunities now accepted for donation

Intermediate-risk donors: 5 intermediate-risk declines now accepted + 0 intermediate-risk donors = 5 intermediate-risk donors

Excess-risk donors (> intermediate-risk): 7 appropriate declines now accepted + 4 excess-risk donors = 11 excess-risk donors. Excludes 1 actual excess-risk donor now declined for donation

Supplementary Figure 2.S1: Verified cancers and whether they were known at time of referral (perceived), by primary site



Verified cancers are those with a matching record in the CCR

Perceived cancers are those known at the time of donation (e.g. recorded in OTDS donor referral logs)

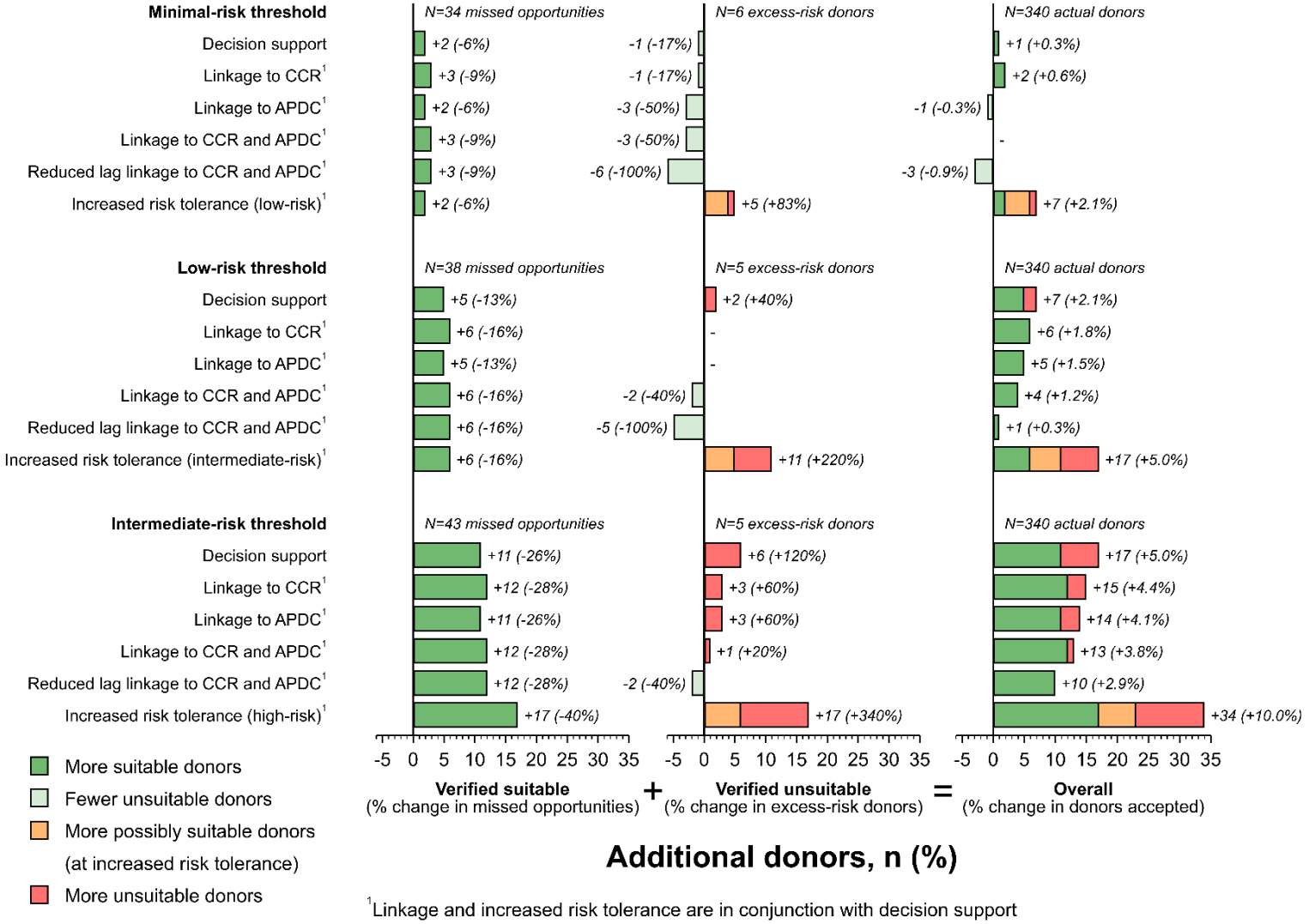
Cancer includes all malignant or potentially malignant tumours

Potentially suitable includes those with family consent who are otherwise medically suitable besides cancer

[1]Non-melanoma skin cancers are not notifiable to the CCR

[2]Kidney cancers identified during organ retrieval are notifiable to the CCR, but are often not reported

Supplementary Figure 2.S2: Change in number of verified suitable and unsuitable donors with each potential strategy to reduce missed opportunities and excess-risk donors – sensitivity analyses under varying risk tolerance thresholds



[1]Linkage and increased risk tolerance are in conjunction with decision support

Chapter 3: Cancer transmissions and non-transmissions

3.1 Preface

This chapter presents an analysis of SAFEBOD data that identified transplant procedures where the donor had a cancer (either at the time of donation, historically, or in the case of living donors, diagnosed up to one after donation), and examined recipient's outcomes after transplantation. The aim of this study was to determine whether there were any cases of cancer transmission or non-transmission (i.e., a transplant procedure where a transmission could potentially have occurred but didn't).

An abstract from this study was submitted and presented at the 20th Congress of the European Society for Organ Transplantation (ESOT) in Milan, Italy. The abstract was one of the top ranked submissions and was therefore invited to be submitted as a full paper to Transplant International, where it is now published [1].

3.1.1 Identifying transmissions and non-transmissions

This study relied on cancer data from SAFEBOD datasets that I had previously coded as part of another study (chapter 2 of this thesis) [2]. By comparing details of a donor's cancer history (including up to one year after donation in the case of living donors) with details of a recipient's cancer outcomes after transplantation, it can be determined whether a transplant procedure has resulted in donor-to-recipient transmission of cancer. International guidelines have already been established to assist with this determination, known as imputability (i.e., the likelihood that a cancer in a transplant recipient can be attributed to the donor) [3,4]. Specifically, it can be difficult to determine whether a recipient's cancer is donor-transmitted, or merely donor-derived (i.e., a de-novo cancer that just so happens to occur in the transplanted organ). As this was a retrospective analysis of existing

administrative data, assessing imputability was further complicated by the absence of biopsy data in cases of suspected transmission.

To minimize the risk of bias, potential transmissions were assessed by two co-authors: Prof. Angela Webster (co-supervisor for this thesis, and expert in transplant nephrology), and Prof. Claire Vajdic (expert in cancer epidemiology). Any disagreements were resolved by a third co-author, Dr. Melanie Wyld (co-supervisor for this thesis and expert in transplant nephrology). The assistance of these experts was incredibly valuable and greatly appreciated, and I therefore attempted to present the data on potential transmissions in an easy-to-understand format to make efficient use of their time. I created an Excel spreadsheet [5] with one row for each transplant recipient in the study cohort. I included columns with relevant information about the donor (age, sex, donor type, mode of death if applicable), the recipient (age and sex), and the transplant procedure (organs transplanted and date). I colour-coded the text of each row corresponding to whether the donor was living or deceased at the time of donation, and shaded groups of rows in alternating white and grey so that recipients from the same donor could be more readily identified.

I also created columns for donors' and recipients' cancer history. This included all cancer information from every dataset in SAFEBOD, combined into a single text field. I removed replicated cancers within each dataset (e.g., a cancer recorded against every episode of care within APDC). Each unique cancer appeared in its own paragraph, in order of the approximate date of diagnosis, with information about the dataset the information originated from, the date it was recorded, the approximate diagnosis date, primary site (including ICD-10-AM code if available), malignancy status (benign, in-situ, or malignant),

presence of metastases, and the specific type of cancer (including histology code if available). This provided a quick summary of all cancer records for an individual and made it easy to see the progression of cancers over time (e.g., a diagnosis of a benign colorectal tumour eventually being upgraded to a malignancy).

Finally, I wrote a background summary of the aims of the study and information about how transmissions and non-transmissions should be defined, as well as a summary of what information was available from each SAFEBOD dataset. This helped ensure consistency of decisions across all three experts. These summaries are presented in Table 3.1 and Table 3.2.

Table 3.1 Background summary provided to three experts to assist with determining imputability of cancer transmissions

Topic	Details
Population:	Deceased donor transplants from a NSW donor to a NSW recipient, 2000-2012 Living donor transplants from a NSW donor to a NSW recipient, 2004-2012
Inclusion criteria:	Potential transmissions. This means at least one of the following is true: The donor had cancer before transplant The donor had cancer after transplant (Living donors only. It's possible a cancer diagnosed after transplant was present at the time of transplant) The recipient had cancer after transplant We identified 271 transplants (donor-recipient pairs) that were potential transmissions This includes 197 deceased donor transplants and 74 living donor transplants
Aim:	To classify each transplant (donor-recipient pair) based on the likelihood a transmission has occurred, and whether it should be counted as a non-transmission
Method:	The NOTIFY guidelines provide a framework for assessing the likelihood that a transplant was a transmission https://www.notifylibrary.org/sites/default/files/Booklet_2018_1.pdf But these guidelines aren't thorough enough to automate this process We still need clinical expertise and experience to consider each transplant on a case-by-case basis
Transmissions:	A transmission is when a recipient has a cancer that is donor-transmitted It's possible that a recipient develops a de-novo cancer in the transplanted organ, in which case it would be 'donor-derived' (i.e. not a transmission) We can't be sure whether a recipient's cancer was donor-transmitted, donor-derived, or unrelated to the donor So identifying transmissions isn't simply a yes or no question Instead, we classify each transplant based on the likelihood that it was a transmission vs. not a transmission The likelihood categories are: Definite/likely/possible/excluded If you feel like an extra category would be informative, please feel free to use this. E.g. adding a category for 'unlikely' for transmissions that cannot be completely ruled out We have tried to present all of the information you would need to classify each transplant. If you need more information about any transplants, please mention this as a comment

Topic	Details
Non-transmissions:	Non-transmissions are not the opposite of transmissions. The terminology can be confusing. A non-transmission is when a donor has a cancer that could potentially have been transmitted, but wasn't This includes cases where a recipient's cancer is donor-derived (i.e. transmission is excluded), as well as cases where the recipient never had cancer Unfortunately, there are no guidelines for assessing non-transmissions It may be easier to think of these as a yes or no question (i.e. a transplant either is or isn't a non-transmission) But you could also add categories of likelihood if you are uncertain (e.g. a living donor with cancer diagnosed after transplant where you aren't sure if the cancer was present before transplant) In cases where a donor has cancer but the recipient does not, it may be useful to ask: "If the recipient had evidence of the same cancer shortly after transplant, would I have thought this was a transmission?" If the answer is yes, then it must be a non-transmission, since it potentially could have been a transmission If the answer is no, then perhaps the donor's cancer could not possibly have been transmitted. So it would be nothing (a non-event)

Table 3.2 Summary of cancer information available from each SAFEBOD dataset, provided to three experts to assist with determining imputability of cancer transmissions

Dataset	Details
NSW CCR (ICD-10)	NSW Central Cancer Registry from 1972-2013. Details are based on the ICD-10 code and histology reported in the NSW central cancer registry Note that the cancer registry only provides and month and year of diagnosis, so we have assumed the 15th of the month as a placeholder
NSW CCR (ICD-O)	NSW Central Cancer Registry from 1972-2013. Details based on the ICD-O code and histology reported in the NSW central cancer registry. Note that the ICD-O codes were looked up against a list of ICD-10 codes to fill in the details of the cancer. Most of the time the details are the same, but there are some examples where ICD-10 and ICD-O differ. Every cancer in the cancer registry has an ICD-10 and ICD-O code, so it's best to rely on the details taken from the ICD-10 code.
APDC	NSW hospital admissions from 2000 to 2017. Cancer details are based on the ICD-10 codes. The cancer date is based on the hospital admission date
EDDC	NSW Emergency department visits from 2005 to 2017. Cancer details are based on ICD-10 codes
COD	NSW Cause of Death Unit Record File from 2000 to 2015. Cancer details are based on ICD-10 codes
RBDM	NSW Registry of Births, Deaths, and Marriages from 2000 to 2017. Cancers are sometimes mentioned as a cause of death. We have read through text fields to capture as much information as possible about the cancer
ORCHARD	Potential deceased donors in NSW from 2005-2015. Includes details of potential donor medical suitability discussions which may mention cancer. We have manually read through these text fields and captured as much information as possible about the cancer. Sometimes the approximate date of the cancer is provided (e.g. "~10 years ago"). Otherwise we used the date of donor referral as the date of cancer. This is typically 1-2 days before transplant

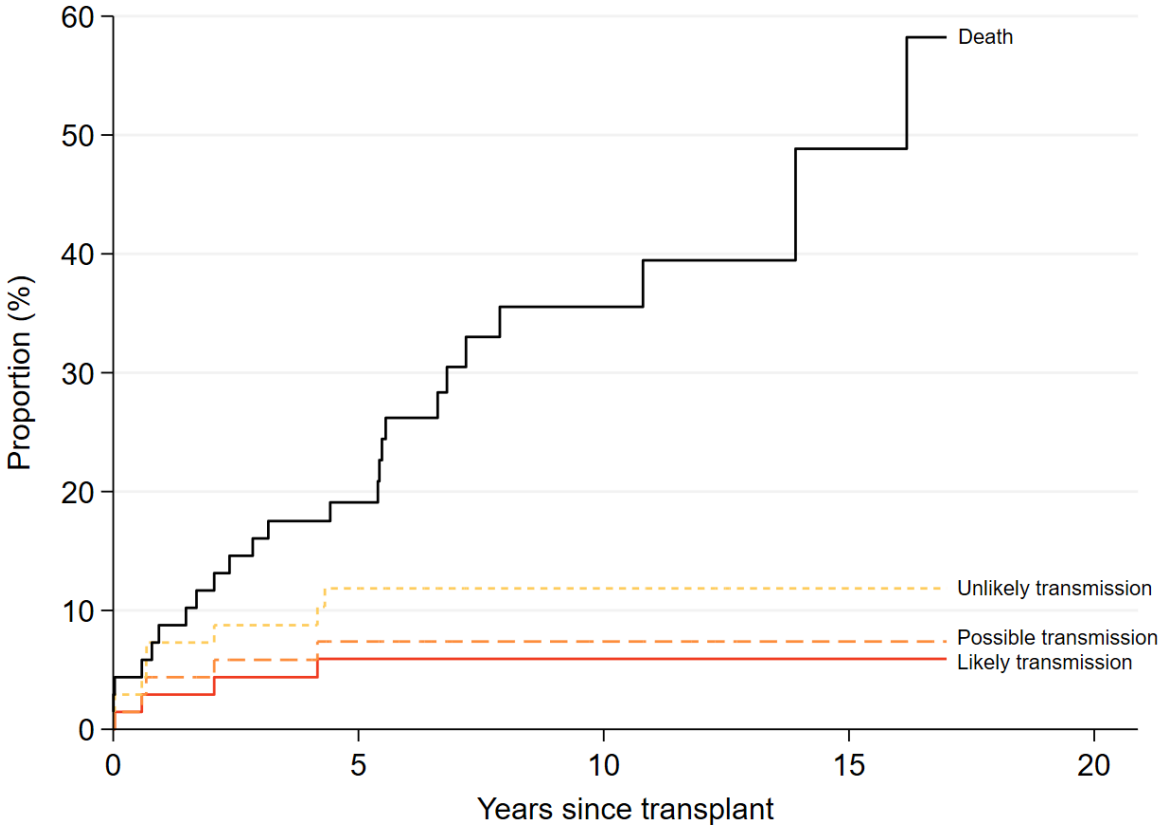
Dataset	Details
ANZOD	Australian and New Zealand Organ Donor Registry from 1970 to 2016. Includes details of any cancer in the donor that was known at the time of donation. Sites are coded using ANZODs own coding, not necessarily the same as ICD coding. In some cases, only a text description is provided. Information may sometimes be entered in retrospectively
ANZDATA	Australian and New Zealand Dialysis and Transplant Registry from 1970 to 2016. Includes data on all kidney transplant recipients, and kidney transplant procedures. For recipients, any cancers known at the time of transplant will be reported. The reasons for transplant failure sometimes mention cancer as well, so we have read through these to extract as much information as possible If the recipient received a transplant from a donor with cancer, we have included the details of that cancer against the donor. The date of cancer will then be the date of transplant
ANZCOTR	Australian and New Zealand Cardiothoracic Organ Transplant Registry from 2000 to 2015 Includes data on all heart and lung transplant recipients and transplant procedures. For recipients, any cancers known at the time of transplant will be reported. The reasons for transplant failure sometimes mention cancer as well, so we have read through these to extract as much information as possible If the recipient received a transplant from a donor with cancer, we have included the details of that cancer against the donor. The date of cancer will then be the date of transplant
ANZLTR	Australian and New Zealand Liver Transplant Registry from 2000 to 2015 Includes data on all liver transplant recipients and transplant procedures. For recipients, any cancers known at the time of transplant will be reported. The reasons for transplant failure sometimes mention cancer as well, so we have read through these to extract as much information as possible If the recipient received a transplant from a donor with cancer, we have included the details of that cancer against the donor. The date of cancer will then be the date of transplant

3.1.2 Death as a competing risk for cancer transmission

One limitation that is inevitable for any study attempting to estimate risk of cancer transmission is the presence of death as a competing risk. If a transplant recipient dies soon after transplant, there may not have been enough time for a transmitted cancer to be diagnosed. This means that any estimate of the number of transmissions will be biased downwards as some transmissions may have been undetected due to death occurring first.

To check how much influence this limitation might have on the results of this chapter, I estimated the cumulative incidence of cancer transmission in the presence of death as a competing risk using the methods described by Austin et al., 2016 [6]. Cancer transmissions were defined using three different likelihood thresholds; 1) including n=4 likely transmissions, 2) including 4 likely + 1 possible transmissions (n=5), and 3) including 4 likely + 1 possible + 3 unlikely transmissions (n=8). I compared the overall cumulative incidence of death after transplant (for which cancer transmission is <u>not</u> a competing risk) with the cumulative incidence of cancer transmission using these three definitions. These cumulative incidences are presented in Figure 3.1. The overall estimated cumulative incidence of cancer transmission was 5.9% for likely transmissions, 7.4% for likely/possible transmissions, and 11.9% for likely/possible/unlikely transmissions. This means that hypothetically, in the absence of death as a competing risk, we might have observed 4.03 likely transmissions (n=68 x 5.9%), 5.02 likely/possible transmissions (n=68 x 7.4%), and 8.06 likely/possible/unlikely transmissions (n=68 x 11.9%). As this hypothetical number of transmissions is virtually the same as the number observed, the presence of death as a competing risk is unlikely to have an important impact on the results of this chapter.

Figure 3.1: Cumulative incidence of death compared to the cumulative incidence of cancer transmission with death as a competing risk



3.1.3 References

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3.2 Abstract

Evidence on cancer transmission from organ transplantation is poor. We sought to identify cases of cancer transmission or non-transmission from transplantation in an Australian cohort of donors and recipients. We included NSW solid organ deceased donors 2000-2012 and living donors 2004-2012 in a retrospective cohort using linked data from the NSW Biovigilance Register (SAFEBOD). Central Cancer Registry (CCR) data 1972-2013 provided a minimum one-year post-transplant follow-up. We identified cancers in donors and recipients. For each donor-recipient pair, transmission was judged likely, possible, unlikely, or excluded using categorization from international guidelines. In our analysis, transmissions included those judged likely, while those judged possible, unlikely, or excluded were non-transmissions. In our cohort there were 2,502 recipients and 1,431 donors (715 deceased, 716 living). There were 2,544 transplant procedures, including 1,828 (72%) deceased and 716 (28%) living donor transplants. Among 1,431 donors, 38 (3%) had past or current cancer and they donated to 68 recipients (median 6.7 years follow-up). There were 64 (94%) non-transmissions, and four (6%) transmissions from two living and two deceased donors (all kidney cancers discovered during organ recovery). Donor transmitted cancers are rare, and selected donors with a past or current cancer may be safe for transplantation.

3.3 Introduction

Organ transplantation is a life-saving treatment for many people with end-stage organ failure. In Australia, people with end-stage kidney disease have a five-year survival of approximately 50% when treated with dialysis(1, 2), compared to 90% for those who receive a kidney transplant(3). Five-year post-transplant survival is also high after liver transplant (80%)(4), heart transplant (80%)(5), and lung transplant (70%)(5). Despite the clear benefits of transplantation, safety risks must also be carefully considered including the potential for donor to recipient transmission of infectious disease or cancer. Cancer transmission is of particular concern because it may be fatal for the recipient(6), and many potential donors with a history of cancer are therefore declined for transplantation. Recipients and transplant clinicians face a delicate trade-off between maximizing organ donation opportunities and minimizing the risk of transmission(7).

The Transplantation Society of Australia and New Zealand (TSANZ) has published clinical guidelines for organ transplantation from deceased donors(8). These guidelines provide an overview of the evidence surrounding the risk of cancer transmission by cancer site, and are similar to guidelines in the UK(9), Europe(10), and the US(11). However, the quality of evidence available for estimating cancer transmission risks is poor(12). Relatively few donors with a known history of cancer are accepted for donation(13). Those who are accepted are highly selected, hence cancer transmission is a rare occurrence(14, 15). Indeed, the recommendations for donors with a central nervous system (CNS) tumor, for instance, are ultimately based on studies with no observed transmissions(16, 17).

The Safety and Biovigilance in Organ Donation (SAFEBOD) Public Health Register was established in New South Wales (NSW) in 2018, with one of its aims to identify cases of donor to recipient cancer transmission and non-transmission(18). New South Wales is the largest Australian state with approximately 8.1 million people(19), and it is demographically representative of the entire country. We sought to use the SAFEBOD register to investigate cancer transmissions and non-transmissions in a cohort of donors and recipients over a 13-year period.

3.4 Methods

3.4.1 Study cohort

We performed a retrospective cohort study of solid organ donors and recipients linked to health records using data from the NSW Biovigilance Public Health Register (SAFEBOD). Records were linked probabilistically using personal identifiers such as name, date of birth, and address. SAFEBOD was initiated under the NSW Public Health Act 2010 and was approved by the University of Sydney Human Research Ethics Committee (project number 2016/758). Further details of the SAFEBOD study linkage have been published previously(18).

Our study population included all solid organ transplants performed in NSW from deceased (1st January 2000 to 31st December 2012) and living (1st January 2004 to 31st December 2012) donors. We had complete follow-up data for living donors, recipients, and transplant outcomes until 31st December 2016. Linked data from the population-based NSW Central Cancer Registry (CCR) is lagged by approximately 5 years, hence data is only available until the end of 2013 despite linkage for SAFEBOD being performed in 2018. We therefore chose

31st December 2012 as the end of our study period to ensure at least one year of post-transplant follow-up for cancer was available for all participants. We excluded transplants where either the donor or recipient had a non-NSW postcode at transplant, since cancers diagnosed across state boundaries may not always be notified to the NSW CCR.

3.4.2 Identifying cancers

In Australia, all cancer diagnoses must be notified to the relevant state or territory cancer registry under statute. Cancers are classified using both the International Statistical Classification of Diseases for Oncology 3rd Edition (ICD-O)(20) and the International Statistical Classification of Diseases and Related Health Problems Tenth Revision Australian Modification (ICD-10-AM)(21). We considered any donor or recipient tumor that was notifiable to the CCR to be a cancer. This included all malignant and in-situ tumors but excluded non-melanoma skin cancers which are not notifiable(22).

We assigned each cancer a site based on its ICD-O code reported in the CCR. Other cancer details such as diagnosis date and level of spread were primarily based on CCR, however the CCR only includes the highest level of spread within 4 months of diagnosis. Therefore we also sought further details of any cancers from other SAFEBOD sources including: the Admitted Patient Data Collection (ADPC), death records from the Registry of Births, Deaths, and Marriages (RBDM), the Australian and New Zealand Organ and Tissue Donor Registry (ANZOD), the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA), the Australian and New Zealand Cardiothoracic Organ Transplant Registry (ANZCOTR), and the Australian and New Zealand Liver and Intestine Transplant Registry (ANZLITR).

We documented all donor and recipient cancers from before and after transplant. For living donors, we considered whether cancers diagnosed after transplant may have been present prior to donation. For deceased donors, we considered the possibility that cancers discovered during organ recovery may not have been notified to the CCR, despite the statutory notification rules. Although new cancer diagnoses are notifiable even if discovered after death, it is possible that due to administrative confusion these cancers may not have been notified or may have been notified against the recipient rather than the donor (e.g., if a kidney cancer is discovered during organ recovery, resected, and then the kidney used for transplant). We also considered that some donor cancers may have been undiagnosed at the time of death, so we would only find out about the cancer via a transplant recipient if a transmission occurred (e.g., a metastatic cancer diagnosed in a recipient shortly after transplant may be judged a likely transmission, which implies the donor had cancer prior to donation).

3.4.3 Transmission likelihood

We categorized each transplant procedure (i.e., each donor-recipient pair) by the likelihood that a transmission had occurred (a donor-transmitted cancer), compared to an alternative explanation (e.g., a donor-derived *de novo* cancer arising in the recipient). We used categories likely, possible, unlikely, or excluded, based on international guidelines for investigating the imputability of malignancy transmission(23-25). We did not include categories for definite or proven transmission because this would require access to more granular case-by-case information than we were able to acquire using linked health data (for example, detailed pathology reports). The guidelines are subjective since the distinction between donor-derived cancers (i.e., *de novo* cancer in a recipient, arising in donor cells,

that was not present at transplantation) and donor-transmitted cancers (i.e., pre-existing cancer transmitted with donor cells at the time of transplantation) is often difficult to discern. Therefore, records for each transplant procedure (i.e., each donor-recipient pair) were reviewed on a case-by-case basis by two co-authors with expertise in transplant nephrology and cancer epidemiology (ACW and CMV). Any disagreements were resolved with another co-author with expertise in transplant nephrology (MW).

The characteristics considered when evaluating the likelihood of transmission were age, sex, donation pathway (living vs. deceased), donor mode of death, and all cancers before or after transplant for the donor and all recipients of their organs (including date of diagnosis, primary site, level of spread, and source of information within SAFEBOD). Broadly, we considered transmission to be likely if a donor had past or current cancer and the recipient developed metastatic cancer or cancer in the transplanted organ. Transmission was considered possible if there was no reported cancer in the donor, but the recipient developed metastatic cancer or cancer in the transplanted organ shortly after transplantation. Transmission was considered unlikely (but still a possibility) if the recipient developed non-metastatic or late onset cancer that could potentially have originated in the donor, despite a lack of corroborating evidence in any donor records. In all other cases (e.g., recurrence of a recipient's previous cancer, or no cancer), transmission was excluded.

3.4.4 Data analysis

We summarized the donor and recipient characteristics and outcomes of all transmissions and non-transmissions and reported these as proportions of donors and transplant procedures. We also focused on certain donor cancers of particular interest, kidney cancers

and brain cancers. Kidney cancers discovered during organ recovery may in some circumstances be resected (where this is thought to be curative) and the kidney used for transplantation. Brain cancers typically occur in younger people who are otherwise relatively healthy compared to the average donor, and certain types of brain cancer are less likely to metastasize and are acceptable for donation under current guidelines(8).

In addition, we also restricted our analysis to donors with any reported past or current cancer. Some donor cancers may only be discovered if a transmission occurs, hence there may also be donors with cancer that remains undiscovered because it does not result in transmission. To account for this possible bias, we performed sensitivity analyses by further restricting our analysis to donor cancers 1) reported against the donor in any data source, 2) notified against the donor in the CCR, and 3) recognized by clinicians at the time of donation.

We defined a transmission as any transplant procedure (donor-recipient pair) where transmission was judged likely, while a non-transmission was any transplant procedure where transmission was judged possible, unlikely, or excluded. In sensitivity analyses we considered alternative likelihood thresholds for defining transmissions and non-transmissions.

3.5 Results

3.5.1 Study cohort

We included 2,502 NSW recipients of 1,431 NSW donors in our analysis, as health records for interstate donors and recipients were not present in SAFEBOD. These recipients

underwent 2,544 transplant procedures, including 1,828 (71%) from 715 deceased donors and 716 (29%) from living donors (Figure 3.2).

3.5.2 Donor cancers

Among 1,431 donors, 38 (3%) had evidence of at least one past or current cancer (43 cancers total). This included 17 (45%) deceased and 21 (55%) living donors who donated to 68 NSW recipients (with a further 6 interstate recipients excluded from our analysis). The median post-transplant follow-up for recipients was 6.7 years (IQR 4.8-10.3). Of these donors, 38 (100%) had cancer reported against the donor in at least one data source, 33 (87%) had cancer notified against the donor in the CCR, and for 37 (97%) the cancer was recognized by clinicians at the time donation decisions were made. The most common cancers in donors were kidney (n=14, 37%), brain (n=7, 18%), prostate (n=6, 16%), melanoma (n=4, 11%), breast (n=3, 8%), and thyroid (n=3, 8%). Donor cancers are summarized in Supplementary Table 3.S1.

3.5.3 Summary of transmissions and non-transmissions

Among 68 transplant procedures from 38 donors with past or current cancer, there were four (6%) transmissions from two living and two deceased donors, and 64 (94%) non-transmissions from 19 living and 16 deceased donors (Figure 3.). One deceased donor with two recipients was counted as a transmission to one recipient and a non-transmission to the other recipient. The overall transmission rate was 0.16% of 2,544 transplant procedures, and 0.28% of all donors transmitted cancer to at least one recipient. Donor and recipient characteristics of all transmissions and non-transmissions are presented in Supplementary Table 3.S1.

Our findings were robust to restricting which donor cancers were included, as well as to alternative likelihood thresholds for defining transmissions and non-transmissions (Supplementary Table 3.S2). In sensitivity analysis scenarios, the transmission rate ranged from 4%-23%, while the non-transmission rate ranged from 77%-96%. Even in the most conservative scenario including all transmissions judged likely, possible, or unlikely, transplants from donors with a past or current cancer were much more likely to be a non-transmission (77%) compared to a transmission (23%).

3.5.4 Details of kidney cancer transmissions and non-transmissions

All 14 donors with kidney cancer (four deceased, 10 living) had their cancer discovered during organ recovery. These donors donated to 19 NSW recipients, resulting in 15 (79%) non-transmissions and 4 (21%) transmissions. Details of transmissions and non-transmissions from donors with kidney cancer are summarized for deceased donors in Table 3.3, and for living donors in Table 3.4.

The first deceased donor had an adenocarcinoma (not notified to the CCR) resected from one kidney before transplant and donated their other kidney to a different recipient. The resected kidney failed due to adenocarcinoma (ICD-O histology 8310) after 8 months (transmission) and was removed. The recipient was still alive after 13 years post-transplant follow-up. The other recipient survived 10 years with a functioning transplant (non-transmission).

The second deceased donor had their kidney with adenocarcinoma (not notified to the CCR) discarded but donated their liver and other kidney. The kidney recipient survived 7 years

with a functioning transplant (non-transmission), while the liver recipient survived 6 years (non-transmission).

The third deceased donor had cancer resected from one kidney before transplant, and also donated their other kidney, liver, and heart. The cancer was reported to be an adenocarcinoma in ANZOD but was notified to the CCR against the recipient at the time of transplant as a renal cell carcinoma (ICD-O 8312). Both the resected kidney and liver recipients were still alive with a functioning transplant after 6 years follow-up (non-transmissions). The other kidney was lost immediately with the recipient surviving 1 year (non-transmission), while the heart recipient survived 5 years (non-transmission).

The final deceased donor's kidneys were discarded due to an adenocarcinoma discovered during organ recovery, but it was not reported whether this was diagnosed in one or both kidneys. This cancer was not notified to the CCR so no further histology details are available. The donor's lungs were nevertheless donated to a single recipient who developed metastatic adenocarcinoma of uncertain site with lung metastases (ICD-O 8140) 6-months post-transplant and died 1 month later (transmission).

The 10 living donors with kidney cancer all had their cancer resected, and the kidney used for transplant. One donor had a renal cell carcinoma (ICD-O 8312), and their recipient developed metastatic renal cell carcinoma (ICD-O 8312) 3-years post-transplant (transmission). It was not reported whether this was in the native or transplanted kidney, nor whether the cancer was removed with a partial or full nephrectomy. The recipient was still alive 6 years post-transplant. Another donor had adenocarcinoma (ICD-O 8310), and

their recipient had renal cell carcinoma (not notified to the CCR) in the transplanted kidney 2-years post-transplant (transmission), which was removed 1 month later. The recipient was still alive 4 years post-transplant. Of the remaining eight donors, five had adenocarcinoma (ICD-O 8310), one had renal cell carcinoma (ICD-O 8312), one had chromophobe cell renal carcinoma (ICD-O 8317), and one had papillary adenocarcinoma (ICD-O 8260). The eight recipients of these donor were all non-transmissions, with two recipients surviving 1 and 4 years respectively, and six recipients still alive after a median 5 years' post-transplant follow-up (IQR 4.4-6.3).

3.5.5 Details of brain cancer non-transmissions

There were seven donors with brain cancer, including six deceased donors whose terminal hospital admission was related to brain cancer diagnosed up to a year prior to donation, and one living donor with a brain cancer diagnosed 17 years prior. The six deceased donors with current brain cancer included four with glioblastoma (grade 4), one with oligodendroglioma (grade 2), and one with glioma (unknown grade). All were accepted for donation in accordance with current guidelines(8). They donated to 25 NSW recipients, and all 25 (100%) were non-transmissions. Details of these non-transmissions are summarized in Table 3.5.

The living donor with glioma (unknown grade) also had a renal cell carcinoma (ICD-O 8312) discovered during organ recovery. The tumor was resected before transplant, but despite this the transplant resulted in a transmission (described above). We counted this as a kidney cancer transmission, hence there were no brain cancer transmissions in our study.

3.5.6 Details of other cancer non-transmissions

There were six donors (three deceased, three living) with current or past prostate cancer who donated to nine recipients (median post-transplant follow-up 6.5 years, IQR 5.0-12.5), all of which were non-transmissions. This included a living donor with chromophobe cell renal carcinoma discovered during organ recovery (described above), as well as a deceased donor who had metastatic prostate cancer with regional spread 11 years prior to donation whose two kidney transplant recipients were still alive with a functioning transplant after 4 years follow-up.

There were four donors (two deceased, two living) with current or past melanoma who donated to five recipients (median post-transplant follow-up 5.4 years, IQR 5.0-5.4), all of which were also non-transmissions. This included the same living donor with chromophobe cell renal carcinoma and prostate cancer described previously. These melanomas were all recognized at time of donation; one living donor had an in-situ melanoma discovered during donor work-up, one deceased donor had a 0.13mm Breslow thickness melanoma removed 2 years prior, and the thickness of the remaining two melanomas was not reported.

There were two living donors with breast cancer diagnosed 4 and 6 years prior to donation whose kidney recipients were still alive with a functioning transplant after 9 years and 5 years post-transplant follow-up, respectively (non-transmissions). In addition, one female living donor with kidney cancer described above also had a metastatic breast cancer diagnosed 1 year prior to donation. It is unclear whether clinicians were unaware of the donor's cancer history, or if they recognized the cancer and considered the risk of transmission to the male recipient acceptable. Fortunately, this was a non-transmission. The

recipient's kidney failed due to BK virus nephropathy 1-year post-transplant, but the recipient was still alive after 6 years post-transplant follow-up.

There were two living donors with thyroid cancer diagnosed 6 years and 18 years prior to donation. One kidney failed 2-years post-transplant due to focal sclerosing glomerulonephritis, but the recipient was still alive after 12 years post-transplant follow-up (non-transmission). The other recipient was still alive with a functioning transplant after 9 years post-transplant follow-up (non-transmission). Additionally, one deceased donor had metastatic thyroid cancer diagnosed 34 years prior to donation that was not recognized by clinicians at the time of transplant. The single kidney recipient died 1-month post-transplant due to acute myocardial infarction, hence this was considered a non-transmission.

3.6 Discussion

We analyzed an observational cohort of transplant procedures between NSW donors and recipients during 2000-2012 and identified cases of cancer transmissions and non-transmission. Overall, cancer transmissions were rare (0.16% of transplant procedures). Even among transplants from donors with past or current cancer, non-transmission (94%) was much more common than transmission (6%). In cases where transmissions occurred, recipient outcomes were variable.

Our study's main strength is that we have identified cancer transmissions and non-transmissions using data linkage to a population-based cancer registry and other administrative health records to supplement transplant registry records. Previous population-wide studies of donors and recipients have demonstrated a very low risk of

cancer transmission. One study from the US reported transmission rates of 0.012% among transplant procedures and 0.025% among donors(14), while another study in the UK reported slightly higher rates of 0.05% among transplant procedures and 0.1% among donors(15). However, these studies relied only on cancers reported to transplant registries (not cancer registries), and without access to donor records some donor-transmitted cancers may not have been recognized. This may explain why their transmission rates are lower than our observed rates.

Recipient outcomes from donor kidneys with a tumor discovered during organ recovery that is resected before transplant (restored kidney transplant) have been studied previously. For small renal cell carcinomas, guidelines suggest the risk of transmission after tumor resection is minimal (<0.1%) for tumors ≤1cm, or low (0.1-2%) for tumors 1-2.5cm(8). A 2018 systematic review found no cancer recurrences after 5 years post-transplant follow-up of 107 patients from 17 studies(26). One included study noted a cancer recurrence 9-years post-transplant, however it was not reported whether this was donor-transmitted or donor-derived(27). This contrasts with our study, in which we observed three transmissions in 16 recipients from 12 donors with resected kidney tumors. While previous studies only monitored recipients of resected kidneys, we also included recipients of other organs, as well as recipients of donors whose tumor-affected kidney was discarded rather than resected. This accounted for one additional transmission to a double lung recipient.

Previous studies have also focused on transmission rates from specific cancers, with CNS tumors of particular interest due to a theoretical risk of transmission. We did not find any cases of transmission of a CNS tumor, which aligns with earlier findings in Australia(16) and

the UK(17). This is despite some brain malignancies (e.g., glioblastoma) being considered intermediate (2-10%) risk of transmission in TSANZ and other guidelines (8, 9, 11, 28).

This study benefited from a linked dataset with complete population coverage, which provides confidence that most transmissible cancers have been captured. Our use of other SAFEBOD datasets to supplement the CCR (such as hospitalizations and transplant registries) ensures that all transmissions have been included. In fact, we found several donor cancers that were not notified to the CCR and would have been missed had we relied on CCR data alone.

Nevertheless, some donor cancers may have been missed if they were diagnosed interstate, prior to 1972, or in a living donor post-transplant and after 2013. This means non-transmissions may have been underestimated. Similarly, we could not ascertain transmissions to recipients out of state or diagnosed after 2013. Additionally, nearly all donor cancers in our cohort were recognized by clinicians at the time they were accepted for donation. These donors have been carefully selected for transplantation in a risk-averse clinical setting; hence our observed transmission rate is likely an underestimate of the risk of transmission from a donor with past or current cancer. Only one donor in our cohort had a cancer that was not known to clinicians at the time of donation (a thyroid cancer notified to the CCR 34 years prior).

Our reliance on population cancer registry and administrative datasets meant that clinical and histopathological information was not available for interrogation. We were unable to ascertain the size or grade of most cancers we identified, which limited our ability to make

clinical recommendations for individual donor cancers. Instead, we have relied on data extracted from original pathology reports by trained coders at the NSW CCR, and our findings remain relevant at the population level.

These results support safe use of carefully selected donors with a past or current cancer for transplantation. We have added to the evidence base which could inform further development and refinement of guidelines for organ donation from donors with a past or current cancer(8). Considering the variability in recipient outcomes following cancer transmission, our findings encourage incorporating patient preferences into decisions to accept or decline an offered organ to ensure the risks of accepting a transplant from a donor with cancer are balanced against the risks of remaining on an organ waiting list. Future work will build on these findings to evaluate the economic costs and benefits of increasing organ donation through accepting more donors with a risk of cancer transmission.

3.7 Conclusions

Overall, cancer transmission via organ transplantation is rare. Kidney cancers discovered during organ recovery posed the greatest risk of transmission, but non-transmission was nevertheless the most likely outcome. Donors with a past or current cancer who are carefully screened may be safe for transplantation.

3.8 Acknowledgements

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3.10 Tables

Table 3.3: Cancer transmissions and non-transmissions in NSW 2000-2012 from deceased donors with kidney cancer

Donor							***Recipient***					
#	**Year**	**Path**	**Age**	**Sex**	**Cancer type(s)**	**Diagnosis[a]**	**#**	**Organs**	**Age**	**Sex**	**Transmission**	**Recipient outcome, at end of follow-up (31st December 2016)**
1	2003	DBD	55+	M	Adenocarcinoma[b]	Recovery	1	Single kidney	25-34	M	Likely	Kidney tumor resected before transplant. Transplant failed due to cancer after 8 months (not in the CCR). Still alive
							2	Single kidney	45-54	F	Non-transmission	Died due to myocardial infarction after 10 years with functioning transplant
2	2008	DBD	55+	M	Adenocarcinoma[b]	Recovery	1	Single kidney	55-64	M	Non-transmission	Tumor found in right kidney during organ recovery, discarded, and left kidney transplanted. Died due to cardiogenic shock after 7 years with functioning transplant
							2	Whole liver	55-64	M	Non-transmission	Died with transplant failure due to fungal sepsis after 6 years
3	2010	DBD	35-54	F	Renal cell carcinoma[c]	Recovery	1	Single kidney	45-54	F	Unlikely	Kidney tumor resected before transplant. Kidney cancer reported in the CCR against the recipient at time of transplant, with no evidence of recurrence. Alive with functioning transplant
							2	Single kidney	45-54	F	Non-transmission	Transplant failed due to immediate rejection, died 1 year later
							3	Whole liver	55-64	F	Non-transmission	Alive with functioning transplant
							4	Heart	55-64	F	Non-transmission	Non-melanoma skin cancer reported after 2 years (not notifiable). Died with transplant failure due to cancer 3 years later

Donor							*Recipient*					
#	**Year**	**Path**	**Age**	**Sex**	**Cancer type(s)**	**Diagnosis[a]**	**#**	**Organs**	**Age**	**Sex**	**Transmission**	**Recipient outcome, at end of follow-up (31st December 2016)**
4	2011	DCD	55+	M	Adenocarcinoma[b]	Recovery	1	Double lung	65-74	F	Likely	Donor kidneys discarded due to kidney cancer found during organ recovery. Metastatic cancer of uncertain site (bone, lung, and liver metastases) diagnosed after 6 months. Died due to cancer 1 month later with functioning transplant

CCR, Central Cancer Registry; DBD, donation after brainstem death; DCD, donation after circulatory death

[a] When cancer was first diagnosed in the donor (years prior, during a deceased donor's terminal hospital admission, during a living donor's work-up, or during organ recovery); [b] Cancer not notified to the CCR; [c] Cancer notified to the CCR against the recipient

Each row represents an individual recipient. Recipients with the same donor are grouped together with alternating white/gray shading

Table 3.4: Cancer transmissions and non-transmissions in NSW 2000-2012 from living donors with kidney cancer

Donor						***Recipient***					
#	**Year**	**Age**	**Sex**	**Cancer type(s)**	**Diagnosis[a]**	**#**	**Organs**	**Age**	**Sex**	**Transmission**	**Recipient outcome, at end of follow-up (31st December 2016)**
5	2006	35-54	F	Renal cell carcinoma	Recovery	1	Single kidney	45-54	M	Non-transmission	Kidney tumor resected before transplant. Alive with functioning transplant
6	2010	35-54	F	Renal cell carcinoma Glioma	Recovery 17 years	1	Single kidney	65-74	M	Likely	Kidney tumor resected before transplant. Metastatic kidney cancer diagnosed after 3 years (not reported if native or transplanted kidney). Alive with functioning transplant
7	2010	55+	F	Papillary adenocarcinoma Breast[b] (m)	Recovery 1 year	1	Single kidney	65-74	M	Non-transmission	Kidney tumor resected before transplant. Transplant failed due to BK virus nephropathy after 1 year, still alive
8	2011	55+	F	Adenocarcinoma	Recovery	1	Single kidney	55-64	M	Non-transmission	Kidney tumor resected before transplant. Alive with functioning transplant
9	2011	55+	M	Adenocarcinoma	Recovery	1	Single kidney	65-74	F	Unlikely	Kidney tumor resected before transplant. Donor metastatic lung cancer reported 3 years after transplant (not in the CCR). Donor died due to cancer 2 years later. Recipient metastatic liver cancer reported after 4 years (not in the CCR, pre-transplant history of non-melanoma skin cancer). Recipient died due to cancer 2 months later with functioning transplant
10	2011	55+	M	Chromophobe cell renal carcinoma Melanoma Prostate	Recovery Work-up 2 years	1	Single kidney	65-74	M	Non-transmission	Kidney tumor resected before transplant. Alive with functioning transplant
11	2012	55+	F	Adenocarcinoma	Recovery	1	Single kidney	55-64	M	Non-transmission	Kidney tumor resected before transplant. Transplant failed due to acute rejection after 1 year, died 5 months later
12	2012	35-54	M	Adenocarcinoma	Recovery	1	Single kidney	65-74	F	Non-transmission	Kidney tumor resected before transplant. Non-melanoma skin cancer reported after 11 months (not notifiable). Alive with functioning transplant

Donor						*Recipient*					
#	**Year**	**Age**	**Sex**	**Cancer type(s)**	**Diagnosis[a]**	**#**	**Organs**	**Age**	**Sex**	**Transmission**	**Recipient outcome, at end of follow-up (31st December 2016)**
13	2012	55+	M	Adenocarcinoma	Recovery	1	Single kidney	65-74	M	Likely	Kidney tumor resected before transplant. Cancer in transplanted kidney reported after 2 years (not in the CCR). Transplant failed due to cancer 1 month later, still alive
14	2012	35-54	F	Adenocarcinoma	Recovery	1	Single kidney	65-74	M	Non-transmission	Kidney tumor resected before transplant. Alive with functioning transplant

CCR, Central Cancer Registry; (m), metastases

[a] When cancer was first diagnosed in the donor (years prior, during donor work-up, or during organ recovery); [b] Uncertain if recognized by clinicians at time of donation

Table 3.5: Cancer transmissions and non-transmissions in NSW 2000-2012 from deceased donors with brain cancer

Donor							***Recipient***					
#	**Year**	**Path**	**Age**	**Sex**	**Cancer type**	**Diagnosis[a]**	**#**	**Organs**	**Age**	**Sex**	**Transmission**	**Recipient outcome, at end of follow-up (31st December 2016)**
15	2000	DBD	15-34	F	Glioblastoma	Admission	1	SPK	-	-	Unknown	Interstate recipient
							2	Single kidney	-	-	Unknown	Interstate recipient
							3	Whole liver	35-44	F	Non-transmission	Alive with functioning transplant
							4	Double lung	15-24	F	Non-transmission	Alive with functioning transplant
16	2000	DBD	55+	F	Glioblastoma	Admission	1	Single kidney	25-34	M	Non-transmission	Died due to ischemic heart disease after 16 years with functioning transplant
							2	Single kidney	45-54	M	Non-transmission	Non-melanoma skin cancer reported after 4 years (not notifiable). Alive with functioning transplant
							3	Whole liver	65-74	F	Non-transmission	Non-melanoma skin cancer reported after 9 years (not notifiable). Alive with functioning transplant
							4	Double lung	55-64	F	Non-transmission	Non-melanoma skin cancer reported after 12 years (not notifiable). Died due to septicemia 3 years later with functioning transplant
17	2004	DBD	35-54	F	Oligodendroglioma	1 year	1	SPK	25-34	F	Non-transmission	Kidney failed due to chronic allograft nephropathy after 8 years. Pancreas failed due to acute rejection 23 months later. Still alive
							2	Single kidney	45-54	M	Non-transmission	Alive with functioning transplant
							3	Whole liver	55-64	F	Non-transmission	Died with transplant failure due to acute rejection after 2 years
							4	Double lung	25-34	F	Non-transmission	Died with transplant failure due to bronchiolitis obliterans after 2 years

Donor							*Recipient*					
#	**Year**	**Path**	**Age**	**Sex**	**Cancer type**	**Diagnosis[a]**	**#**	**Organs**	**Age**	**Sex**	**Transmission**	**Recipient outcome, at end of follow-up (31st December 2016)**
18	2007	DBD	35-54	F	Glioblastoma	Admission	1	Single kidney	25-34	M	Non-transmission	Died with transplant failure due to withdrawal from immunosuppressants after 7 years
							2	Single kidney	55-64	M	Non-transmission	Non-melanoma skin cancer reported after 2 years (not notifiable). Alive with functioning transplant
							3	Whole liver	25-34	F	Non-transmission	Died with transplant failure due to perforated duodenal ulcer after 2 years
							4	Double lung	25-34	F	Non-transmission	Alive with functioning transplant
							5	Heart	65-74	M	Non-transmission	Non-melanoma skin cancer reported after 20 months (not notifiable). Alive with functioning transplant
19	2007	DBD	15-34	F	Glioblastoma	Admission	1	Single kidney	65-74	M	Non-transmission	Non-melanoma skin cancer reported after 2 years (not notifiable). Alive with functioning transplant
							2	Single kidney	55-64	M	Non-transmission	Alive with functioning transplant
							3	Whole liver	55-64	M	Non-transmission	Metastatic throat cancer reported after 6 years (not in the CCR). Died due to cancer 4 months later with functioning transplant
							4	Double lung	45-54	M	Non-transmission	Died due to respiratory failure after 1 year
							5	Heart	45-54	F	Non-transmission	Non-melanoma skin cancer reported after 7 months (not notifiable). Alive with functioning transplant
20	2009	DBD	15-34	M	Glioma	Admission	1	Single kidney	45-54	F	Non-transmission	Alive with functioning transplant
							2	Single kidney	55-64	M	Non-transmission	Alive with functioning transplant
							3	Split liver	45-54	F	Non-transmission	Alive with functioning transplant
							4	Split liver	0-4	F	Non-transmission	Alive with functioning transplant
							5	Double lung	35-44	M	Non-transmission	Prostate cancer diagnosed after 2 years. Died due to respiratory failure 3 years later

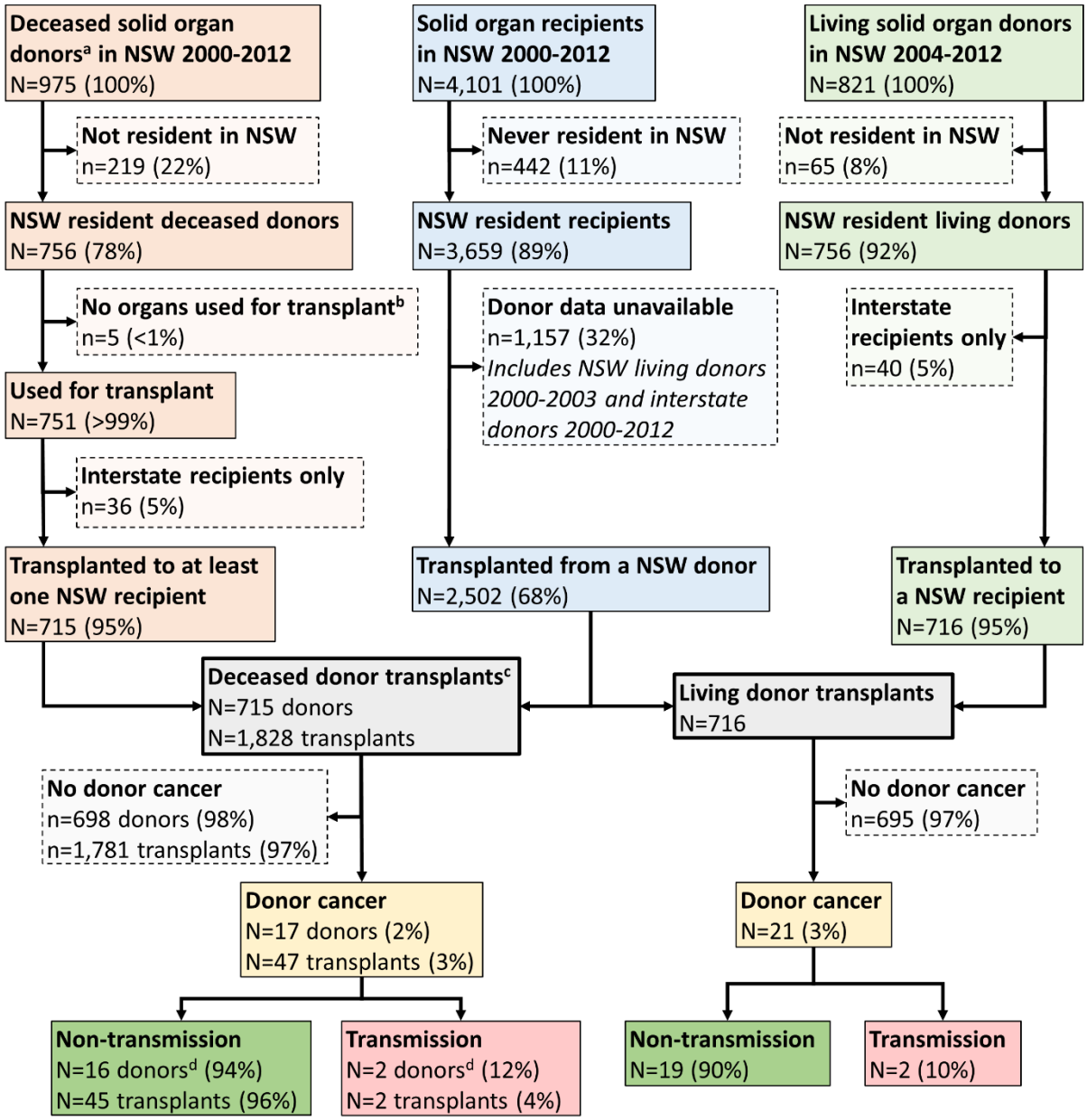
CCR, Central Cancer Registry; DBD, donation after brainstem death; SPK, simultaneous pancreas-kidney transplant

[a] When cancer was first diagnosed in the donor (years prior, or during a deceased donor's terminal hospital admission)

Each row represents an individual recipient. Recipients with the same donor are grouped together with alternating white/gray shading

3.11 Figures

Figure 3.2: Flowchart of donors and recipients included in the study cohort, and transmissions and non-transmissions



[a] *Actual donors (commenced organ recovery)*
[b] *Donor discard rate. Includes organs not recovered, and organs discarded*
[c] *Transplant procedures, which may include multiple transplanted organs*
[d] *Includes one donor with two recipients: one transmission and one non-transmission*

3.12 Supplementary material

Supplementary Table 3.S1: Cancer transmissions and non-transmissions from NSW organ transplant procedures 2000-2012, sorted by cancer site, donation pathway, and year of transplantation

Donor							***Recipient***					
#	**Year**	**Path**	**Age**	**Sex**	**Cancer type(s)**	**Diagnosis[a]**	**#**	**Organs**	**Age**	**Sex**	**Transmission**	**Recipient outcome, at end of follow-up (31st December 2016)**
1	2003	DBD	55+	M	Adenocarcinoma[b]	Recovery	1	Single kidney	25-34	M	Likely	Kidney tumor resected before transplant. Transplant failed due to cancer after 8 months (not in the CCR). Still alive
							2	Single kidney	45-54	F	Non-transmission	Died due to myocardial infarction after 10 years with functioning transplant
2	2008	DBD	55+	M	Adenocarcinoma[b]	Recovery	1	Single kidney	55-64	M	Non-transmission	Tumor found in right kidney during organ recovery, discarded, and left kidney transplanted. Died due to cardiogenic shock after 7 years with functioning transplant
							2	Whole liver	55-64	M	Non-transmission	Died with transplant failure due to fungal sepsis after 6 years
3	2010	DBD	35-54	F	Renal cell carcinoma[c]	Recovery	1	Single kidney	45-54	F	Unlikely	Kidney tumor resected before transplant. Kidney cancer reported in the CCR against the recipient at time of transplant, with no evidence of recurrence. Alive with functioning transplant
							2	Single kidney	45-54	F	Non-transmission	Transplant failed due to immediate rejection, died 1 year later
							3	Whole liver	55-64	F	Non-transmission	Alive with functioning transplant
							4	Heart	55-64	F	Non-transmission	Non-melanoma skin cancer reported after 2 years (not notifiable). Died with transplant failure due to cancer 3 years later

Donor							*Recipient*					
#	**Year**	**Path**	**Age**	**Sex**	**Cancer type(s)**	**Diagnosis[a]**	**#**	**Organs**	**Age**	**Sex**	**Transmission**	**Recipient outcome, at end of follow-up (31st December 2016)**
4	2011	DCD	55+	M	Adenocarcinoma[b]	Recovery	1	Double lung	65-74	F	Likely	Donor kidneys discarded due to kidney cancer found during organ recovery. Metastatic cancer of uncertain site (bone, lung, and liver metastases) diagnosed after 6 months. Died due to cancer 1 month later with functioning transplant
5	2006	Live	35-54	F	Renal cell carcinoma	Recovery	1	Single kidney	45-54	M	Non-transmission	Kidney tumor resected before transplant. Alive with functioning transplant
6	2010	Live	35-54	F	Renal cell carcinoma Glioma	Recovery 17 years	1	Single kidney	65-74	M	Likely	Kidney tumor resected before transplant. Metastatic kidney cancer diagnosed after 3 years (not reported if native or transplanted kidney). Alive with functioning transplant
7	2010	Live	55+	F	Papillary adenocarcinoma Breast[e] (m)	Recovery 1 year	1	Single kidney	65-74	M	Non-transmission	Kidney tumor resected before transplant. Transplant failed due to BK virus nephropathy after 1 year, still alive
8	2011	Live	55+	F	Adenocarcinoma	Recovery	1	Single kidney	55-64	M	Non-transmission	Kidney tumor resected before transplant. Alive with functioning transplant

Donor							*Recipient*					
#	**Year**	**Path**	**Age**	**Sex**	**Cancer type(s)**	**Diagnosis[a]**	**#**	**Organs**	**Age**	**Sex**	**Transmission**	**Recipient outcome, at end of follow-up (31st December 2016)**
9	2011	Live	55+	M	Adenocarcinoma	Recovery	1	Single kidney	65-74	F	Unlikely	Kidney tumor resected before transplant. Donor metastatic lung cancer reported 3 years after transplant (not in the CCR). Donor died due to cancer 2 years later. Recipient metastatic liver cancer reported after 4 years (not in the CCR, pre-transplant history of non-melanoma skin cancer). Recipient died due to cancer 2 months later with functioning transplant
10	2011	Live	55+	M	Chromophobe cell renal carcinoma Melanoma Prostate	Recovery Work-up 2 years	1	Single kidney	65-74	M	Non-transmission	Kidney tumor resected before transplant. Alive with functioning transplant
11	2012	Live	55+	F	Adenocarcinoma	Recovery	1	Single kidney	55-64	M	Non-transmission	Kidney tumor resected before transplant. Transplant failed due to acute rejection after 1 year, died 5 months later
12	2012	Live	35-54	M	Adenocarcinoma	Recovery	1	Single kidney	65-74	F	Non-transmission	Kidney tumor resected before transplant. Non-melanoma skin cancer reported after 11 months (not notifiable). Alive with functioning transplant
13	2012	Live	55+	M	Adenocarcinoma	Recovery	1	Single kidney	65-74	M	Likely	Kidney tumor resected before transplant. Cancer in transplanted kidney reported after 2 years (not in the CCR). Transplant failed due to cancer 1 month later, still alive
14	2012	Live	35-54	F	Adenocarcinoma	Recovery	1	Single kidney	65-74	M	Non-transmission	Kidney tumor resected before transplant. Alive with functioning transplant

Donor							*Recipient*					
#	**Year**	**Path**	**Age**	**Sex**	**Cancer type(s)**	**Diagnosis[a]**	**#**	**Organs**	**Age**	**Sex**	**Transmission**	**Recipient outcome, at end of follow-up (31st December 2016)**
15	2000	DBD	15-34	F	Glioblastoma	Admission	1	SPK	-	-	Unknown	Interstate recipient
							2	Single kidney	-	-	Unknown	Interstate recipient
							3	Whole liver	35-44	F	Non-transmission	Alive with functioning transplant
							4	Double lung	15-24	F	Non-transmission	Alive with functioning transplant
16	2000	DBD	55+	F	Glioblastoma	Admission	1	Single kidney	25-34	M	Non-transmission	Died due to ischemic heart disease after 16 years with functioning transplant
							2	Single kidney	45-54	M	Non-transmission	Non-melanoma skin cancer reported after 4 years (not notifiable). Alive with functioning transplant
							3	Whole liver	65-74	F	Non-transmission	Non-melanoma skin cancer reported after 9 years (not notifiable). Alive with functioning transplant
							4	Double lung	55-64	F	Non-transmission	Non-melanoma skin cancer reported after 12 years (not notifiable). Died due to septicemia 3 years later with functioning transplant
17	2004	DBD	35-54	F	Oligodendroglioma	1 year	1	SPK	25-34	F	Non-transmission	Kidney failed due to chronic allograft nephropathy after 8 years. Pancreas failed due to acute rejection 23 months later. Still alive
							2	Single kidney	45-54	M	Non-transmission	Alive with functioning transplant
							3	Whole liver	55-64	F	Non-transmission	Died with transplant failure due to acute rejection after 2 years
							4	Double lung	25-34	F	Non-transmission	Died with transplant failure due to bronchiolitis obliterans after 2 years

Donor							*Recipient*					
#	**Year**	**Path**	**Age**	**Sex**	**Cancer type(s)**	**Diagnosis[a]**	**#**	**Organs**	**Age**	**Sex**	**Transmission**	**Recipient outcome, at end of follow-up (31st December 2016)**
18	2007	DBD	35-54	F	Glioblastoma	Admission	1	Single kidney	25-34	M	Non-transmission	Died with transplant failure due to withdrawal from immunosuppressants after 7 years
							2	Single kidney	55-64	M	Non-transmission	Non-melanoma skin cancer reported after 2 years (not notifiable). Alive with functioning transplant
							3	Whole liver	25-34	F	Non-transmission	Died with transplant failure due to perforated duodenal ulcer after 2 years
							4	Double lung	25-34	F	Non-transmission	Alive with functioning transplant
							5	Heart	65-74	M	Non-transmission	Non-melanoma skin cancer reported after 20 months (not notifiable). Alive with functioning transplant
19	2007	DBD	15-34	F	Glioblastoma	Admission	1	Single kidney	65-74	M	Non-transmission	Non-melanoma skin cancer reported after 2 years (not notifiable). Alive with functioning transplant
							2	Single kidney	55-64	M	Non-transmission	Alive with functioning transplant
							3	Whole liver	55-64	M	Non-transmission	Metastatic throat cancer reported after 6 years (not in the CCR). Died due to cancer 4 months later with functioning transplant
							4	Double lung	45-54	M	Non-transmission	Died due to respiratory failure after 1 year
							5	Heart	45-54	F	Non-transmission	Non-melanoma skin cancer reported after 7 months (not notifiable). Alive with functioning transplant

Donor							*Recipient*					
#	**Year**	**Path**	**Age**	**Sex**	**Cancer type(s)**	**Diagnosis[a]**	**#**	**Organs**	**Age**	**Sex**	**Transmission**	**Recipient outcome, at end of follow-up (31st December 2016)**
20	2009	DBD	15-34	M	Glioma	Admission	1	Single kidney	45-54	F	Non-transmission	Alive with functioning transplant
							2	Single kidney	55-64	M	Non-transmission	Alive with functioning transplant
							3	Split liver	45-54	F	Non-transmission	Alive with functioning transplant
							4	Split liver	0-4	F	Non-transmission	Alive with functioning transplant
							5	Double lung	35-44	M	Non-transmission	Prostate cancer diagnosed after 2 years. Died due to respiratory failure 3 years later
21	2004	DBD	55+	M	Prostate	Admission	1	Single kidney	25-34	M	Non-transmission	Alive with functioning transplant
							2	Single kidney	-	-	Unknown	Interstate recipient
							3	Whole liver	65-74	M	Non-transmission	Alive with functioning transplant
22	2010	DBD	55+	M	Prostate	4 years	1	Single kidney	55-64	M	Non-transmission	Nasopharyngeal cancer reported after 3 years (not in the CCR). Died due to respiratory failure 21 months later with functioning transplant
							2	Single kidney	45-54	M	Non-transmission	Alive with functioning transplant
23	2012	DCD	55+	M	Prostate (m^d)	11 years	1	Single kidney	55-64	M	Non-transmission	Alive with functioning transplant
							2	Single kidney	55-64	F	Non-transmission	Alive with functioning transplant
							3	Double lung	-	-	Unknown	Interstate recipient
24	2004	Live	55+	M	Prostate	1 year	1	Single kidney	25-34	F	Non-transmission	Alive with functioning transplant
25	2009	Live	55+	M	Prostate	5 years	1	Single kidney	55-64	F	Non-transmission	Alive with functioning transplant
26	2011	DBD	55+	F	Melanoma	7 years	1	Single kidney	65-74	F	Non-transmission	Cancer in native kidney diagnosed after 17 months (pre-transplant history of kidney cancer). Alive with functioning transplant
							2	Single kidney	55-64	M	Non-transmission	Alive with functioning transplant
27	2012	DBD	55+	M	Melanoma	2 years	1	Single kidney	-	-	Unknown	Interstate recipient
							2	Single kidney	-	-	Unknown	Interstate recipient
							3	Whole liver	25-34	M	Non-transmission	Transplant failure due to primary non-function. Re-transplanted from another donor and died 1 month later

Donor							*Recipient*					
#	**Year**	**Path**	**Age**	**Sex**	**Cancer type(s)**	**Diagnosis[a]**	**#**	**Organs**	**Age**	**Sex**	**Transmission**	**Recipient outcome, at end of follow-up (31st December 2016)**
28	2005	Live	35-54	F	Melanoma Cervix	5 years 15 years	1	Single kidney	35-44	M	Non-transmission	Alive with functioning transplant
29	2007	DCD	55+	F	Thyroid[d] (m)	34 years	1	Single kidney	45-54	M	Non-transmission	Died due to acute myocardial infarction after 1 month with functioning transplant
30	2004	Live	35-54	F	Thyroid	18 years	1	Single kidney	15-24	F	Non-transmission	Transplant failure due to focal sclerosing glomerulonephritis after 2 years, still alive
31	2007	Live	35-54	F	Thyroid	6 years	1	Single kidney	45-54	M	Non-transmission	Alive with functioning transplant
32	2007	Live	35-54	F	Breast	4 years	1	Single kidney	25-34	F	Non-transmission	Non-melanoma skin cancer reported after 2 years (not notifiable). Alive with functioning transplant
33	2011	Live	55+	F	Breast	6 years	1	Single kidney	55-64	M	Non-transmission	Non-melanoma skin cancer reported after 23 months (not notifiable). Alive with functioning transplant
34	2010	Live	55+	F	Colorectal	25 years	1	Single kidney	55-64	M	Non-transmission	Alive with functioning transplant
35	2011	Live	55+	F	Leiomyoma	10 years	1	Single kidney	55-64	M	Non-transmission	Alive with functioning transplant
36	2005	Live	55+	M	Lip	6 years	1	Single kidney	75-84	F	Non-transmission	Donor lip cancer diagnosed 6 years prior, with no evidence of recurrence after 18 years follow-up. Donor non-melanoma skin cancer diagnosed during pre-transplant work-up, with recurrence 7 years later. Recipient metastatic cheek cancer diagnosed after 3 years. Died due to asystole 3 months later with functioning transplant
37	2004	Live	15-34	F	Lymphoma	13 years	1	Single kidney	55-64	F	Non-transmission	Non-melanoma skin cancer reported after 8 years (not notifiable). Alive with functioning transplant

Donor							*Recipient*					
#	**Year**	**Path**	**Age**	**Sex**	**Cancer type(s)**	**Diagnosis[a]**	**#**	**Organs**	**Age**	**Sex**	**Transmission**	**Recipient outcome, at end of follow-up (31st December 2016)**
38	2010	DBD	35-54	M	Uncertain[b]	Admission	1	Single kidney	65-74	F	Non-transmission	Alive with functioning transplant
							2	Single kidney	65-74	M	Unlikely	Donor's family reported a history of cancer that could not be verified retrospectively in any linked health datasets. Recipient diagnosed with metastatic lymphoma after 9 months. Died due to cancer 4 years later with functioning transplant
							3	Whole liver	45-54	M	Possible	Donor's family reported a history of cancer that could not be verified retrospectively in any linked health datasets. Recipient diagnosed with metastatic pancreas cancer after 8 months. Died due to cancer 3 months later with functioning transplant
39	2000	DBD	35-54	F	Not reported[b, d]	-	1	Single kidney	45-54	M	Unlikely	Melanoma diagnosed after 16 months. Multiple recurrences, with lymph node metastases diagnosed 14 years later. Alive with functioning transplant
							2	Single kidney	35-44	F	Non-transmission	Alive with functioning transplant
							3	Double lung	-	-	Unknown	Interstate recipient

Donor							*Recipient*					
#	**Year**	**Path**	**Age**	**Sex**	**Cancer type(s)**	**Diagnosis[a]**	**#**	**Organs**	**Age**	**Sex**	**Transmission**	**Recipient outcome, at end of follow-up (31st December 2016)**
40	2002	DBD	35-54	M	Not reported[b, d]	-	1	Single kidney	45-54	M	Non-transmission	Kidney failed due to chronic allograft nephropathy after 8 years. Died due to chronic kidney failure 19 months later.
							2	Single kidney	65-74	M	Unlikely	Multiple myeloma diagnosed after 2 years. Died due to cancer 2 years later with functioning transplant.
							3	Whole liver	45-54	M	Non-transmission	Non-melanoma skin cancer reported after 3 years (not notifiable). Alive with functioning transplant
							4	Pancreas	-	-	Unknown	Interstate recipient
41	2003	DBD	35-54	M	Not reported[b, d]	-	1	SPK	45-54	F	Non-transmission	Alive with functioning transplants
							2	Single kidney	45-54	F	Unlikely	Thyroid cancer diagnosed after 5 months. Metastatic ovarian cancer reported 11 years later (not in the CCR). Alive with functioning transplant
							3	Whole liver	55-64	F	Non-transmission	Died with transplant failure due to hepatitis C after 2 years
							4	Double lung	-	-	Unknown	Interstate recipient
							5	Heart	-	-	Unknown	Interstate recipient
42	2005	DBD	55+	F	Not reported[b, d]	-	1	Single kidney	65-74	M	Unlikely	Metastatic colorectal cancer diagnosed after 2 years. Died due to peripheral vascular disease 5 years later with functioning transplant
							2	Single kidney	-	-	Unknown	Interstate recipient

Donor							*Recipient*					
#	**Year**	**Path**	**Age**	**Sex**	**Cancer type(s)**	**Diagnosis[a]**	**#**	**Organs**	**Age**	**Sex**	**Transmission**	**Recipient outcome, at end of follow-up (31st December 2016)**
43	2005	DBD	35-54	M	Not reported[b, d]	-	1	SPK	35-44	F	Unlikely	Kidney cancer diagnosed in native kidney after 20 months. Alive with functioning transplant
							2	Single kidney	55-64	F	Non-transmission	Breast cancer in-situ diagnosed after 3 years. Alive with functioning transplant
							3	Whole liver	-	-	Unknown	Interstate recipient
							4	Double lung	55-64	M	Non-transmission	Lymphoma diagnosed after 9 months. Died with transplant failure due to cancer 4 months later
							5	Heart	55-64	M	Non-transmission	Metastatic lung cancer diagnosed after 5 years. Died due to cancer 1 year later with functioning transplant
44	2008	DBD	35-54	F	Not reported[b, d]	-	1	SPK	-	-	Unknown	Interstate recipient
							2	Single kidney	-	-	Unknown	Interstate recipient
							3	Whole liver	-	-	Unknown	Interstate recipient
							4	Double lung	55-64	M	Possible	Metastatic lung cancer diagnosed after 6 months. Died with transplant failure due to cancer 2 months later
45	2008	DBD	35-54	M	Not reported[b, d]	-	1	Single kidney	-	-	Unknown	Interstate recipient
							2	Single kidney	55-64	M	Non-transmission	Alive with functioning transplant
							3	Whole liver	45-54	M	Unlikely	Metastatic tonsil cancer diagnosed after 6 months. Died due to cancer 17 months later with functioning transplant

Donor							*Recipient*					
#	**Year**	**Path**	**Age**	**Sex**	**Cancer type(s)**	**Diagnosis[a]**	**#**	**Organs**	**Age**	**Sex**	**Transmission**	**Recipient outcome, at end of follow-up (31st December 2016)**
46	2009	DBD	35-54	M	Not reported[b, d]	-	1	Single kidney	55-64	M	Non-transmission	Non-melanoma skin cancer reported after 22 months (not notifiable). Alive with functioning transplant
							2	Single kidney	55-64	M	Non-transmission	Non-melanoma skin cancer reported after 2 years (not notifiable). Alive with functioning transplant
							3	Whole liver	45-54	M	Unlikely	Colorectal cancer diagnosed after 9 months. Died with transplant failure due to hepatitis C 14 months later
47	2010	DBD	35-54	M	Not reported[b, d]	-	1	Single kidney	65-74	M	Non-transmission	Alive with functioning transplant
							2	Single kidney	55-64	F	Non-transmission	Non-melanoma skin cancer reported after 14 months (not notifiable). Alive with functioning transplant
							3	Whole liver	45-54	F	Non-transmission	Alive with functioning transplant
							4	Double lung	35-44	F	Non-transmission	Alive with functioning transplant
							5	Heart	55-64	F	Unlikely	Metastatic colorectal cancer diagnosed after 15 months. Died due to cancer 2 years later with functioning transplant
48	2011	DBD	55+	F	Not reported[b, d]	-	1	Single kidney	55-64	M	Non-transmission	Transplant failure due to chronic allograft nephropathy after 3 years. Metastatic tongue cancer reported 6 months later (not in the CCR). Died due to cancer 8 months later.
							2	Single kidney	65-74	M	Unlikely	Kidney cancer in transplanted kidney diagnosed after 15 months. Died due to intracranial haemorrhage 2 years later with functioning transplant
							3	Whole liver	-	-	Unknown	Interstate recipient

Donor							*Recipient*					
#	**Year**	**Path**	**Age**	**Sex**	**Cancer type(s)**	**Diagnosis[a]**	**#**	**Organs**	**Age**	**Sex**	**Transmission**	**Recipient outcome, at end of follow-up (31st December 2016)**
49	2011	DBD	55+	F	Not reported[b, d]	-	1	Single kidney	55-64	F	Unlikely	Breast cancer diagnosed after 7 months. Alive with functioning transplant
							2	Single kidney	-	-	Unknown	Interstate recipient
							3	Whole liver	55-64	M	Non-transmission	Alive with functioning transplant
50	2012	DBD	15-34	M	Not reported[b, d]	-	1	SPK	25-34	F	Non-transmission	Alive with functioning transplant
							2	Single kidney	5-14	F	Non-transmission	Alive with functioning transplant
							3	Whole liver	45-54	F	Unlikely	Metastatic lung cancer diagnosed after 19 months. Died due to cancer within 1 month with functioning transplant
							4	Heart-lung	25-34	M	Non-transmission	Died within 1 month due to transplant surgery complications
51	2012	DBD	55+	F	Not reported[b, d]	-	1	Single kidney	55-64	M	Possible	Kidney cancer diagnosed after 4 months, not reported if native or transplanted kidney. Alive with functioning transplant
							2	Single kidney	65-74	M	Non-transmission	Alive with functioning transplant
							3	Whole liver	45-54	F	Possible	Metastatic melanoma reported after 2 years (not in the CCR). Died with transplant failure due to cancer 2 years later
							4	Double lung	55-64	F	Non-transmission	Non-melanoma skin cancer in-situ reported after 5 months (not notifiable). Died due to acute renal failure 2 years later with functioning transplant

Donor							*Recipient*					
#	**Year**	**Path**	**Age**	**Sex**	**Cancer type(s)**	**Diagnosis[a]**	**#**	**Organs**	**Age**	**Sex**	**Transmission**	**Recipient outcome, at end of follow-up (31st December 2016)**
52	2012	DBD	55+	M	Not reported[b, d]	-	1	Single kidney	55-64	M	Non-transmission	Alive with functioning transplant
							2	Single kidney	45-54	F	Non-transmission	Alive with functioning transplant
							3	Whole liver	45-54	M	Non-transmission	Alive with functioning transplant
							4	Double lung	55-64	M	Unlikely	Colorectal cancer diagnosed after 12 months. Alive with functioning transplant
53	2010	DCD	55+	M	Not reported[b, d]	-	1	Single kidney	55-64	M	Unlikely	Melanoma diagnosed after 8 months. Alive with functioning transplant
							2	Single kidney	65-74	M	Non-transmission	Alive with functioning transplant
54	2004	Live	35-54	F	Not reported[b, d]	-	1	Single kidney	45-54	M	Unlikely	Kidney cancer diagnosed after 2 years, not reported if native or transplanted kidney. Pre-transplant history of lip cancer. In-situ melanoma diagnosed 11 months later. Transplant failure due to BK virus nephropathy 3 years later. Died due to endocarditis 3 months later
55	2006	Live	35-54	M	Not reported[b, d]	-	1	Single kidney	45-54	M	Possible	Kidney cancer diagnosed after 6 months, not reported if native or transplanted kidney. Alive with functioning transplant

CCR, Central Cancer Registry; DBD, donation after brainstem death; DCD, donation after circulatory death; (m), metastases; SPK, simultaneous pancreas-kidney transplant

[a] When cancer was first diagnosed in the donor (years prior, during a deceased donor's terminal hospital admission, during a living donor's work-up, or during organ recovery); [b] Cancer not notified to the CCR; [c] Cancer notified to the CCR against the recipient; [d] Not recognized by clinicians at time of donation; [e] Uncertain if recognized by clinicians at time of donation

Each row represents an individual recipient. Recipients with the same donor are grouped together with alternating white/gray shading

Supplementary Table 3.S2: Number of donors with cancer, transplant procedures, transmissions, and non-transmissions in each sensitivity analysis scenario

Scenario			**Results**					
Donor cancers	*Transmissions*	*Non-transmissions*	*Donors with cancer*	*Transplants*	*Transmissions (%)*		*Non-transmissions (%)*	
All	Likely	Possible, unlikely, excluded	38	68	4	(6)	64	(94)
All	Likely, possible	Unlikely, excluded	41	74	9	(12)	65	(88)
All	Likely, possible, unlikely	Excluded	55	112	26	(23)	86	(77)
Reported against donor in any source	Likely	Possible, unlikely, excluded	38	68	4	(6)	64	(94)
Reported against donor in any source	Likely, possible	Unlikely, excluded	38	68	5	(7)	63	(93)
Reported against donor in any source	Likely, possible, unlikely	Excluded	38	68	8	(12)	60	(88)
Notified against donor in the CCR	Likely	Possible, unlikely, excluded	33	56	2	(4)	54	(96)
Notified against donor in the CCR	Likely, possible	Unlikely, excluded	33	56	2	(4)	54	(96)
Notified against donor in the CCR	Likely, possible, unlikely	Excluded	33	56	3	(5)	53	(95)
Recognized at time of donation	Likely	Possible, unlikely, excluded	37	67	4	(6)	63	(94)
Recognized at time of donation	Likely, possible	Unlikely, excluded	37	67	5	(7)	62	(93)
Recognized at time of donation	Likely, possible, unlikely	Excluded	37	67	8	(12)	59	(88)

Base case

Highest transmission rate/lowest non-transmission rate

Lowest transmission rate/highest non-transmission rate

Chapter 4: Economic evaluation – statistical modelling

4.1 Preface

This chapter presents the development of some statistical models that were used to derive input parameters for an economic evaluation of increasing utilisation of kidneys from deceased donors with primary brain malignancy (PBM economic evaluation). The development of the economic model is included in chapter 5 of this thesis, and the cost-effectiveness analysis and clinical interpretation is included in chapter 6.

This chapter is not published elsewhere, however this statistical modelling was performed as part of an economic evaluation and is included as supplementary material published in *Transplantation Direct* [1].

4.2 Introduction

The statistical modelling in this chapter was for an economic evaluation that was part of the Maximising Organ Donor Utility System-wide (MODUS) study. This study aims to use existing individual-level data relating to people with kidney failure to better understand kidney waiting list dynamics, and to explore potential increases in deceased donation through improving access to donor information at time of referral, more accurate estimation of absolute biovigilance risks, and varying risk tolerance thresholds for accepting donors [2].

The individual-level data for the MODUS study was provided by ANZDATA and ANZOD. This data included all people in Australia and New Zealand who received kidney replacement therapy (KRT) or entered a deceased donor kidney waiting list from 2006-2019.

4.3 Methods

All statistical analyses for this study were performed in RStudio [3,4]. Analysis code is published on Github [5].

4.3.1 Donor and patient characteristics modelling

The term patient is used throughout this chapter, rather than recipient, to distinguish between people on the waiting list for a kidney transplanted and those who receive a kidney transplant. The patient characteristics included in the economic evaluation were age at first waitlisting, sex, blood group, number of comorbidities (chronic lung disease, coronary artery disease, peripheral vascular disease, cerebrovascular disease, diabetes, hepatitis C, and history of cancer), and number of previous kidney transplants. The donor characteristics were age, sex, donor type (living, DCD, donation after brain death (DBD), or DBD expanded criteria [6]), Australian kidney donor profile index (KDPI) [7], and presence of primary brain malignancy (PBM).

In order to simulate patient and donor characteristics in the PBM economic evaluation, I first decided on an appropriate distribution for each characteristic, and then performed a statistical analysis of individual-level MODUS data to determine the parameter values that should be used in the simulation. I estimated the mean value for each parameter, as well as the standard error of this estimate which was used to randomly vary the input parameter for a probabilistic sensitivity analysis (PSA).

The individual-level MODUS data was divided into two distinct cohorts. The first cohort included patients ever waitlisted in Australia, while the second cohort included transplant

recipients. The first cohort of waitlisted patients was used for the models of time to transplant, while the second cohort of transplanted patients was used for models of post-transplant outcomes (cancer and graft failure).

4.3.2 Simulating jointly-distributed characteristics

Rather than simply assuming that patient and donor characteristics were independent, I developed statistical models to simulate the joint distribution of all characteristics. For example, instead of simulating a patient's age, and then independently simulating their sex, I ensured that combinations of age and sex were simulated to reflect the observed data. I did this by simulating patient and donor characteristics in a specific order, with the distribution of each characteristic conditional on the values of all previously simulated characteristics. Patient characteristics were simulated first, and donor characteristics were simulated afterwards and only if required (i.e., if the patient received a transplant). The order in which patient characteristics were simulated was: number of previous kidney transplants, blood group, sex, age at first waitlisting, and number of comorbidities. The order in which donor characteristics were simulated was: presence of PBM, donor type, sex, age, and KDPI.

To confirm that the approach of simulating joint distributions based on sequential conditional distributions was appropriate, I performed a small simulation study. I considered four individual characteristics (age, sex, blood group, and number of comorbidities), and simulated them independently, as well as sequentially in three different orderings. These orderings were: 1) Original (blood group, sex, age, number of comorbidities), 2) Reverse (number of comorbidities, age, sex, blood group), and 3) Alternative (sex, blood group, age,

number of comorbidities). I first compared the independently simulated characteristics to those simulated using the original ordering, and then I compared the original ordering with the reverse and alternative orderings.

4.3.3 Time-to-event model selection

In addition to patient and donor characteristics, I also developed statistical models to simulate the time to certain events occurring, which corresponded to health state transitions in the PBM economic model. These events were transplantation (separate models for deceased and living donor transplantation), cancer diagnosis after transplantation (separate models for deceased and living donor transplantation), and transplant failure (separate models for deceased and living donor transplantation, and for recipients with and without cancer). Therefore, there were eight different events to be modelled. Each model was censored for all relevant competing events, corresponding to the other possible health state transitions in the economic evaluation (Figure 5.1). The competing events used for censoring in each model are summarised in Table 4.1.

My approach of using separate models for each event rather than a single multi-state model allowed me to incorporate the best available data for each transition. In a multi-state modelling approach, the probability of every transition must be estimated using the same dataset from the same cohort. However, with separate models for each event I was able to, for example, combine national life tables with published standardised mortality rates for patients on dialysis or transplant to estimate the probability of death, rather than estimating this probability from a single ANZDATA dataset. For other transitions such as receiving a transplant, the probability could still be estimated using data from ANZDATA. A

limitation of this approach is that some of the time-to-event models may appear to have misleading interpretations in the presence of competing events, for example by appearing to show everyone eventually experiencing the event even if this wasn't observed in the data (due to many uncensored records experiencing the event). However, when transition probabilities derived from these models are combined with all other transition probabilities for use in the simulation, competing events will be accounted for correctly.

For each event, I compared 9 alternative time-to-event models using the R package flexsurv [8]. The models considered were: generalised F (stable [9]), generalised gamma (Prentice 1974 [10]), exponential, Weibull, log-normal, gamma, Gompertz, log-logistic, and a spline (with manually selected number of knots to optimise model fit). Models were compared based on assessment of their visual fit, as well as comparison of their Akaike Information Criterion (AIC) values. In cases where multiple models produced a similar fit, the simpler model was preferred (i.e., the model with fewer parameters).

Transition probabilities for each 3-month cycle of the simulation were derived from the time-to-event models by subtracting the cumulative probability of having experienced the event by the start of the 3-month cycle from the cumulative probability of having experienced the event by the end of the 3-month cycle.

Table 4.1 Competing events for which time to event models were censored

Model event	**Competing events/censored at:**
Deceased donor transplant	Death, living donor transplant, cancer diagnosis, loss to follow-up, end of study period[1]
Living donor transplant	Death, deceased donor transplant, cancer diagnosis, loss to follow-up, end of study period[1]
Cancer after deceased donor transplant	Death, transplant failure, loss to follow-up, end of study period[1]
Cancer after living donor transplant	Death, transplant failure, loss to follow-up, end of study period[1]
Deceased donor transplant failure without cancer	Death, cancer diagnosis, loss to follow-up, end of study period[1]
Living donor transplant failure without cancer	Death, cancer diagnosis, loss to follow-up, end of study period[1]
Deceased donor transplant failure with cancer	Death, loss to follow-up, end of study period[1]
Living donor transplant failure with cancer	Death, loss to follow-up, end of study period[1]

[1] End of study period was 31st December 2019

4.4 Results

The first cohort (waitlisted patients) included N = 8,230 patients who commenced kidney replacement therapy from 27th June 2006 (the earliest date from which waitlisting data was available) to 31st December 2019 and who were ever waitlisted in Australia for their first deceased donor kidney transplant. The second cohort (transplant recipients) included N = 18,039 patients who received 20,830 deceased or living donor transplants in Australia from 29th June 1966 (first kidney transplant in Australia) to 31st December 2019. The first cohort of waitlisted patients was used for the models of patient characteristics and time to transplant, while the second cohort of transplanted patients was used for models of post-transplant outcomes (cancer and graft failure).

The distributions selected to model each patient and donor characteristic, along with the estimated parameter values are summarised in Table 4.2 (reproduced from Supplementary Table 2 in Hedley et al., 2023 [1].

Table 4.2 Distributions and parameters used to simulate patient characteristics

Parameter	**Number of previous transplants (Poisson)**	**Blood group (Multinomial)** A	B	AB	**Female (Binomial)**	**Age at waitlisting (Normal)**	**Number of comorbidities (Poisson)**
Coefficient (SE)	***Coef. (SE)***	***Coef. (SE)***	***Coef. (SE)***	***Coef. (SE)***	***Coef. (SE)***	***Coef. (SE)***	***Coef. (SE)***
Standard deviation (σ)	-	-	-	-	-	14.51	-
Intercept	-3.79 (0.07)	-0.19 (0.02)	-1.21 (0.03)	-2.32 (0.06)	-0.53 (0.03)	50.21 (0.27)	-1.57 (0.06)
Number of previous transplants	-	0.03 (0.16)	-0.08 (0.24)	0.68 (0.27)	0.20 (0.15)	-8.62 (1.06)	-0.08 (0.09)
Blood group A	-	-	-	-	-0.02 (0.05)	0.40 (0.35)	-0.04 (0.03)
Blood group B	-	-	-	-	-0.06 (0.07)	-0.25 (0.50)	-0.03 (0.04)
Blood group AB	-	-	-	-	-0.19 (0.12)	0.31 (0.79)	-0.13 (0.06)
Female	-	-	-	-	-	-1.54 (0.33)	-0.22 (0.03)
Age at waitlisting	-	-	-	-	-	-	0.03 (0.001)
Effect size (95% CI)	***RR (95% CI)***	***RRR (95% CI)***	***RRR (95% CI)***	***RRR (95% CI)***	***OR (95% CI)***	***MD (95% CI)***	***RR (95% CI)***
Standard deviation (σ)	-	-	-	-	-	-	-
Intercept	0.02 (0.02, 0.03)	0.83 (0.79, 0.87)	0.30 (0.28, 0.32)	0.10 (0.09, 0.11)	0.59 (0.55, 0.63)	50.21 (49.68, 50.74)	0.21 (0.19, 0.23)
Number of previous transplants		1.03 (0.75, 1.42)	0.92 (0.58, 1.48)	1.97 (1.16, 3.37)	1.22 (0.91, 1.63)	-8.62 (-10.70, -6.55)	0.93 (0.77, 1.11)
Blood group A		-	-	-	0.98 (0.89, 1.08)	0.40 (-0.29, 1.10)	0.96 (0.91, 1.01)
Blood group B		-	-	-	0.94 (0.82, 1.08)	-0.25 (-1.23, 0.72)	0.97 (0.90, 1.04)
Blood group AB		-	-	-	0.83 (0.66, 1.04)	0.31 (-1.24, 1.86)	0.88 (0.78, 0.99)
Female		-	-	-	-	-1.54 (-2.19, -0.89)	0.80 (0.76, 0.84)
Age (per 10y) at waitlisting		-	-	-	-	-	1.33 (1.30, 1.35)

Coef., coefficient; SE, standard error; 95% CI, 95% confidence interval; RR, rate ratio; RRR, relative risk ratio; OR, odds ratio; MD, mean difference

Results from the small simulation study of jointly distributed characteristics are presented in Table 4.3. Compared to simulating characteristics independently, my approach of simulating characteristics in the original sequence (blood group, sex, age, comorbidities) resulted in broadly similar characteristics, except for number of comorbidities which was 1% higher using the original sequence compared to independent simulation (RR 1.01, 95%CI 1.00, 1.02, p=0.02). While observed differences in simulated characteristics between the two approaches were small, the p-values tended to decrease moving down the sequence from the first to the last characteristics simulated. This suggests that as the number of previously simulated characteristics used to simulate the next characteristic increases, the level of evidence for a difference between the two approaches also increases. The sequential approach therefore more accurately reflects the true distribution compared to the independent approach, especially for characteristics further along in the ordering.

Compared to the original ordering, there was virtually no evidence of a difference in characteristics simulated using either the reverse or alternative ordering. Therefore, the specific ordering used to simulate characteristics is unimportant, as long as the characteristics are simulated in any sequence to capture their joint distribution.

Table 4.3 Results of a small simulation comparing independent and three different sequential orderings to simulate jointly distributed characteristics

	Original[1] (vs. independent)			**Reverse[2] (vs. original)**			**Alternative[3] (vs. original)**		
Characteristic	Effect (95% CI)		P-value	Effect (95% CI)		P-value	Effect (95% CI)		P-value
1. Blood group (RRR)			0.31			0.92			0.86
A	1.02	(1.00, 1.04)		1.00	(0.98, 1.01)		1.00	(0.98, 1.02)	
B	1.00	(0.97, 1.02)		1.00	(0.97, 1.03)		1.01	(0.98, 1.04)	
AB	1.01	(0.96, 1.05)		0.99	(0.95, 1.03)		0.99	(0.95, 1.04)	
2. Female (OR)	1.01	(0.99, 1.03)	0.40	0.99	(0.97, 1.01)	0.16	0.98	(0.97, 1.00)	0.07
3. Age (MD)	0.10	(-0.03, 0.23)	0.13	-0.03	(-0.15, 0.10)	0.67	-0.06	(-0.19, 0.07)	0.35
4. Comorbidities (RR)	1.01	(1.00, 1.02)	0.02	0.99	(0.98, 1.00)	0.14	1.00	(0.99, 1.01)	0.71

RRR, relative risk ratio; OR, odds ratio; MD, mean difference; RR, rate ratio

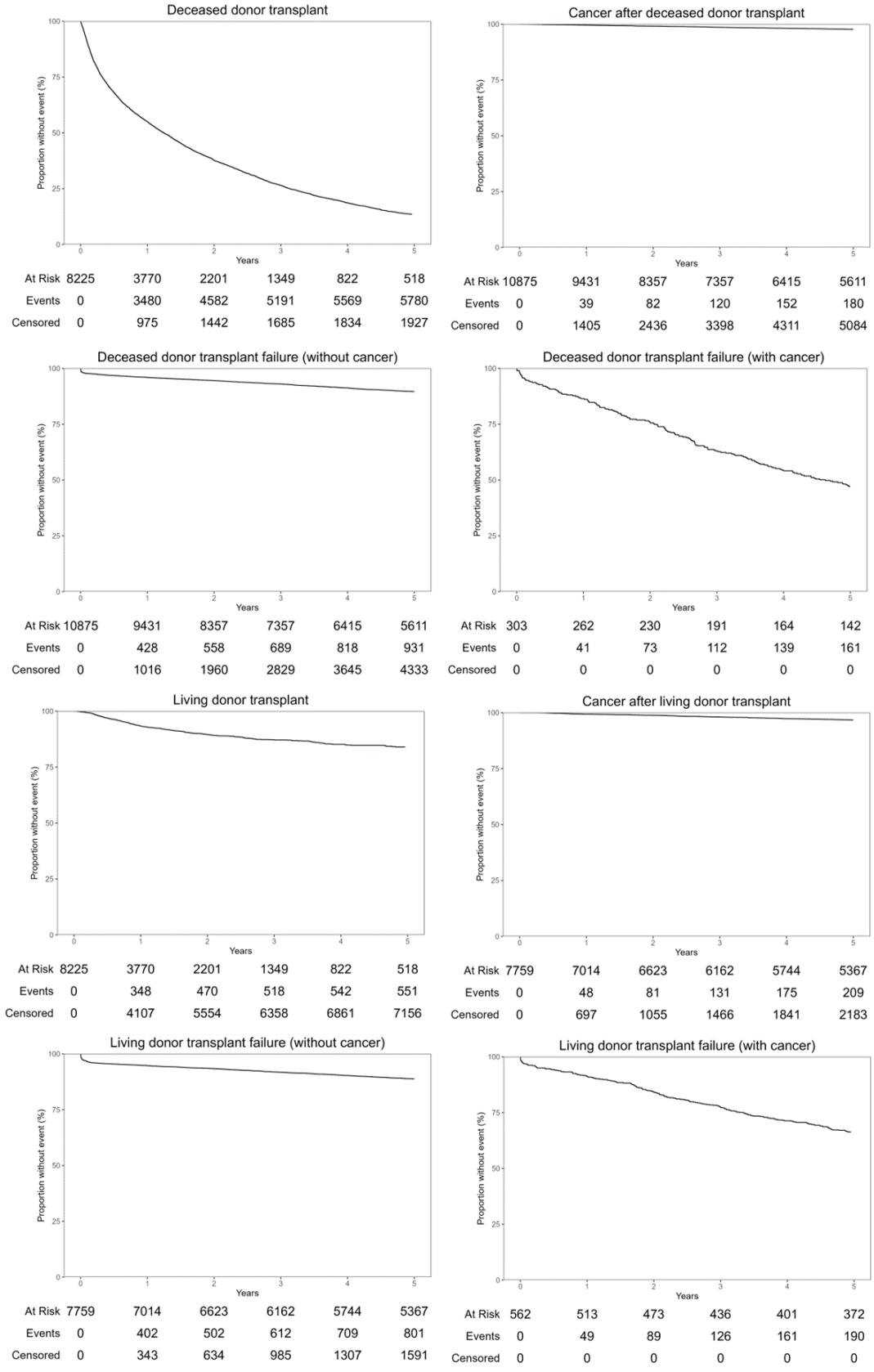
[1] Blood group, sex, age, number of comorbidities

[2] Number of comorbidities, age, sex, blood group

[3] Sex, blood group, age, number of comorbidities

Kaplan-Meier plots for each of the eight events over a 5-year period, including the number at risk, events experienced, and censoring at each year, are presented in Figure 4.1. The graphs used to compare models based on visual fit for all eight events are presented in Figures 4.2 to 4.9 (deceased donor transplant in Figure 4.2, living donor transplant in Figure 4.3, cancer after deceased donor transplant in Figure 4.4, cancer after living donor transplant in Figure 4.5, deceased donor transplant failure without cancer in Figure 4.6, deceased donor transplant failure with cancer in Figure 4.7, living donor transplant failure without cancer in Figure 4.8, and living donor transplant failure with cancer in Figure 4.9). A summary of the AIC values from each alternative model for all events associated with deceased donor transplants is presented in Table 4.4, and for events associated with living donor transplants in Table 4.5. The selected distributions and their parameter values are presented in Table 4.6 for time-to-event models associated with deceased donor transplants, and in Table 4.7 for models associated with living donor transplants. Tables 4.5 and 4.6 have been adapted from Supplementary Table 8 and Supplementary Table 9 published in Hedley et al., 2023 [1].

Figure 4.1 Kaplan-Meier plots over a 5-year period for all eight events being modelled, including number at risk, events, and censoring at each year



Kaplan-Meier plots for deceased and living donor transplant failure with cancer were censored at death, however all observed deaths happened alongside transplant failure and were therefore not censored.

Figure 4.2 Comparison of visual fit of models for time to deceased donor transplant

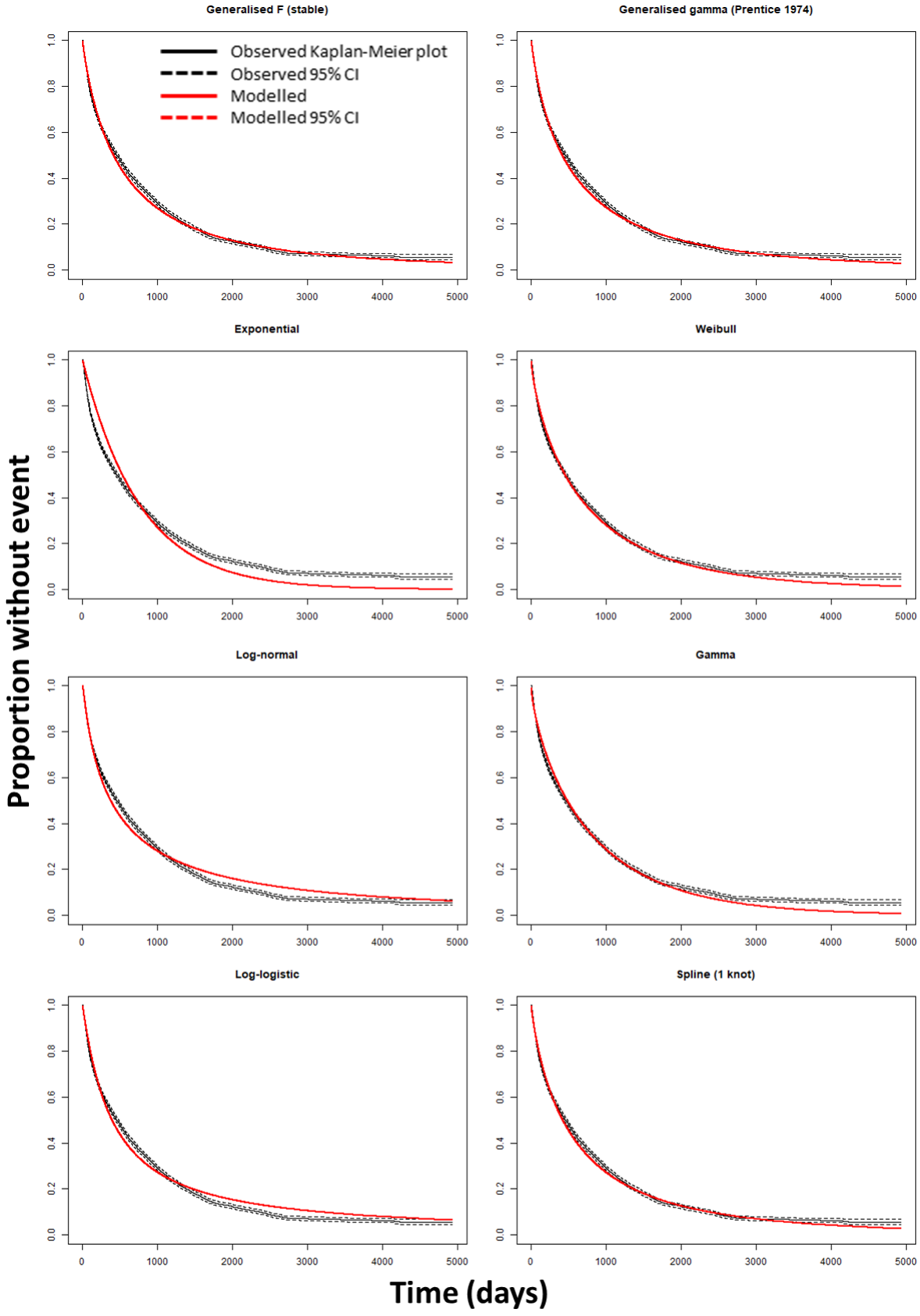


Figure 4.3 Comparison of visual fit of models for time to living donor transplant

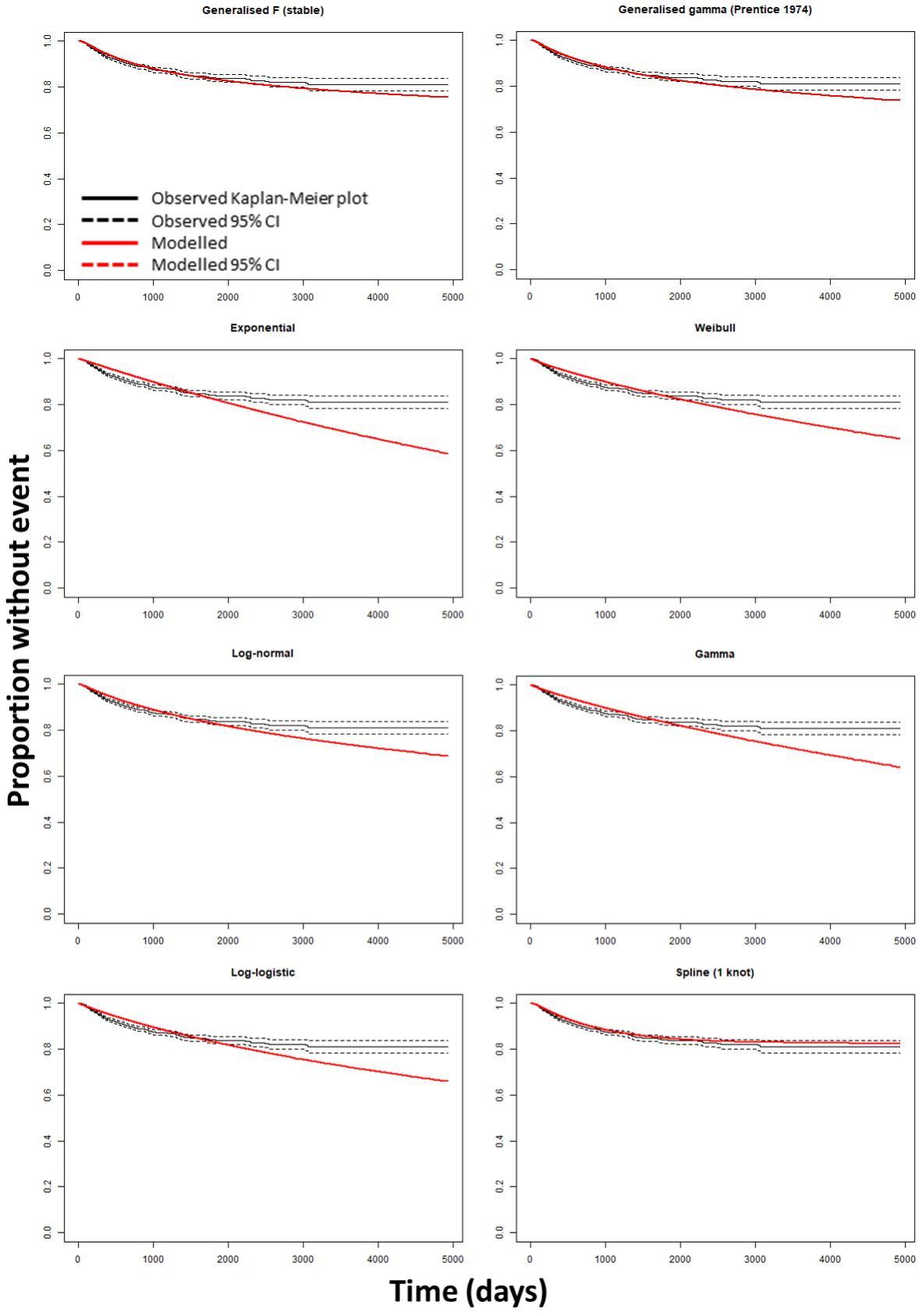


Figure 4.4 Comparison of visual fit of models for time to cancer after deceased donor transplant

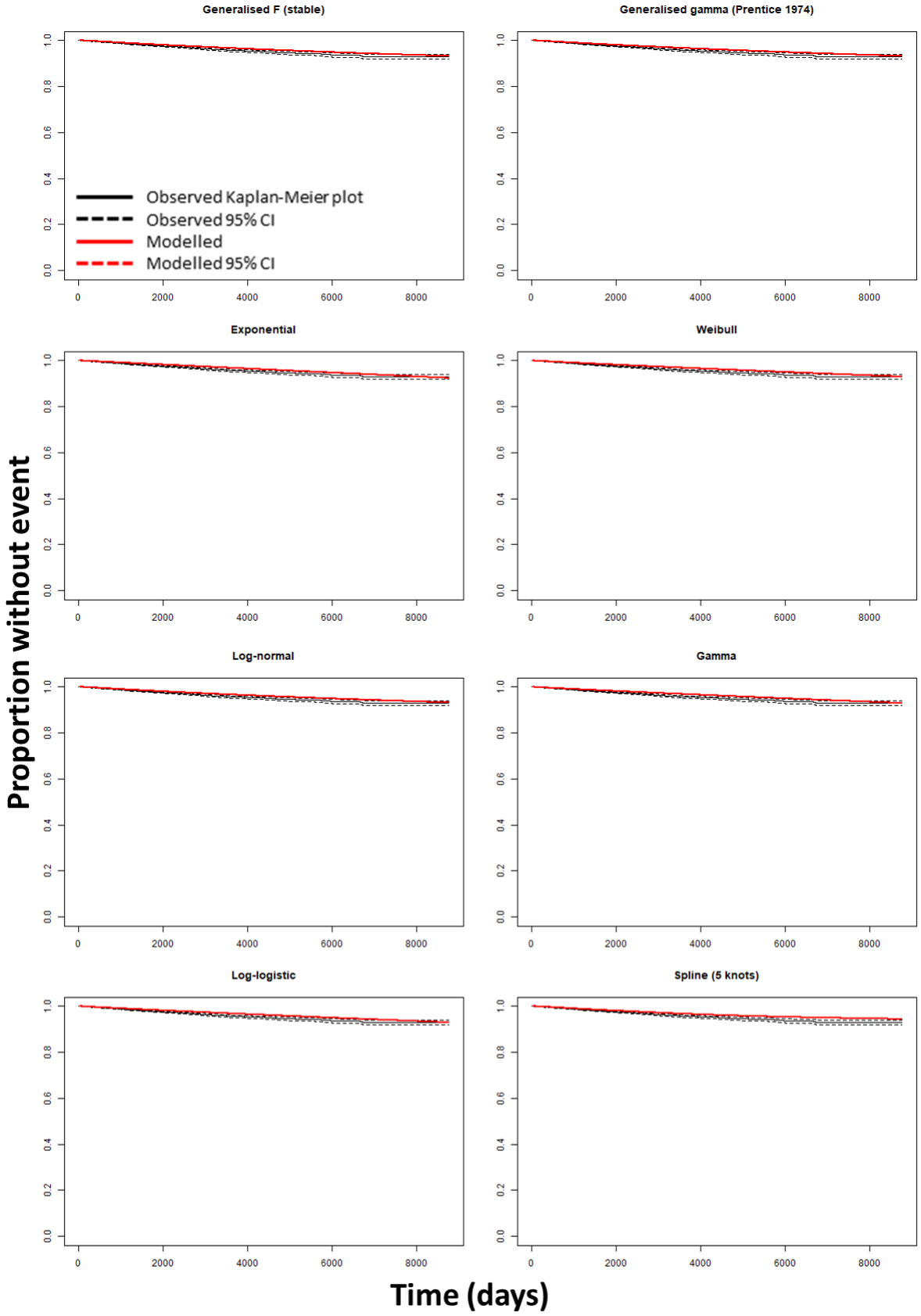


Figure 4.5 Comparison of visual fit of models for time to cancer after living donor transplant

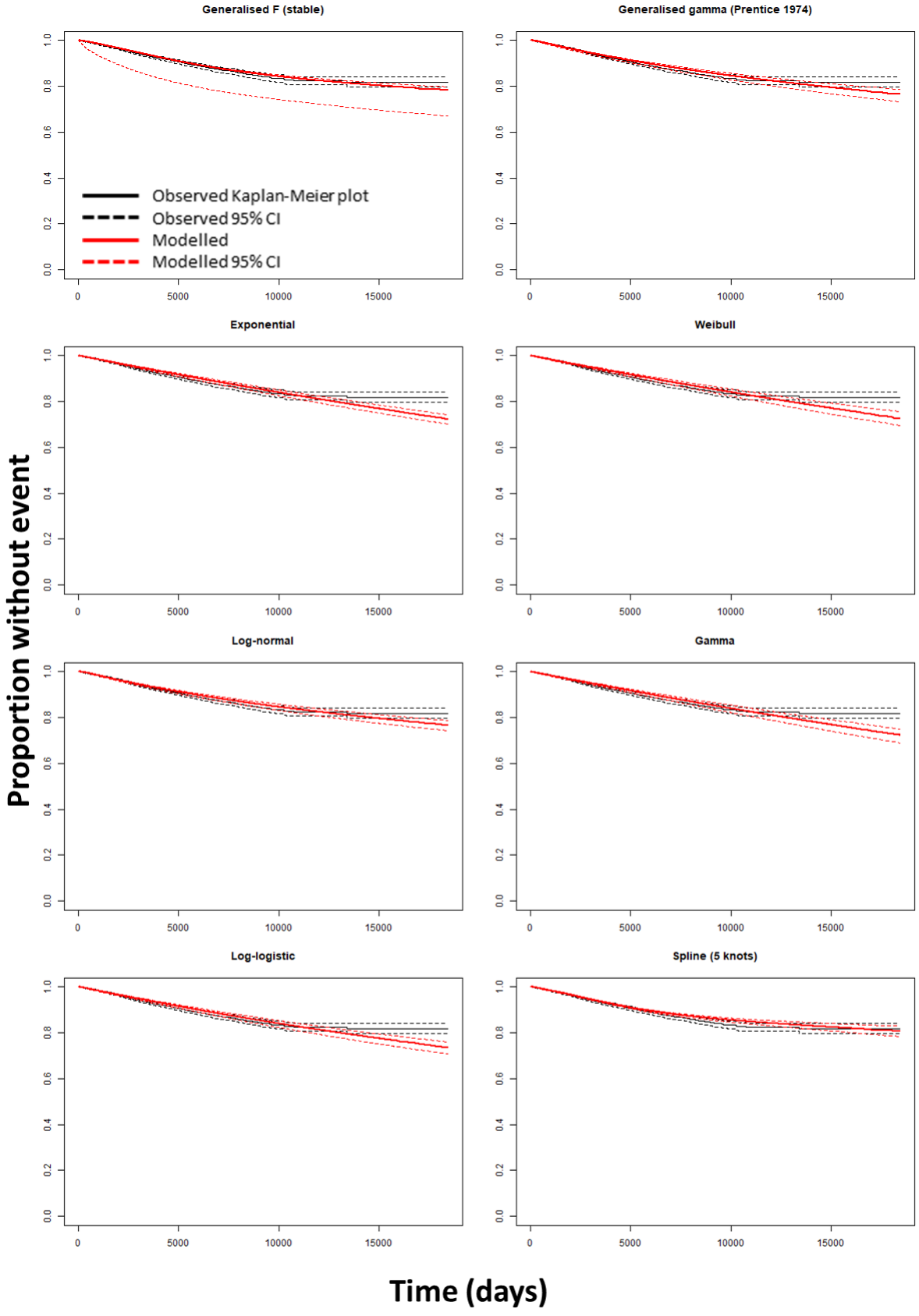


Figure 4.6 Comparison of visual fit of models for time to deceased donor transplant failure (without cancer)

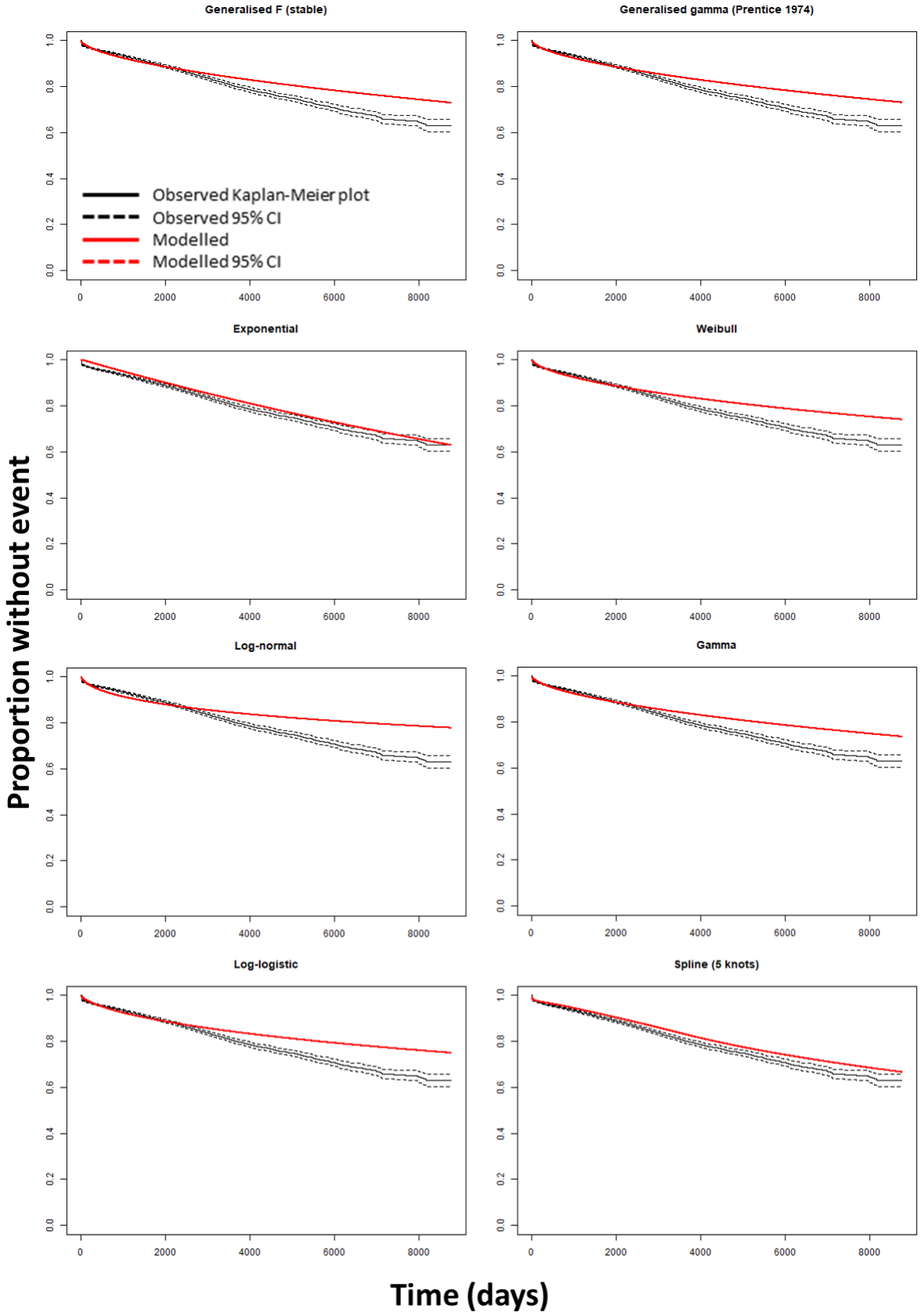


Figure 4.7 Comparison of visual fit of models for time to deceased donor transplant failure (with cancer)

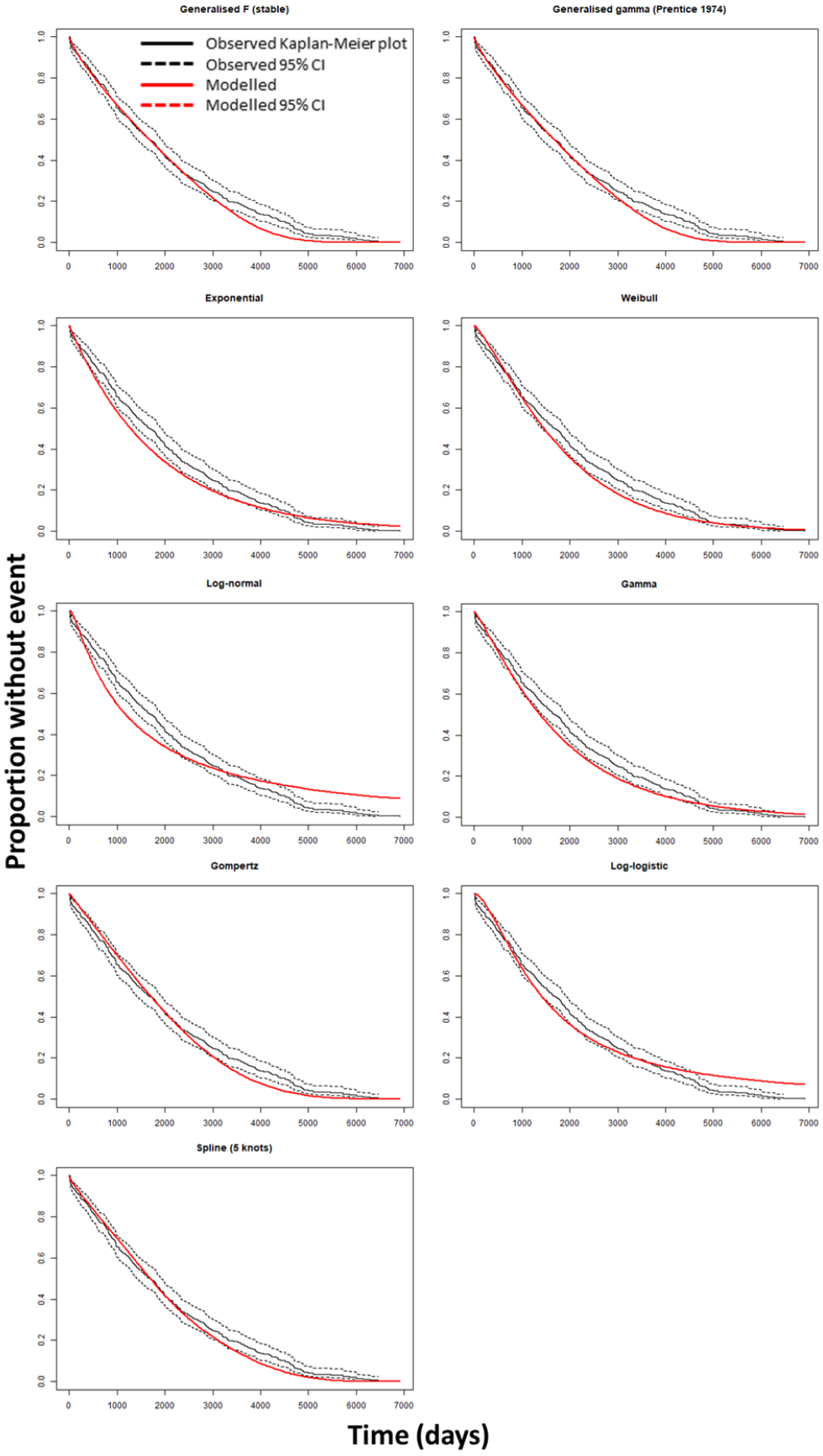


Figure 4.8 Comparison of visual fit of models for time to living donor transplant failure (without cancer)

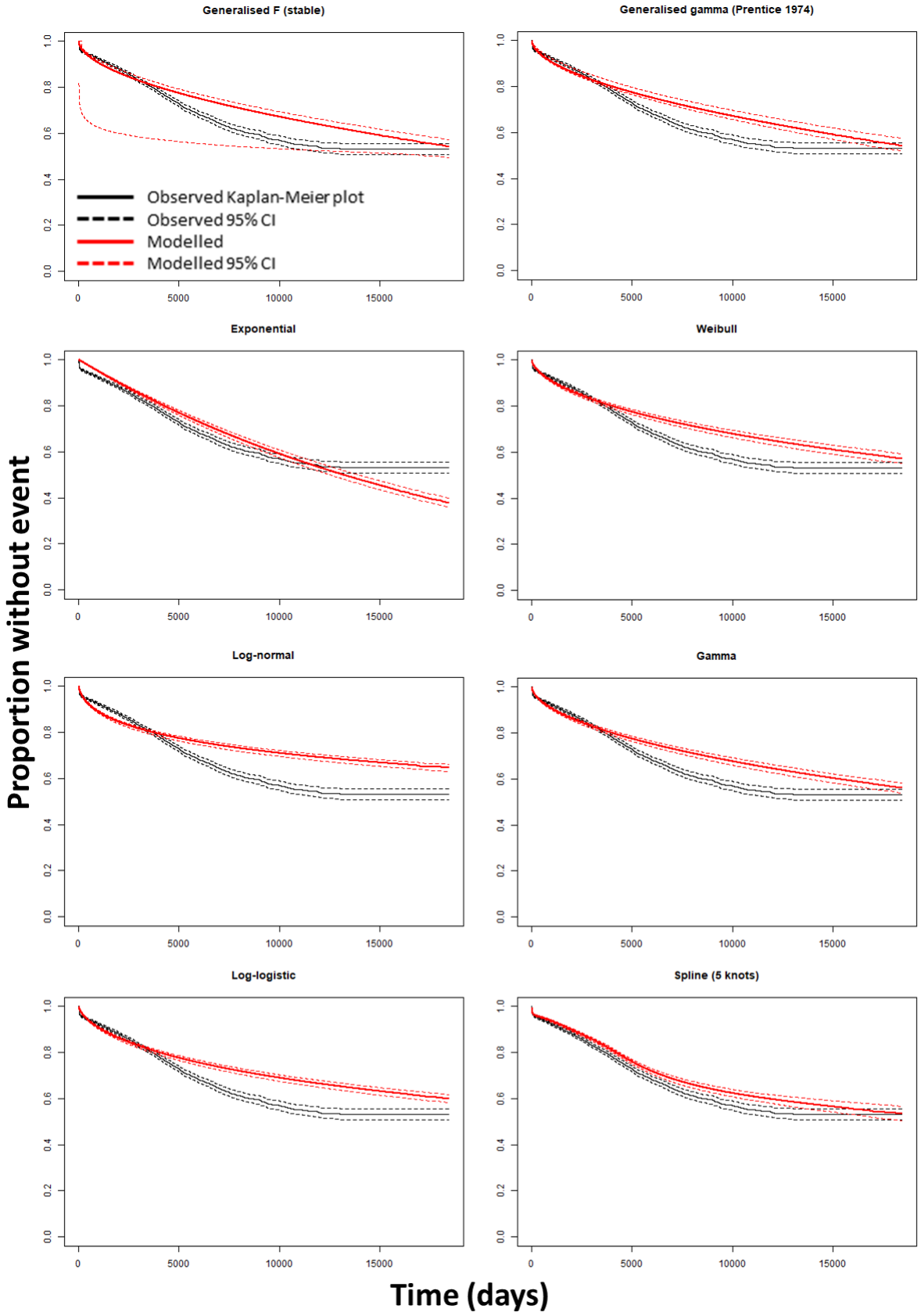


Figure 4.9 Comparison of visual fit of models for time to living donor transplant failure (with cancer)

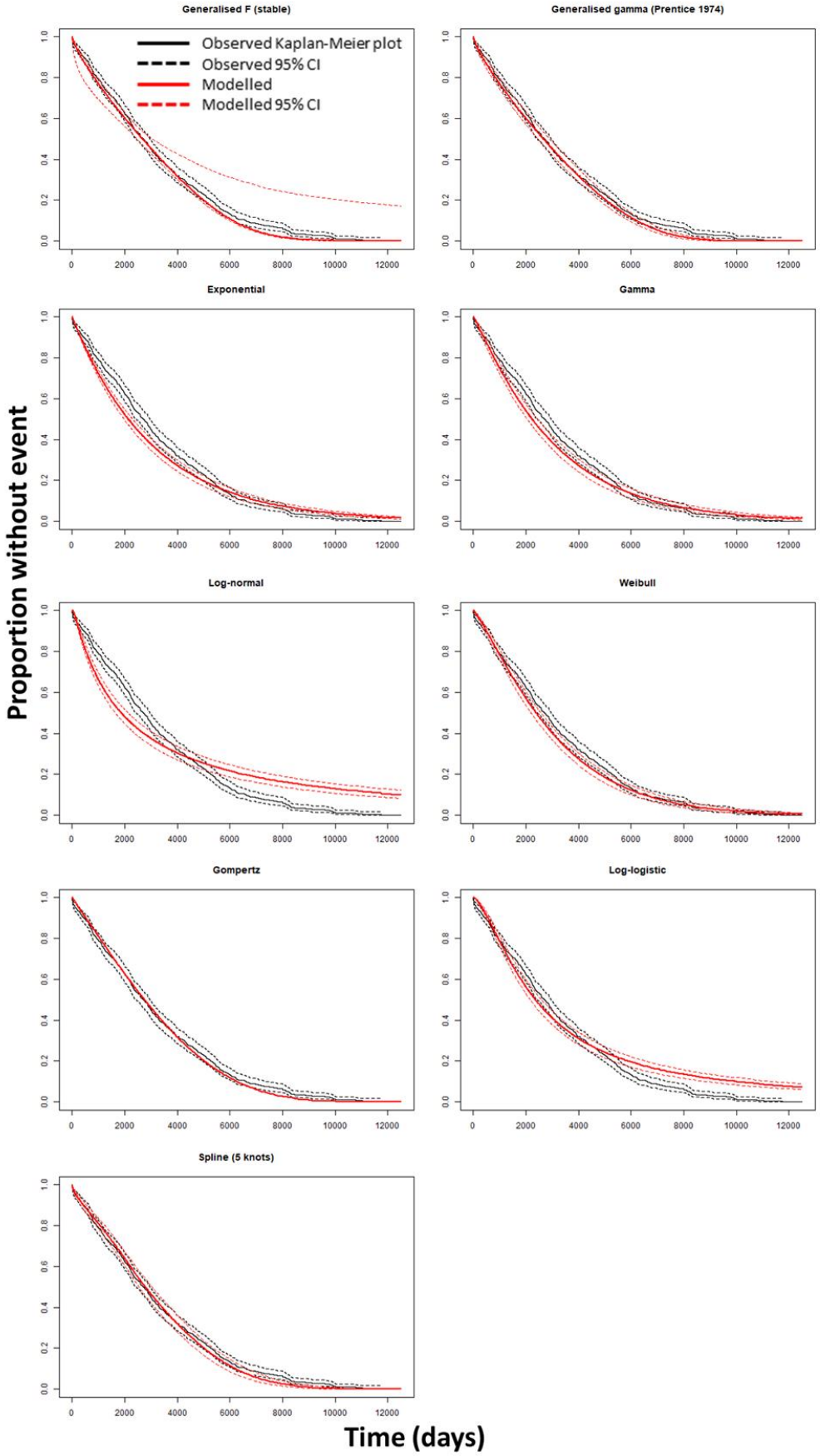


Table 4.4 Summary of AIC values from time-to-event models associated with deceased donor transplants

Model	Transplant	Cancer after transplant	Transplant failure (without cancer)	Transplant failure (with cancer)
Generalised F (stable)	90,131	7,457	33,647	5,136
Generalised gamma (Prentice 1974)	90,134	7,456	33,654	5,134
Exponential	91,097	7,464	34,313	5,191
Weibull	90,274	7,463	33,717	5,174
Log-normal	90,366	7,454	34,139	5,334
Gamma	90,421	7,463	33,668	5,186
Gompertz	Model failed	Model failed	Model failed	5,133
Log-logistic	90,244	7,461	33,806	5,261
Spline (1 knot)	90,189	-	-	-
Spline (5 knots)	-	7,461	33,261	5,132

Table 4.5 Summary of AIC values from time-to-event models associated with living donor transplants

Model	Transplant	Cancer after transplant	Transplant failure (without cancer)	Transplant failure (with cancer)
Generalised F (stable)	10,993	13,342	38,184	10,067
Generalised gamma (Prentice 1974)	10,994	13,348	38,182	10,065
Exponential	11,106	13,363	39,070	10,175
Weibull	11,088	13,365	38,336	10,151
Log-normal	11,018	13,346	38,853	10,531
Gamma	11,092	13,365	38,246	10,171
Gompertz	Model failed	Model failed	Model failed	10,084
Log-logistic	11,070	13,358	38,503	10,336
Spline (1 knot)	10,951	-	-	-
Spline (5 knots)	-	13,340	37,682	10,056

Table 4.6 Distributions and parameter values for time-to-event models associated with deceased donor transplants

Parameter, mean (SE)	Kidney transplant	Cancer after transplant	Transplant failure (without cancer)	Transplant failure (with cancer)
Distribution	Weibull	Weibull	Spline (5 knots)	Generalised gamma (Prentice 1974)
Shape	0.76 (0.01)	0.92 (0.05)	-	-
Scale	0.01 (0.0004)	0.000003 (0.000002)	-	-
Mu (μ)	-	-	-	8.28 (0.27)
Sigma (σ)	-	-	-	0.49 (0.07)
Q	-	-	-	2.54 (0.48)
Gamma 0 (γ0)	-	-	-5.04 (0.18)	-
Gamma 1 (γ1)	-	-	0.44 (0.03)	-
Gamma 2 (γ2)	-	-	0.04 (0.004)	-
Gamma 3 (γ3)	-	-	-0.09 (0.05)	-
Gamma 4 (γ4)	-	-	0.14 (0.18)	-
Gamma 5 (γ5)	-	-	-0.50 (0.34)	-
Gamma 6 (γ6)	-	-	0.51 (0.25)	-
Knot 0	-	-	0	-
Knot 1	-	-	4.44	-
Knot 2	-	-	6.66	-
Knot 3	-	-	7.41	-
Knot 4	-	-	7.91	-
Knot 5	-	-	8.32	-
Knot 6	-	-	9.22	-
Number of previous transplants	0.29 (0.08)	0.24 (0.12)	0.37 (0.04)	0.06 (0.08)
Blood group A	0.49 (0.03)	0.23 (0.13)	0.05 (0.05)	0.04 (0.07)
Blood group B	-0.10 (0.04)	0.18 (0.18)	0.09 (0.08)	-0.17 (0.10)
Blood group AB	1.05 (0.06)	-0.01 (0.28)	0.14 (0.11)	-0.58 (0.14)
Female	-0.10 (0.03)	-0.08 (0.12)	0.06 (0.05)	0.06 (0.08)
Age at waitlisting	-0.002 (0.001)	-	-	-
Number of comorbidities	-0.01 (0.01)	-0.15 (0.07)	0.20 (0.03)	-0.05 (0.04)

Parameter, mean (SE)	Kidney transplant	Cancer after transplant	Transplant failure (without cancer)	Transplant failure (with cancer)
Age at transplant	_	0.01 (0.005)	-0.03 (0.002)	0.07 (0.01)
DBD standard criteria donor	_	1.43 (0.31)	0.003 (0.08)	0.59 (0.18)
DBD expanded criteria donor	_	1.30 (0.33)	0.10 (0.09)	0.44 (0.21)
Donor female	_	-0.24 (0.12)	0.02 (0.05)	-0.03 (0.07)
Donor age	_	-0.01 (0.01)	0.002 (0.003)	-0.005 (0.01)
KDPI	_	0.02 (0.004)	0.01 (0.002)	0.002 (0.002)
Age at cancer diagnosis	-	-	-	-0.08 (0.01)

Table 4.7 Distributions and parameter values for time-to-event models associated with living donor transplants

Parameter, mean (SE)	Kidney transplant	Cancer after transplant	Transplant failure (without cancer)	Transplant failure (with cancer)
Distribution	Generalized F (stable)	Weibull	Spline (5 knots)	Generalised gamma (Prentice 1975)
Shape	-	0.99 (0.04)	-	-
Scale	-	0.00003 (0.00001)	-	-
Mu (μ)	6.81 (0.55)	-	-	9.58 (0.13)
Sigma (σ)	2.98 (0.31)	-	-	0.56 (0.04)
Q	-3.01 (0.93)	-	-	2.27 (0.20)
P	0.95 (0.65)	-	-	-
Gamma 0 (γ0)	-	-	-4.26 (0.14)	-
Gamma 1 (γ1)	-	-	0.41 (0.02)	-
Gamma 2 (γ2)	-	-	0.09 (0.01)	-
Gamma 3 (γ3)	-	-	-0.30 (0.09)	-
Gamma 4 (γ4)	-	-	0.47 (0.31)	-
Gamma 5 (γ5)	-	-	-1.04 (0.45)	-
Gamma 6 (γ6)	-	-	0.94 (0.26)	-
Knot 0	-	-	0	-
Knot 1	-	-	5.88	-
Knot 2	-	-	7.47	-
Knot 3	-	-	8.02	-
Knot 4	-	-	8.41	-
Knot 5	-	-	8.78	-
Knot 6	-	-	9.79	-
Number of previous transplants	0.12 (0.32)	0.08 (0.11)	0.22 (0.05)	0.07 (0.06)
Blood group A	-0.33 (0.11)	-0.09 (0.09)	-0.04 (0.04)	0.04 (0.05)
Blood group B	-0.05 (0.15)	-0.39 (0.16)	-0.11 (0.07)	0.004 (0.09)
Blood group AB	-0.22 (0.29)	-0.20 (0.26)	0.11 (0.11)	-0.17 (0.15)
Female	-0.002 (0.10)	-0.05 (0.09)	-0.08 (0.04)	0.05 (0.05)
Age at waitlisting	0.02 (0.004)	-	-	-

Parameter, mean (SE)	Kidney transplant	Cancer after transplant	Transplant failure (without cancer)	Transplant failure (with cancer)
Number of comorbidities	0.29 (0.06)	-0.26 (0.09)	0.04 (0.04)	-0.15 (0.05)
Age at transplant	-	-0.001 (0.003)	-0.03 (0.001)	0.02 (0.004)
Donor female	-	0.28 (0.09)	0.61 (0.04)	-0.14 (0.05)
Donor age	-	-0.01 (0.003)	-0.0007 (0.002)	-0.01 (0.002)
Age at cancer diagnosis	-	-	-	-0.03 (0.004)

4.5 References

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Chapter 5: Economic evaluation – economic modelling

5.1 Preface

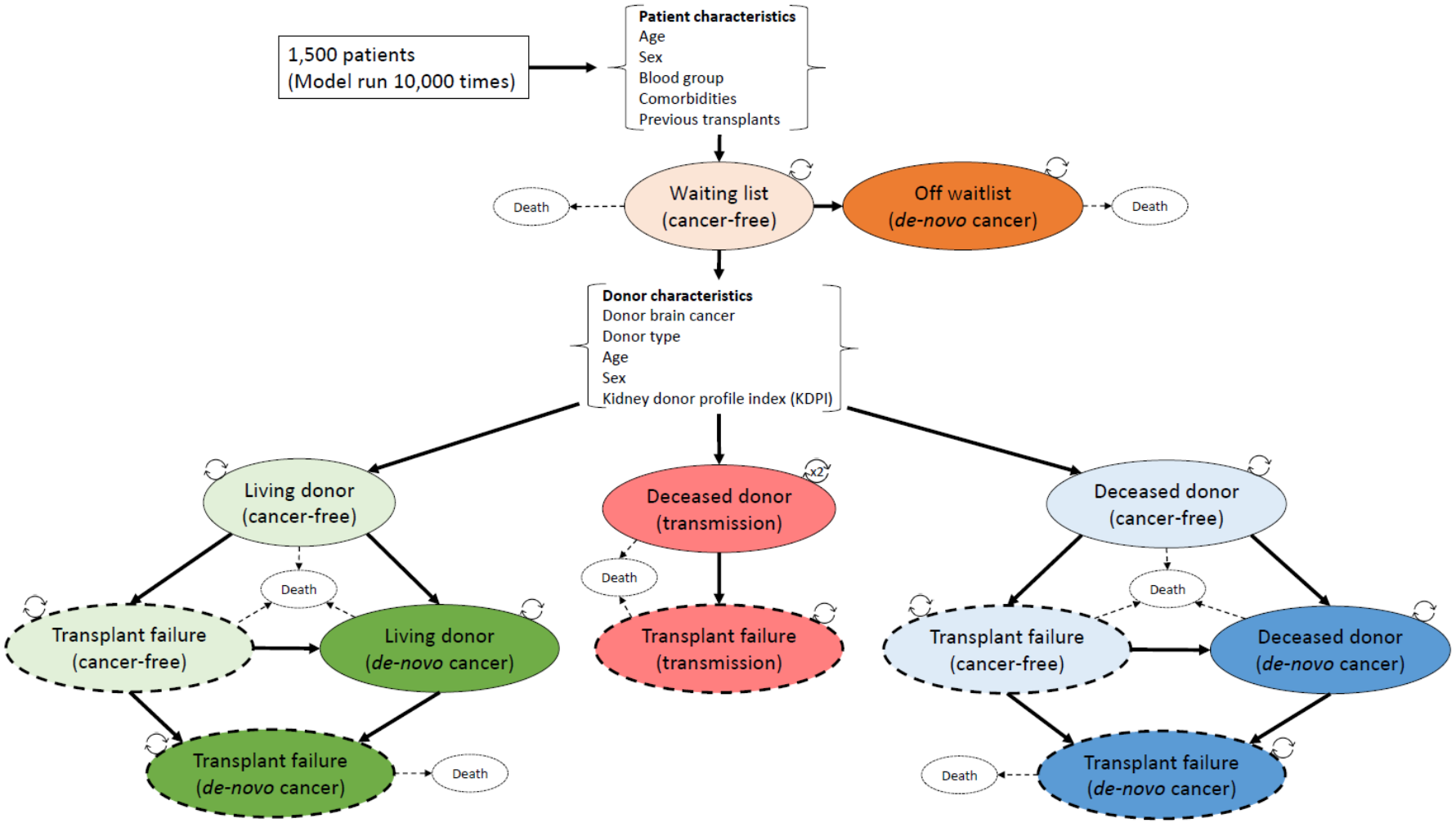
This chapter presents the development of the economic model used to evaluate the cost-effectiveness of increasing utilisation of kidneys from deceased donor with primary brain malignancy (PBM economic evaluation). The statistical modelling used to determine input parameters for simulation of patient and donor characteristics as well as for estimating some health state transition probabilities is presented in chapter 4 of this thesis. The cost-effectiveness analysis and clinical interpretation is included in chapter 6.

This chapter is published as an appendix to the economic evaluation in chapter 6, which is published in *Transplantation Direct* [1].

5.1.1 Model structure

The economic model was a Markov model patient-level simulation of 1500 people with kidney failure waiting for a deceased donor kidney transplant. Individual patients were simulated to transition between health states including waitlisted, transplant, transplant failure, and death, with separate health states for deceased vs. living donor transplants, and for those who are cancer-free vs. *de-novo* cancer vs. donor transmitted cancer. We specifically modelled *de-novo* cancers to ensure costs and QALYs associated with cancer were captured adequately across all patients, and not just restricted to those who received a kidney from a donor with cancer. The model was re-run for 10,000 simulations over a time-horizon of 25-years, which is essentially a lifetime for a typical person with kidney failure [2]. The cycle-length (i.e., the minimum time that patients spend in each health state) was 3 months. The model structure is presented in Figure 5.1 (reproduced from Figure 1 in Hedley et al., 2023 [1]).

Figure 5.1 Structure of the Markov model used to simulate individual patients



A Markov model was chosen because it is commonly used in health economic evaluations [3], and in particular for economic evaluations relating to kidney transplantation. The advantages and disadvantages of Markov model individual patient-level simulations have been described previously [4]. I chose an individual-level model rather than a cohort-level model to capture variability across individual patients, which is one of the main focuses of the MODUS study [5]. Chapter 7 of this thesis explores the impact of using an alternative model structure.

5.1.2 Challenges with developing the model

One of the main disadvantages of an individual-level model (compared to a cohort-level model) is its complexity, and this economic model was no exception. One of the most cumbersome challenges was the time it took for the model to run. On my laptop (a Dell Latitude 7290 with an Intel® Core™ i5-7300U processor and 8GB RAM) the base-case economic model took approximately 80 hours to run. Developing the model involved a lot of trial and error, with some mistakes in the model code only becoming apparent after many simulations, and therefore many wasted hours of computer running time.

To make this process as efficient as possible, I came up with a few improvements. Firstly, I ran the model on an older, spare laptop whenever possible, to avoid rendering my main work laptop unusable for days at a time. Although the running time was slightly longer as a result of using a slower machine, it did not prevent me from working on other tasks while waiting for the model to run. Secondly, I found that opening multiple sessions of R on the same laptop and running simulations in parallel was faster than using just a single session. For example, running two sessions simultaneously (one running even numbered simulations

and the other running odd numbered simulations) was approximately 1.5x faster than a single session alone. Unsurprisingly, there were diminishing returns to this method (i.e., doubling the number of sessions less than doubled the running speed). I also found that running too many sessions simultaneously caused the laptop to overheat, so I opted to run only two sessions at a time. This was nevertheless a huge improvement, as it reduced the running time enough to finish running the model over a single weekend (i.e., Friday 5pm to Monday 9am).

Another improvement I implemented to reduce running time as much as possible was to only simulate patients as needed, rather than simulating them once for each treatment arm. For example, if a patient was simulated to receive a living donor transplant in the current practice arm, I checked whether this outcome would have been different if the probability of receiving a deceased donor transplant had been at the higher value from other treatment arms (i.e., due to more donors being accepted). In most cases, a small increase in the probability of receiving a deceased donor transplant would not have changed the simulated outcome for a particular patient, hence there was no need to re-simulate this patient for other treatment arms. To illustrate with a simpler analogy, if a dice roll must be 5 or 6 for an event to occur, and this threshold is reduced so that a 4, 5, or 6 means the event occurs, there would be no point re-rolling unless the original roll was a 4 since the outcome would be the same under both thresholds.

5.1.3 Random number generation in R

While developing this model, I encountered a complication with simulating random numbers from a binomial distribution in R using the *rbinom()* function. Most random

number generating functions will increment the random number seed, so that the same random numbers can be generated again if the starting seed is reset to the same value each time. However, *rbinom()* increments the random number seed differently depending on the values input into the function. If the number (n) and probability (p) have a product less than 30, than the random number seed will increment once, whereas if the produce is greater than or equal to 30, the random number seed will increment twice. This issue was also noted by a user on Stack Exchange [6].

This can cause problems for a simulation model because randomly generated numbers can change depending on the probability being used to generate them. For example, if a patient is simulated to receive a living donor transplant in one arm, then increasing the probability of receiving a deceased donor transplant could result in them being simulated to not receive a transplant at all in another arm (which is an impossible counterfactual). As a simple analogy, imagine a dice roll must be 5 or 6 for an event to occur in one arm, and 4, 5, or 6 for the event to occur in another arm. If a simulated roll gives a value of 4, then the event should not occur in the first arm and should occur in the second arm. If the dice is re-rolled differently in each arm, then it would be possible to roll a 5 the first time (i.e., the event occurs), and a 3 the second time (i.e., the event does not occur), which would be incorrect because the probability of the event in the second arm was higher.

Discovering this issue was difficult, since it is expected that patients will have different outcomes in different treatment arms. So observing different outcomes in each treatment arm was expected. However, once I had identified the problem, the solution was

straightforward – I simply used another function, *runiform() < 0.5*, to generate random values from a binomial distribution.

5.1.4 Interactive model using R Shiny

My original plan for my economic model was to create an interactive application using the Shiny R package [7], which would allow users to vary input parameters and assumptions and see their effects on model results in real time. I eventually decided against creating such an application because my model was a simulation-based model which took hours to run and would therefore not be suitable in an interactive environment. However, in the early stages of my economic evaluation I did develop a Shiny application to demonstrate how changes to input parameters would impact the number of people and time spent in each health state. This application is accessible here: https://github.com/james-hedley/PBM_economic_evaluation.

Although I wasn't able to use this Shiny application to present my final economic model, building it was still a very useful exercise. Firstly, it allowed me to develop a skill which I will almost certainly use in my work in future. And secondly because it helped communicate the structure of my model to my supervisors and others in my research group, especially those who were unfamiliar with economic models. In particular, I found that using visual cues such as a slider for key model inputs such as cancer transmission risk helped enforce that these model inputs were assumptions that could be varied under sensitivity analysis. Furthermore, the Shiny application helped convince my supervisors of the advantages of developing my economic model in R rather than using more traditional software such as Treeage or Excel. Although the initial model development was more time consuming, once it

had been set up it was much easier to make changes to the model structure, to run sensitivity analyses, and to make the model interactive if required.

5.2 Introduction

The economic model described in this chapter was for an economic evaluation that was part of the Maximising Organ Donor Utility System-wide (MODUS) study. This chapter describes the calculation and derivation of inputs used in the economic model, including transition probabilities, health state utility values, and health state and event costs. It also provides justification for modelling assumptions, as well as explanation of the uncertainty analyses that were conducted. The results of the economic evaluation are presented in Chapter 6 of this thesis.

5.3 Methods

5.3.1 Health state transitions

Patients entered the model on the deceased donor transplant waitlist, receiving dialysis. If they developed cancer whilst waiting, they were moved off waitlist and continued dialysis but were ineligible for a transplant, consistent with national guidelines [8]. Some patients found a suitable living donor (either a relative/friend or through paired kidney exchange) whilst on the deceased donor waitlist [9], while others received a deceased donor kidney from the waitlist, or died.

We assumed that living donor transplants did not carry a risk of PBM transmission, so these recipients remained in the transplanted health state until transplant failure, *de-novo* cancer, or death. If PBM was transmitted from a deceased donor to a recipient, they had the same

probability of transplant failure or death as a recipient diagnosed with *de-novo* cancer. We assumed that the transmission would be diagnosed after nine months (i.e., three model cycles), which was the average time from transplant to diagnosis among nine kidney transplant recipients with transmission from a donor with brain cancer identified in published case reports [10-15]. After nine months, the transplanted kidney was removed, and the patient remained in transplant failure with donor-transmitted cancer health state until death. Recipients without a transmission remained in the transplanted health state until they developed a *de-novo* cancer, transplant failure, or death.

After transplant failure, patients returned to dialysis but did not return to the waitlist. Instead, they remained on dialysis until death. We did not account for subsequent transplants in our model as 89% of kidney transplants are in first-time recipients [9]. We also assumed cancer was irreversible, so once a patient was diagnosed with cancer (*de-novo* or donor-transmitted) the cancer remained until death. We acknowledge that in contemporary clinical practice cancer can be effectively treated, however we did not account for this to reduce model complexity and because patients with cancer may still have worse outcomes and higher healthcare utilization than those without cancer, even after their cancer is in remission.

Evidence of the risk of transmission from donors with PBM is limited, and some population-level studies have failed to identify any cases of transmission [16,17]. We therefore relied on upper-limit estimates of transmission risk used in national donation guidelines [8]. We assumed that all potential donors with PBM who would currently be accepted for transplantation were classified as low-risk, which means a transmission risk of 2%. For new

donors that would be accepted under our proposed interventions, those classified as not contraindicated/minimal-risk had a transmission risk of 0.1%, low-risk was 2%, and intermediate-risk was 6.4%. Since our transmission risk estimates were based on upper limits, we assumed they already accounted for the additional risk associated with radiation, chemotherapy, craniotomy, or ventriculoperitoneal shunt in the donor (<1% increase in transmission risk according to national guidelines [8]). We estimated the weighted average transmission risk among all newly accepted donors under each intervention.

We assumed that patients with a donor-transmitted cancer would experience the same rates of transplant failure and mortality as those who develop *de-novo* cancer. Evidence surrounding transplant recipient outcomes after donor brain cancer transmission is scarce, largely based on reviews of limited case reports [18,19]. A US registry-based study included 14 transplant recipients with confirmed transmission from a donor with a malignant central nervous system (CNS) tumor [20]. Of these, 11 (79%) died within 26 months follow-up, however this was only reported in aggregate across all transplanted organs. Published reviews [18,19] identified nine unique case reports of transmissions from five donors with glioblastoma multiforme [11-13,18,21,22], one with malignant meningioma [10], one with malignant glioma [23], one with CNS non-Hodgkin's lymphoma [15] (which would be contraindicated in current national guidelines [8]), and one with medulloblastoma [14]. They donated organs to 23 recipients (14 kidney, four liver, three heart, one lung, and one kidney-pancreas), with 15 transmissions (eight kidney, four liver, one heart, one lung, and one kidney-pancreas). The lung recipient [18] and three liver recipients [21-23] died within 10 months post-transplant, while the fourth liver recipient's outcome was not reported [18]. Outcomes for kidney recipients were more favorable; six had their transplanted kidney removed and were still alive on

dialysis after follow-up [10-14], one had their transplanted kidney removed and after 10 months in remission was retransplanted with no evidence of recurrence [15], one had their transplanted kidney removed and underwent chemotherapy but died eight weeks later due to cytomegalovirus pneumonia and pericarditis with autopsy showing no signs of tumor recurrence [15], and one kidney-pancreas recipient had their transplanted pancreas removed after three days due to arterial thrombosis, and their transplanted kidney removed after four months but died one month later [14]. Transmission was identified on average nine months after transplant (range 4 – 18 months).

We assumed that all patients with a transmitted cancer would have their transplanted kidney removed (i.e., nephrectomy) after nine months. Although it may be possible to treat a transmitted cancer without removing the transplanted kidney, our assumption that all patients would undergo nephrectomy was conservative (i.e., favored current practice), and was consistent with available case-reports.

A case-control study of 12,805 kidney recipients in the Netherlands reported median survival after *de-novo* cancer diagnosis of 2.1 years [24]. Considering that only two of nine (22%) transmissions from case reports of kidney recipients resulted in death during follow-up, our assumption that outcomes for patients with a donor-transmitted cancer would be similar to those with *de-novo* cancer seems appropriate.

5.3.2 Comparators

Reasons for underutilization of kidneys from deceased donors with PBM include inaccurate perception of PBM risk in potential donors with insufficient medical history available at the

time of donation decisions, inconsistent decisions among different clinicians with tendencies to focus on increased relative risk rather than absolute risk, and reluctance to accept potential donors labeled as intermediate risk (6.4% transmission risk) according to donation guidelines.

We therefore considered three interventions that have previously been proposed to address these issues [25], and compared them with current practice (i.e., individual clinicians deciding which potential donors with PBM to accept or decline). Exactly how these interventions might be implemented is beyond the scope of this study, but briefly they were: 1) decision support for clinicians in accurately estimating absolute donor risk for cancer transmission; 2) improved data accuracy with real-time data-linkage to hospital records and cancer registries to improve classification of potential donor cancer type and hence transmission risk; and 3) increased risk-tolerance to allow use of donors with intermediate-risk PBM (estimated transmission risk 6.4%) [8,25].

Both real-time data-linkage and increase risk tolerance were assumed to be in combination with decision support to ensure that donation decisions would adhere to guidelines [8]. In our previous study we did not identify any potential donors who would have been accepted if all three interventions (decision support, real-time data linkage, and increased risk tolerance) had been applied together. Nor did we identify any actual donors who would have been declined under all three interventions in combination with each other. In the absence of any evidence that combining these interventions would impact the number of donors with PBM or their average transmission risk [25], we therefore did not consider the combined effect of these three interventions.

Compared with current practice, each intervention would alter the model in two ways: 1) increasing the probability of receiving a deceased donor transplant (by increasing the number of deceased donor kidneys available), and 2) changing the cancer transmission risk associated with deceased donor transplant (e.g., by introducing more donors with PBM). We estimated potential impacts using data from a published study of 472 potential donors from NSW 2010-2013, of whom 340 (72%) became actual donors (including 8 with PBM), and 172 (28%) were declined due to cancer [25]. We assumed two kidneys were available for transplant from all 340 donors, which is consistent with national average of 1.91 (888 kidneys from 463 donors) in 2020 [26]. We also assumed two kidneys per donor would be available from any additional donors with PBM, hence the proportional increase in donation would be the same regardless of whether it was expressed in terms of donors or kidneys.

5.3.3 Transition probabilities

5.3.3.1 Mortality

Mortality was based on Australian life tables for 2017-2019, stratified by age and sex [27]. We adjusted mortality by 10-year age group and sex specific standardized mortality ratios (SMRs) for dialysis and transplant (compared to the general Australian population) derived from figures published in the ANZDATA annual report [28,29]. For patients with cancer, we further adjusted mortality (multiplicatively) based on relative survival reported by the Australian Institute for Health and Welfare (AIHW) for 2013-2017, stratified by 5-year age group, sex, and years since diagnosis [30]. Average relative survival across all cancer sites was weighted by annual incidence of each cancer. We applied SMRs for the nearest age-group to each simulated patient.

5.3.3.2 Cancer

The probability of developing any cancer whilst on dialysis (i.e., on the waiting list or after transplant failure) was based on cancer incidence reported by AIHW, stratified by 5-year age group and sex, and summed over all cancer sites [30]. We multiplied this by an estimated incidence rate ratio (IRR) of 1.60, based on the overall incidence of cancer among dialysis patients (22.2/1,000) [31] divided by the overall incidence of cancer in the Australian population (1390.4/100,000) [30].

The probability of developing cancer after receiving a transplant was based on time-to-event modelling described in Chapter 4. If a deceased donor had brain cancer, there was a risk of cancer transmission in addition to the underlying risk of the recipient developing *de-novo* cancer. We assumed that under current practice, donors with brain cancer would only be accepted for transplantation if they were considered minimal or low risk according to national donation guidelines [8]. We therefore applied the upper-limit estimate for transmission risk from low-risk brain cancers of 2% to all transplants regardless of patient or donor characteristics.

5.3.3.3 Transplant and transplant failure

The probability of receiving a transplant, and subsequent transplant failure were based on time-to-event models described in Chapter 4 of this thesis.

5.3.4 Utility values

For patients on dialysis or with a transplant, we calculated the simple average of utilities reported in two studies on quality of life in chronic kidney disease (CKD): an Australian

meta-analysis [32] and a multi-national cohort study [33]. The utility values for patients on dialysis from these quality-of-life studies were 0.70 and 0.76, hence the simple average utility applied to the model was 0.73. For patients with a kidney transplant, the utility values were 0.82 and 0.84, hence the simple average 0.83 was used.

For patients with cancer, we used utility values for the five most common cancer sites (breast, colorectal, lung, melanoma, and prostate) from a recent systematic review [34]. We calculated an average utility for each cancer stage (I, II, III, and IV) as well as overall, weighted by annual incidence by site and stage in Australia in 2011 reported by the AIHW [30]. We applied the average utility across all cancer stages (0.71) to patients with *de-novo* cancer. When a transmission occurs, the cancer in the recipient is likely to be a more advanced stage compared with a *de-novo* cancer since it has necessarily already metastasized in the donor. Therefore, we applied the weighted average utility for stage IV cancers (0.62) to patients with a donor-transmitted cancer.

We assumed that the decrement in quality of life associated with kidney failure was independent of the decrement associated with cancer. Therefore, for patients with both kidney failure and cancer we multiplied the utility values for kidney failure and cancer together. For patients on dialysis with cancer, their utility value was 0.52 (0.73 x 0.71) for *de-novo* cancer and 0.45 (0.73 x 0.62) if the cancer was transmitted. For those with a kidney transplant and cancer, their utility value was 0.59 (0.83 x 0.71) for *de-novo* cancer and 0.51 (0.83 x 0.62) if the cancer was transmitted.

We did not account for a potential quality of life decrement for recipients of a kidney from a donor with PBM, associated with fear of transmission occurring. Such a decrement would likely be small in comparison to the improvement in quality of life after receiving a kidney transplant, and for patients who agree to accept a kidney with a risk of cancer transmission, this fear may be less likely to influence their quality of life.

5.3.5 Costs

All costs were converted to 2021 Australian dollars (AUD) using the consumer price index (CPI) for health, averaged across each calendar year [35]. We included costs associated with dialysis, kidney transplantation, and cancer treatment. All costs were separated into the first 3 months, months 4 to 12, year 2, year 3, year 4, and all subsequent years.

5.3.5.1 Dialysis

The cost of dialysis treatment was calculated as an average across home hemodialysis, hospital hemodialysis, and home peritoneal dialysis, weighted by the proportion of patients using each modality reported in the ANZDATA annual report 2020 [9]. The annual cost of home hemodialysis and home peritoneal dialysis were derived from an Independent Hospital Pricing Authority (IHPA) costing study of home delivered dialysis [36], while the cost of hospital hemodialysis was based on Australian-refined Diagnosis Related Group (AR-DRG) L61Z (Hemodialysis) from the National Hospital Cost Data Collection (NHCDC) 2018-2019 .

5.3.5.2 Transplant

The costs associated with transplant that we included in our model were: organ retrieval, transplant procedure, drug utilization, and nephrologist consultations. These were based on

the costs used in the Kidney Health Australia report of the economic impact of end-stage kidney disease in Australia: projections to 2020 [37].

The cost of retrieving a living donor kidney was based on the average of AR-DRGs for Kidney, Ureter and Major Bladder Interventions for Non-Neoplasm with major, intermediate, and minor complications (L04A, L04B, and L04C), weighted by the number of separations from the NHCDC 2018-2019 [38]. For deceased donors, the cost of kidney retrieval was based on an estimate from the Kidney Health Australia report [37].

The cost of transplanting a kidney into a recipient (from a living or deceased donor) was based on the average of AR-DRGs L10A (Kidney Transplant, Age <=16 Years or Major Complexity) and L10B (Kidney Transplant, Age >=17 Years and Minor Complexity), weighted by the number of separations from the NHCDC 2018-2019 [38].

We included costs for the most commonly prescribed induction, immunosuppression, and prophylaxis drugs for transplant recipients based on the ANZDATA annual report 2020 [9]. Induction drugs were basiliximab and thymoglobulin, immunosuppression drugs were tacrolimus, mycophenolate, and prednisolone, and prophylaxis drugs were valganciclovir, trimethoprim + sulfamethoxazole, and nystatin. The proportion of patients prescribed each drug was based on the ANZDATA annual report 2020 [9], while dosages were based on product information available from the Therapeutic Goods Administration (TGA) [39]. Where information was unavailable, we relied on expert opinion from two specialist nephrologist co-authors (MW and AW). The total costs for induction drugs were derived from a review of the Australian organ donation, retrieval, and transplantation system, while unit costs for

immunosuppression and prophylaxis drugs were extracted from the Pharmaceutical Benefits Scheme Schedule [40].

We did not include additional costs for cancer screening or monitoring in recipients of a kidney from a donor with known PBM. It is unpredictable where the transmitted cancer might first appear in the recipient, and in the absence of a global test for cancer we assumed that monitoring would be included in routine post-transplant follow-up.

5.3.5.3 Nephrologist visits

The frequency of nephrologist consultations for patients on dialysis or with a kidney transplant was based on national guidelines [41] and the expert opinion of two specialist nephrologist co-authors (MW and AW). The cost associated with each nephrologist visit was based on Medicare Benefits Schedule items 104 (initial visit) and 116 (subsequent visit) [42].

5.3.5.4 Cancer

The costs associated with cancer diagnosis and treatment were based on a longitudinal study of health care in 266,000 people from NSW aged 45 and over, and included costs associated with hospital admissions, emergency department presentations, government subsidized prescription medications (PBS), and government subsidized medical services (MBS) [43]. Costs were provided for each of the first 5 years after diagnosis, and we assumed that all subsequent years would incur the same cost as year 5. For *de-novo* cancers we used the overall cost across all cancers. There were no costs reported specifically for brain cancer. We assumed that transmitted cancers would incur a higher cost due to their advanced stage at diagnosis, hence for transmitted cancers we used the cost associated with kidney cancer

because this was higher than the average across all cancers and because transmitted cancers were likely to be diagnosed in the transplanted kidney.

5.3.5.5 Nephrectomy

Patients with a donor-transmitted cancer have their transplanted kidney removed after at most nine months. The cost of kidney removal is based on the average of AR-DRGs for Kidney, Ureter and Major Bladder Interventions for Non-Neoplasm with major, intermediate, and minor complications (L04A, L04B, and L04C), weighted by the number of separations from the NHCDC 2018-2019 [38].

5.3.6 Uncertainty analyses

We performed a probabilistic sensitivity analysis to assess uncertainty in model parameters, a worst-case scenario where transmission resulted in immediate death, and a threshold analysis to determine the transmission risk at which increased risk tolerance would no longer be cost-effective.

For the probabilistic sensitivity analysis, we assumed a uniform distribution for discount rates (0-10%) and the increase in donation and average transmission risk (0-200% of base-case value). Statistical model parameters followed normal distributions based on means and standard errors (SE). Utilities followed beta distributions based on mean (base-case) and reported SE [32] (for cancer utilities we assumed minimum and maximum reported utilities corresponded to the 0.05th and 99.95th percentiles [34]). We considered two alternative methods for combining simultaneous utilities: the minimum (upper estimate), and the sum minus one (lower estimate) [44]. Costs followed uniform distributions (±15%) [45].

We assessed which model inputs had the most influence on results by determining the marginal impact of a percentage change in each input, using linear regression of costs and QALYs adjusted for the randomly selected values of all inputs across 10,000 probabilistic sensitivity analysis simulations. We also performed an extreme worst-case scenario analysis where cancer transmission would result in immediate death for the recipient, as well as threshold analysis where the average transmission risk of new donors under decision support with increased risk tolerance was varied in increments of 5% from 10% to 50%, to determine how high the transmission risk would need to be before the intervention would no longer be cost-effective.

5.3.7 Willingness-to-pay threshold

Our willingness-to-pay (WTP) threshold was $28,000 per QALY as this was used in a recent Australian economic evaluation of kidney donation policy [45] and has been demonstrated to be appropriate in an Australian setting [46]. This is lower than the commonly used $50,000 threshold [47], hence the probability of interventions being cost-effective may be conservative.

5.4 Results

Standardized mortality ratios (SMRs) for patients with kidney failure stratified by age and sex are presented in Table 5.1 (reproduced from Supplementary Table 4 in Hedley et al., 2023 [1]).

Table 5.1: Standardized mortality ratios (SMRs) for patients with kidney failure, by age and sex compared to the general Australian population

Age	Female		Male	
	Dialysis	Transplant	Dialysis	Transplant
25	143.1	9.0	61.6	-
35	63.9	4.1	38.0	3.1
45	52.5	4.2	23.8	3.3
55	26.6	4.5	16.1	2.9
65	15.5	3.8	9.9	2.5
75	6.8	1.8	5.3	1.9
85	3.3	2.1	2.6	1.6

Estimated from ANZDATA annual reports [9]

The average relative survival for patients with cancer stratified by 5-year age group, sex, and number of years since cancer diagnosis is presented in Table 5.2 (reproduced from Supplementary Table 5 in Hedley et al., 2023 [1].

Table 5.2: Average relative survival with cancer by 5-year age group, sex, and years after diagnosis

	Average relative survival compared with the general population, %									
	Females					*Males*				
Age	0-1y	1-2y	2-3y	3-4y	4y+	0-1y	1-2y	2-3y	3-4y	4y+
0-4	98.5	97.4	97.0	96.8	96.6	97.5	96.8	96.4	96.0	95.9
5-9	98.9	98.5	98.4	98.3	98.3	98.7	98.0	97.7	97.5	97.4
10-14	98.5	97.7	97.3	96.7	96.5	99.0	98.1	97.3	97.3	97.3
15-19	98.6	97.5	96.8	96.0	95.6	98.8	97.2	96.6	95.7	95.8
20-24	98.9	97.6	97.2	96.8	96.2	98.4	96.7	96.1	95.5	95.0
25-29	98.4	97.1	96.7	95.9	95.5	97.8	96.2	95.7	95.1	94.6
30-34	97.4	94.9	95.2	94.5	94.0	96.1	95.0	94.9	94.9	94.5
35-39	96.1	93.8	92.9	92.9	92.3	95.5	92.9	92.5	92.9	92.6
40-44	94.4	90.7	89.2	89.1	88.5	92.8	88.5	86.2	85.5	85.0
45-49	92.0	88.5	86.7	84.8	84.2	89.7	85.9	83.2	81.9	80.7
50-54	89.9	85.1	83.5	82.2	81.0	88.0	81.2	78.9	77.6	77.1
55-59	87.6	82.0	79.2	78.5	77.1	84.6	79.1	76.8	75.9	74.2
60-64	86.8	80.8	77.1	75.3	75.1	83.3	76.5	72.8	70.3	68.0
65-69	84.1	77.7	73.2	72.0	70.4	79.9	72.8	69.7	67.3	67.6
70-74	81.5	74.7	71.4	71.6	70.3	77.6	72.7	68.7	66.5	64.5
75-79	77.3	71.2	70.6	68.3	66.2	75.3	68.8	65.5	63.3	61.3
80-84	72.3	68.3	66.6	65.9	65.3	71.5	66.8	64.0	65.2	64.8
85+	62.8	62.4	62.6	61.6	64.2	65.5	63.9	63.5	63.8	67.5

Derived from cancer data from the Australian Institute of Health and Welfare (AIHW) [30]

Mortality rates applied to all simulated patients stratified by age, sex, treatment, and years since cancer diagnosis are summarized in Table 5.3 (reproduced from Supplementary Table 6 in Hedley et al., 2023 [1].

Table 5.3: Annual mortality rates by age, sex, treatment, and years since cancer diagnosis

Age	Sex	General population	Dialysis	Dialysis with cancer					Transplant	Transplant with cancer				
				0-1 years	1-2 years	2-3 years	3-4 years	4+ years		0-1 years	1-2 years	2-3 years	3-4 years	4+ years
0	Male	0.00364	0.22436	0.24412	0.22925	0.22788	0.22717	0.22587	0.01761	0.04264	0.02380	0.02206	0.02117	0.01952
0	Female	0.00297	0.42496	0.43363	0.43130	0.42759	0.42622	0.42601	0.02676	0.04142	0.03748	0.03121	0.02888	0.02852
1	Male	0.00025	0.01541	0.04050	0.02162	0.01987	0.01898	0.01733	0.00121	0.02666	0.00751	0.00574	0.00483	0.00315
1	Female	0.00024	0.03434	0.04889	0.04498	0.03875	0.03644	0.03609	0.00216	0.01720	0.01315	0.00672	0.00433	0.00397
2	Male	0.00014	0.00863	0.03389	0.01488	0.01312	0.01222	0.01056	0.00068	0.02614	0.00698	0.00521	0.00430	0.00262
2	Female	0.00012	0.01717	0.03198	0.02800	0.02166	0.01931	0.01895	0.00108	0.01613	0.01208	0.00565	0.00325	0.00289
3	Male	0.00012	0.00740	0.03269	0.01366	0.01190	0.01099	0.00933	0.00058	0.02604	0.00688	0.00511	0.00420	0.00253
3	Female	0.00010	0.01431	0.02916	0.02517	0.01881	0.01645	0.01609	0.00090	0.01596	0.01191	0.00547	0.00307	0.00271
4	Male	0.00010	0.00616	0.03148	0.01243	0.01067	0.00976	0.00810	0.00048	0.02595	0.00679	0.00502	0.00411	0.00243
4	Female	0.00008	0.01145	0.02634	0.02234	0.01597	0.01360	0.01324	0.00072	0.01578	0.01173	0.00529	0.00289	0.00253
5	Male	0.00009	0.00555	0.01832	0.01288	0.00878	0.00705	0.00649	0.00044	0.01327	0.00780	0.00369	0.00195	0.00139
5	Female	0.00007	0.01002	0.02104	0.01425	0.01072	0.01117	0.01002	0.00063	0.01176	0.00491	0.00134	0.00180	0.00063
6	Male	0.00008	0.00493	0.01771	0.01226	0.00817	0.00644	0.00588	0.00039	0.01322	0.00775	0.00364	0.00190	0.00134
6	Female	0.00006	0.00859	0.01963	0.01283	0.00929	0.00974	0.00859	0.00054	0.01167	0.00482	0.00125	0.00171	0.00054
7	Male	0.00007	0.00431	0.01710	0.01165	0.00755	0.00582	0.00526	0.00034	0.01317	0.00771	0.00359	0.00185	0.00129
7	Female	0.00006	0.00859	0.01963	0.01283	0.00929	0.00974	0.00859	0.00054	0.01167	0.00482	0.00125	0.00171	0.00054
8	Male	0.00007	0.00431	0.01710	0.01165	0.00755	0.00582	0.00526	0.00034	0.01317	0.00771	0.00359	0.00185	0.00129
8	Female	0.00006	0.00859	0.01963	0.01283	0.00929	0.00974	0.00859	0.00054	0.01167	0.00482	0.00125	0.00171	0.00054
9	Male	0.00007	0.00431	0.01710	0.01165	0.00755	0.00582	0.00526	0.00034	0.01317	0.00771	0.00359	0.00185	0.00129
9	Female	0.00006	0.00859	0.01963	0.01283	0.00929	0.00974	0.00859	0.00054	0.01167	0.00482	0.00125	0.00171	0.00054
10	Male	0.00007	0.00431	0.01421	0.01351	0.01196	0.00452	0.00483	0.00034	0.01028	0.00957	0.00802	0.00055	0.00086
10	Female	0.00006	0.00859	0.02301	0.01667	0.01353	0.01379	0.01065	0.00054	0.01508	0.00870	0.00553	0.00579	0.00262
11	Male	0.00008	0.00493	0.01482	0.01412	0.01258	0.00514	0.00545	0.00039	0.01033	0.00962	0.00807	0.00060	0.00091
11	Female	0.00007	0.01002	0.02442	0.01809	0.01496	0.01522	0.01208	0.00063	0.01517	0.00879	0.00562	0.00588	0.00271
12	Male	0.00010	0.00616	0.01604	0.01534	0.01380	0.00637	0.00668	0.00048	0.01042	0.00972	0.00816	0.00069	0.00100
12	Female	0.00009	0.01288	0.02724	0.02093	0.01780	0.01806	0.01493	0.00081	0.01535	0.00896	0.00580	0.00606	0.00289
13	Male	0.00013	0.00801	0.01788	0.01718	0.01563	0.00822	0.00853	0.00063	0.01056	0.00986	0.00831	0.00084	0.00115
13	Female	0.00011	0.01574	0.03006	0.02377	0.02065	0.02091	0.01779	0.00099	0.01552	0.00914	0.00598	0.00624	0.00307
14	Male	0.00017	0.01048	0.02032	0.01962	0.01808	0.01068	0.01099	0.00082	0.01076	0.01005	0.00850	0.00103	0.00134
14	Female	0.00013	0.01860	0.03288	0.02661	0.02350	0.02376	0.02064	0.00117	0.01570	0.00932	0.00615	0.00642	0.00325
15	Male	0.00024	0.01479	0.02633	0.03123	0.02017	0.02475	0.01479	0.00116	0.01286	0.01783	0.00661	0.01126	0.00116

Age	Sex	General population	Dialysis	Dialysis with cancer					Transplant	Transplant with cancer				
				0-1 years	1-2 years	2-3 years	3-4 years	4+ years		0-1 years	1-2 years	2-3 years	3-4 years	4+ years
15	Female	0.00016	0.02289	0.03667	0.03355	0.03042	0.03096	0.02659	0.00144	0.01552	0.01233	0.00913	0.00968	0.00522
16	Male	0.00031	0.01911	0.03059	0.03548	0.02446	0.02902	0.01911	0.00150	0.01319	0.01816	0.00695	0.01159	0.00150
16	Female	0.00018	0.02576	0.03949	0.03638	0.03326	0.03380	0.02944	0.00162	0.01569	0.01251	0.00931	0.00986	0.00540
17	Male	0.00040	0.02466	0.03608	0.04093	0.02998	0.03451	0.02466	0.00193	0.01362	0.01859	0.00738	0.01202	0.00193
17	Female	0.00020	0.02862	0.04231	0.03921	0.03609	0.03663	0.03229	0.00180	0.01587	0.01269	0.00949	0.01004	0.00558
18	Male	0.00048	0.02959	0.04095	0.04578	0.03488	0.03939	0.02959	0.00232	0.01400	0.01897	0.00777	0.01240	0.00232
18	Female	0.00022	0.03148	0.04513	0.04204	0.03893	0.03947	0.03514	0.00198	0.01605	0.01287	0.00966	0.01022	0.00576
19	Male	0.00054	0.03328	0.04460	0.04942	0.03856	0.04305	0.03328	0.00261	0.01429	0.01926	0.00806	0.01269	0.00261
19	Female	0.00023	0.03291	0.04654	0.04346	0.04035	0.04089	0.03657	0.00207	0.01614	0.01296	0.00975	0.01031	0.00585
20	Male	0.00058	0.03575	0.05072	0.05246	0.04167	0.04201	0.04086	0.00281	0.01828	0.02008	0.00893	0.00928	0.00809
20	Female	0.00024	0.03434	0.04453	0.04722	0.03892	0.03806	0.03989	0.00216	0.01269	0.01547	0.00689	0.00600	0.00790
21	Male	0.00060	0.03698	0.05193	0.05367	0.04290	0.04324	0.04208	0.00290	0.01838	0.02018	0.00903	0.00938	0.00818
21	Female	0.00024	0.03434	0.04453	0.04722	0.03892	0.03806	0.03989	0.00216	0.01269	0.01547	0.00689	0.00600	0.00790
22	Male	0.00062	0.03822	0.05314	0.05488	0.04412	0.04446	0.04331	0.00300	0.01847	0.02027	0.00912	0.00948	0.00828
22	Female	0.00024	0.03434	0.04453	0.04722	0.03892	0.03806	0.03989	0.00216	0.01269	0.01547	0.00689	0.00600	0.00790
23	Male	0.00063	0.03883	0.05375	0.05549	0.04474	0.04508	0.04392	0.00305	0.01852	0.02032	0.00917	0.00952	0.00833
23	Female	0.00024	0.03434	0.04453	0.04722	0.03892	0.03806	0.03989	0.00216	0.01269	0.01547	0.00689	0.00600	0.00790
24	Male	0.00064	0.03945	0.05436	0.05609	0.04535	0.04569	0.04453	0.00310	0.01857	0.02037	0.00922	0.00957	0.00837
24	Female	0.00024	0.03434	0.04453	0.04722	0.03892	0.03806	0.03989	0.00216	0.01269	0.01547	0.00689	0.00600	0.00790
25	Male	0.00065	0.04006	0.06145	0.05573	0.04482	0.04565	0.04556	0.00314	0.02535	0.01941	0.00809	0.00894	0.00885
25	Female	0.00024	0.03434	0.04961	0.04723	0.03867	0.04181	0.03859	0.00216	0.01794	0.01548	0.00664	0.00988	0.00655
26	Male	0.00066	0.04068	0.06205	0.05634	0.04544	0.04626	0.04618	0.00319	0.02540	0.01946	0.00813	0.00899	0.00890
26	Female	0.00026	0.03720	0.05242	0.05005	0.04152	0.04465	0.04144	0.00234	0.01811	0.01566	0.00682	0.01006	0.00673
27	Male	0.00067	0.04130	0.06265	0.05694	0.04605	0.04687	0.04679	0.00324	0.02544	0.01951	0.00818	0.00904	0.00895
27	Female	0.00027	0.03863	0.05383	0.05147	0.04295	0.04607	0.04286	0.00243	0.01820	0.01575	0.00691	0.01015	0.00682
28	Male	0.00069	0.04253	0.06386	0.05816	0.04728	0.04810	0.04801	0.00334	0.02554	0.01960	0.00828	0.00913	0.00905
28	Female	0.00028	0.04006	0.05524	0.05288	0.04437	0.04749	0.04429	0.00252	0.01829	0.01584	0.00700	0.01024	0.00691
29	Male	0.00072	0.04438	0.06567	0.05997	0.04912	0.04994	0.04985	0.00348	0.02568	0.01975	0.00842	0.00928	0.00919
29	Female	0.00028	0.04006	0.05524	0.05288	0.04437	0.04749	0.04429	0.00252	0.01829	0.01584	0.00700	0.01024	0.00691
30	Male	0.00075	0.02850	0.06674	0.03942	0.02915	0.02854	0.03269	0.00230	0.04157	0.01351	0.00297	0.00235	0.00661
30	Female	0.00030	0.01917	0.04468	0.04420	0.01917	0.02588	0.02428	0.00122	0.02721	0.02672	0.00122	0.00807	0.00644
31	Male	0.00079	0.03002	0.06820	0.04092	0.03067	0.03006	0.03421	0.00242	0.04169	0.01364	0.00309	0.00247	0.00673
31	Female	0.00033	0.02108	0.04655	0.04607	0.02108	0.02779	0.02619	0.00135	0.02733	0.02684	0.00135	0.00819	0.00656

Age	Sex	General population	Dialysis	Dialysis with cancer					Transplant	Transplant with cancer				
				0-1 years	1-2 years	2-3 years	3-4 years	4+ years		0-1 years	1-2 years	2-3 years	3-4 years	4+ years
32	Male	0.00083	0.03154	0.06966	0.04242	0.03219	0.03158	0.03572	0.00255	0.04181	0.01376	0.00322	0.00259	0.00686
32	Female	0.00037	0.02364	0.04904	0.04856	0.02364	0.03033	0.02873	0.00151	0.02749	0.02700	0.00151	0.00835	0.00672
33	Male	0.00088	0.03344	0.07148	0.04430	0.03409	0.03348	0.03761	0.00270	0.04196	0.01391	0.00337	0.00275	0.00701
33	Female	0.00041	0.02619	0.05153	0.05105	0.02619	0.03286	0.03127	0.00167	0.02764	0.02716	0.00167	0.00851	0.00688
34	Male	0.00094	0.03572	0.07367	0.04655	0.03636	0.03576	0.03988	0.00288	0.04213	0.01409	0.00355	0.00293	0.00719
34	Female	0.00045	0.02875	0.05401	0.05354	0.02875	0.03540	0.03382	0.00184	0.02780	0.02732	0.00184	0.00868	0.00704
35	Male	0.00100	0.03800	0.08123	0.06385	0.04230	0.03800	0.04182	0.00307	0.04787	0.02986	0.00753	0.00307	0.00703
35	Female	0.00050	0.03194	0.07010	0.05457	0.04129	0.03194	0.03815	0.00204	0.04137	0.02537	0.01167	0.00204	0.00844
36	Male	0.00107	0.04066	0.08377	0.06644	0.04495	0.04066	0.04447	0.00328	0.04808	0.03007	0.00774	0.00328	0.00725
36	Female	0.00054	0.03450	0.07255	0.05707	0.04382	0.03450	0.04069	0.00220	0.04153	0.02553	0.01184	0.00220	0.00860
37	Male	0.00114	0.04331	0.08631	0.06903	0.04760	0.04331	0.04712	0.00350	0.04828	0.03028	0.00796	0.00350	0.00746
37	Female	0.00058	0.03705	0.07500	0.05956	0.04635	0.03705	0.04323	0.00237	0.04169	0.02569	0.01200	0.00237	0.00877
38	Male	0.00121	0.04597	0.08885	0.07161	0.05024	0.04597	0.04977	0.00371	0.04849	0.03049	0.00817	0.00371	0.00767
38	Female	0.00064	0.04089	0.07869	0.06330	0.05014	0.04089	0.04704	0.00261	0.04192	0.02593	0.01224	0.00261	0.00901
39	Male	0.00129	0.04901	0.09175	0.07457	0.05327	0.04901	0.05280	0.00396	0.04872	0.03073	0.00842	0.00396	0.00792
39	Female	0.00070	0.04472	0.08237	0.06705	0.05394	0.04472	0.05085	0.00286	0.04216	0.02616	0.01248	0.00286	0.00925
40	Male	0.00138	0.03291	0.10214	0.07824	0.05744	0.04119	0.03904	0.00452	0.07579	0.05119	0.02978	0.01305	0.01083
40	Female	0.00076	0.03987	0.09400	0.07715	0.05607	0.04080	0.04602	0.00317	0.05938	0.04188	0.01999	0.00414	0.00956
41	Male	0.00147	0.03505	0.10414	0.08029	0.05953	0.04332	0.04117	0.00482	0.07607	0.05147	0.03007	0.01335	0.01113
41	Female	0.00082	0.04302	0.09697	0.08018	0.05916	0.04394	0.04915	0.00342	0.05961	0.04212	0.02024	0.00439	0.00981
42	Male	0.00157	0.03744	0.10635	0.08256	0.06186	0.04569	0.04354	0.00515	0.07637	0.05178	0.03038	0.01367	0.01145
42	Female	0.00090	0.04721	0.10093	0.08421	0.06329	0.04813	0.05332	0.00376	0.05993	0.04244	0.02056	0.00472	0.01015
43	Male	0.00170	0.04054	0.10923	0.08551	0.06488	0.04876	0.04662	0.00557	0.07677	0.05219	0.03080	0.01409	0.01188
43	Female	0.00099	0.05193	0.10539	0.08875	0.06793	0.05285	0.05801	0.00413	0.06028	0.04281	0.02093	0.00510	0.01052
44	Male	0.00184	0.04388	0.11233	0.08870	0.06813	0.05207	0.04994	0.00603	0.07719	0.05263	0.03125	0.01455	0.01233
44	Female	0.00107	0.05613	0.10935	0.09278	0.07205	0.05704	0.06218	0.00447	0.06060	0.04313	0.02126	0.00543	0.01085
45	Male	0.00200	0.04769	0.14588	0.08839	0.07724	0.06244	0.06205	0.00655	0.10898	0.04901	0.03738	0.02194	0.02153
45	Female	0.00116	0.06085	0.13620	0.09622	0.07999	0.08107	0.06811	0.00484	0.08469	0.04233	0.02513	0.02627	0.01254
46	Male	0.00217	0.05174	0.14951	0.09227	0.08116	0.06643	0.06604	0.00711	0.10948	0.04955	0.03792	0.02249	0.02208
46	Female	0.00125	0.06557	0.14054	0.10077	0.08462	0.08569	0.07280	0.00522	0.08503	0.04269	0.02549	0.02664	0.01291
47	Male	0.00233	0.05556	0.15293	0.09592	0.08486	0.07019	0.06980	0.00764	0.10995	0.05005	0.03843	0.02301	0.02260
47	Female	0.00136	0.07134	0.14585	0.10632	0.09027	0.09134	0.07852	0.00568	0.08545	0.04313	0.02594	0.02709	0.01337
48	Male	0.00250	0.05961	0.15657	0.09981	0.08879	0.07418	0.07379	0.00819	0.11045	0.05058	0.03897	0.02355	0.02315

Age	Sex	General population	Dialysis	Dialysis with cancer					Transplant	Transplant with cancer				
				0-1 years	1-2 years	2-3 years	3-4 years	4+ years		0-1 years	1-2 years	2-3 years	3-4 years	4+ years
48	Female	0.00148	0.07764	0.15164	0.11238	0.09644	0.09750	0.08477	0.00618	0.08591	0.04361	0.02643	0.02758	0.01386
49	Male	0.00268	0.06391	0.16042	0.10391	0.09295	0.07840	0.07802	0.00878	0.11098	0.05115	0.03954	0.02413	0.02373
49	Female	0.00162	0.08498	0.15840	0.11945	0.10363	0.10468	0.09206	0.00676	0.08645	0.04417	0.02701	0.02815	0.01444
50	Male	0.00287	0.04614	0.16033	0.12051	0.07288	0.06139	0.05259	0.00843	0.12713	0.08574	0.03622	0.02428	0.01513
50	Female	0.00176	0.04673	0.14265	0.09752	0.06540	0.06165	0.06048	0.00785	0.10767	0.06071	0.02727	0.02338	0.02215
51	Male	0.00309	0.04968	0.16344	0.12378	0.07632	0.06487	0.05610	0.00907	0.12770	0.08634	0.03685	0.02491	0.01577
51	Female	0.00191	0.05071	0.14623	0.10129	0.06930	0.06557	0.06440	0.00852	0.10828	0.06134	0.02793	0.02404	0.02281
52	Male	0.00334	0.05370	0.16698	0.12748	0.08022	0.06882	0.06009	0.00981	0.12834	0.08701	0.03757	0.02563	0.01650
52	Female	0.00207	0.05496	0.15005	0.10531	0.07347	0.06976	0.06859	0.00923	0.10892	0.06202	0.02863	0.02474	0.02352
53	Male	0.00363	0.05836	0.17108	0.13178	0.08476	0.07341	0.06472	0.01066	0.12909	0.08780	0.03839	0.02647	0.01734
53	Female	0.00225	0.05974	0.15435	0.10984	0.07815	0.07446	0.07330	0.01003	0.10964	0.06278	0.02941	0.02553	0.02431
54	Male	0.00396	0.06366	0.17575	0.13667	0.08991	0.07863	0.06999	0.01163	0.12995	0.08869	0.03934	0.02742	0.01831
54	Female	0.00244	0.06479	0.15888	0.11461	0.08310	0.07943	0.07827	0.01088	0.11040	0.06358	0.03025	0.02636	0.02514
55	Male	0.00432	0.06945	0.21239	0.13006	0.09698	0.07976	0.09115	0.01268	0.16434	0.07699	0.04189	0.02362	0.03571
55	Female	0.00264	0.07010	0.18535	0.12912	0.10214	0.07899	0.08653	0.01177	0.13426	0.07449	0.04583	0.02122	0.02923
56	Male	0.00472	0.07588	0.21784	0.13608	0.10322	0.08612	0.09744	0.01386	0.16534	0.07809	0.04303	0.02478	0.03686
56	Female	0.00285	0.07567	0.19024	0.13434	0.10753	0.08451	0.09200	0.01271	0.13508	0.07537	0.04673	0.02215	0.03015
57	Male	0.00515	0.08280	0.22369	0.14254	0.10993	0.09296	0.10419	0.01512	0.16641	0.07927	0.04425	0.02603	0.03809
57	Female	0.00308	0.08178	0.19559	0.14006	0.11342	0.09056	0.09800	0.01373	0.13598	0.07633	0.04772	0.02316	0.03116
58	Male	0.00562	0.09035	0.23008	0.14960	0.11726	0.10043	0.11157	0.01650	0.16758	0.08056	0.04559	0.02740	0.03944
58	Female	0.00336	0.08921	0.20210	0.14702	0.12060	0.09792	0.10531	0.01498	0.13707	0.07750	0.04893	0.02440	0.03238
59	Male	0.00614	0.09871	0.23716	0.15742	0.12537	0.10870	0.11973	0.01803	0.16887	0.08199	0.04708	0.02891	0.04093
59	Female	0.00364	0.09665	0.20861	0.15398	0.12778	0.10529	0.11261	0.01623	0.13816	0.07867	0.05013	0.02564	0.03361
60	Male	0.00669	0.06630	0.22192	0.14322	0.11059	0.09898	0.09674	0.01684	0.18070	0.09784	0.06348	0.05125	0.04889
60	Female	0.00397	0.06158	0.18535	0.12613	0.10550	0.08353	0.06334	0.01518	0.14506	0.08292	0.06127	0.03822	0.01702
61	Male	0.00728	0.07215	0.22679	0.14859	0.11616	0.10462	0.10239	0.01833	0.18194	0.09920	0.06490	0.05268	0.05033
61	Female	0.00432	0.06701	0.19006	0.13118	0.11067	0.08883	0.06876	0.01651	0.14623	0.08416	0.06254	0.03952	0.01836
62	Male	0.00791	0.07839	0.23199	0.15432	0.12211	0.11065	0.10843	0.01991	0.18326	0.10066	0.06641	0.05421	0.05186
62	Female	0.00466	0.07228	0.19464	0.13609	0.11570	0.09398	0.07402	0.01781	0.14735	0.08537	0.06378	0.04079	0.01965
63	Male	0.00856	0.08483	0.23736	0.16023	0.12825	0.11686	0.11466	0.02155	0.18462	0.10216	0.06797	0.05579	0.05344
63	Female	0.00499	0.07740	0.19908	0.14086	0.12058	0.09898	0.07913	0.01907	0.14845	0.08655	0.06499	0.04202	0.02091
64	Male	0.00925	0.09167	0.24306	0.16650	0.13476	0.12346	0.12128	0.02329	0.18607	0.10375	0.06962	0.05747	0.05513
64	Female	0.00536	0.08314	0.20406	0.14620	0.12605	0.10459	0.08486	0.02049	0.14968	0.08786	0.06633	0.04341	0.02233

Age	Sex	General population	Dialysis	Dialysis with cancer					Transplant	Transplant with cancer				
				0-1 years	1-2 years	2-3 years	3-4 years	4+ years		0-1 years	1-2 years	2-3 years	3-4 years	4+ years
65	Male	0.01000	0.09910	0.28034	0.17949	0.13722	0.12985	0.09910	0.02518	0.22128	0.11215	0.06642	0.05845	0.02518
65	Female	0.00583	0.09043	0.23495	0.15961	0.14343	0.10543	0.11040	0.02229	0.17764	0.09665	0.07926	0.03841	0.04376
66	Male	0.01083	0.10733	0.28691	0.18698	0.14510	0.13780	0.10733	0.02726	0.22295	0.11406	0.06842	0.06047	0.02726
66	Female	0.00639	0.09911	0.24226	0.16763	0.15161	0.11397	0.11890	0.02443	0.17944	0.09863	0.08128	0.04051	0.04585
67	Male	0.01176	0.11655	0.29427	0.19537	0.15392	0.14670	0.11655	0.02961	0.22482	0.11619	0.07066	0.06273	0.02961
67	Female	0.00705	0.10935	0.25087	0.17709	0.16125	0.12404	0.12891	0.02695	0.18156	0.10096	0.08365	0.04300	0.04832
68	Male	0.01281	0.12695	0.30259	0.20485	0.16389	0.15675	0.12695	0.03225	0.22694	0.11860	0.07319	0.06528	0.03225
68	Female	0.00779	0.12083	0.26052	0.18770	0.17206	0.13533	0.14014	0.02978	0.18394	0.10357	0.08632	0.04578	0.05109
69	Male	0.01401	0.13884	0.31209	0.21568	0.17528	0.16824	0.13884	0.03527	0.22935	0.12135	0.07609	0.06820	0.03527
69	Female	0.00860	0.13339	0.27109	0.19931	0.18390	0.14768	0.15243	0.03287	0.18654	0.10643	0.08923	0.04882	0.05412
70	Male	0.01539	0.08146	0.28736	0.13966	0.13140	0.11133	0.10861	0.02911	0.24675	0.09063	0.08190	0.06069	0.05781
70	Female	0.00954	0.06490	0.23768	0.14310	0.10574	0.06490	0.08196	0.01727	0.19886	0.09946	0.06020	0.01727	0.03520
71	Male	0.01695	0.08972	0.29377	0.14740	0.13921	0.11932	0.11663	0.03206	0.24904	0.09340	0.08469	0.06354	0.06068
71	Female	0.01061	0.07217	0.24362	0.14977	0.11270	0.07217	0.08910	0.01921	0.20044	0.10123	0.06205	0.01921	0.03711
72	Male	0.01870	0.09898	0.30095	0.15607	0.14797	0.12829	0.12562	0.03538	0.25161	0.09650	0.08782	0.06675	0.06389
72	Female	0.01186	0.08068	0.25055	0.15756	0.12083	0.08068	0.09745	0.02147	0.20228	0.10331	0.06421	0.02147	0.03933
73	Male	0.02068	0.10946	0.30909	0.16589	0.15788	0.13843	0.13579	0.03912	0.25451	0.10001	0.09136	0.07037	0.06752
73	Female	0.01326	0.09020	0.25831	0.16629	0.12994	0.09020	0.10680	0.02401	0.20435	0.10563	0.06664	0.02401	0.04181
74	Male	0.02289	0.12116	0.31816	0.17685	0.16894	0.14974	0.14714	0.04330	0.25775	0.10392	0.09531	0.07441	0.07158
74	Female	0.01481	0.10074	0.26691	0.17595	0.14002	0.10074	0.11715	0.02681	0.20664	0.10820	0.06932	0.02681	0.04457
75	Male	0.02542	0.13455	0.34789	0.20949	0.17598	0.16422	0.16161	0.04809	0.28274	0.13052	0.09365	0.08072	0.07784
75	Female	0.01658	0.11279	0.31402	0.18255	0.12079	0.14176	0.13969	0.03002	0.25003	0.10629	0.03876	0.06169	0.05944
76	Male	0.02835	0.15006	0.35958	0.22366	0.19074	0.17920	0.17663	0.05363	0.28692	0.13558	0.09893	0.08607	0.08321
76	Female	0.01856	0.12625	0.32444	0.19496	0.13413	0.15479	0.15275	0.03360	0.25280	0.10959	0.04232	0.06516	0.06291
77	Male	0.03175	0.16806	0.37314	0.24010	0.20788	0.19658	0.19407	0.06006	0.29176	0.14145	0.10505	0.09228	0.08945
77	Female	0.02081	0.14156	0.33627	0.20906	0.14930	0.16959	0.16760	0.03767	0.25595	0.11334	0.04635	0.06910	0.06686
78	Male	0.03568	0.18886	0.38881	0.25910	0.22769	0.21667	0.21422	0.06750	0.29737	0.14824	0.11213	0.09946	0.09665
78	Female	0.02346	0.15959	0.35021	0.22567	0.16717	0.18703	0.18508	0.04247	0.25966	0.11776	0.05111	0.07374	0.07151
79	Male	0.04014	0.21247	0.40660	0.28066	0.25016	0.23947	0.23709	0.07593	0.30372	0.15595	0.12016	0.10761	0.10482
79	Female	0.02653	0.18047	0.36636	0.24491	0.18786	0.20723	0.20533	0.04803	0.26396	0.12288	0.05661	0.07912	0.07690
80	Male	0.04518	0.11890	0.37005	0.17696	0.15538	0.11890	0.12477	0.07169	0.33630	0.13286	0.11012	0.07169	0.07787
80	Female	0.03016	0.09841	0.34816	0.14868	0.12052	0.10826	0.10614	0.06368	0.32306	0.11589	0.08664	0.07391	0.07171
81	Male	0.05085	0.13382	0.38072	0.19090	0.16968	0.13382	0.13959	0.08068	0.34273	0.14127	0.11875	0.08068	0.08681

Age	Sex	General population	Dialysis	Dialysis with cancer					Transplant	Transplant with cancer				
				0-1 years	1-2 years	2-3 years	3-4 years	4+ years		0-1 years	1-2 years	2-3 years	3-4 years	4+ years
81	Female	0.03444	0.11238	0.35826	0.16187	0.13414	0.12207	0.11998	0.07272	0.32959	0.12443	0.09546	0.08285	0.08067
82	Male	0.05727	0.15071	0.39280	0.20668	0.18588	0.15071	0.15637	0.09087	0.35001	0.15078	0.12851	0.09087	0.09693
82	Female	0.03942	0.12862	0.37001	0.17721	0.14999	0.13814	0.13609	0.08324	0.33719	0.13436	0.10572	0.09325	0.09109
83	Male	0.06458	0.16995	0.40655	0.22465	0.20432	0.16995	0.17548	0.10247	0.35830	0.16161	0.13963	0.10247	0.10845
83	Female	0.04519	0.14745	0.38362	0.19499	0.16836	0.15676	0.15476	0.09542	0.34600	0.14586	0.11760	0.10530	0.10317
84	Male	0.07300	0.19211	0.42239	0.24535	0.22556	0.19211	0.19749	0.11583	0.36785	0.17409	0.15244	0.11583	0.12172
84	Female	0.05200	0.16967	0.39968	0.21597	0.19003	0.17874	0.17679	0.10980	0.35640	0.15944	0.13163	0.11952	0.11743
85	Male	0.08261	0.21740	0.48706	0.23751	0.22154	0.21740	0.21740	0.13107	0.43048	0.15340	0.13567	0.13107	0.13107
85	Female	0.05980	0.19512	0.49447	0.20025	0.19512	0.20777	0.19512	0.12627	0.45123	0.13183	0.12627	0.14000	0.12627
86	Male	0.09340	0.24579	0.50567	0.26517	0.24978	0.24579	0.24579	0.14819	0.44170	0.17008	0.15270	0.14819	0.14819
86	Female	0.06851	0.22354	0.51232	0.22849	0.22354	0.23574	0.22354	0.14466	0.46278	0.15011	0.14466	0.15810	0.14466
87	Male	0.10549	0.27761	0.52652	0.29617	0.28143	0.27761	0.27761	0.16738	0.45427	0.18877	0.17178	0.16738	0.16738
87	Female	0.07849	0.25611	0.53277	0.26084	0.25611	0.26780	0.25611	0.16573	0.47601	0.17105	0.16573	0.17884	0.16573
88	Male	0.11900	0.31316	0.54982	0.33081	0.31680	0.31316	0.31316	0.18881	0.46832	0.20966	0.19310	0.18881	0.18881
88	Female	0.08970	0.29268	0.55575	0.29719	0.29268	0.30380	0.29268	0.18940	0.49088	0.19457	0.18940	0.20214	0.18940
89	Male	0.13397	0.35256	0.57564	0.36919	0.35598	0.35256	0.35256	0.21257	0.48389	0.23280	0.21673	0.21257	0.21257
89	Female	0.10258	0.33471	0.58214	0.33895	0.33471	0.34516	0.33471	0.21660	0.50796	0.22159	0.21660	0.22891	0.21660
90	Male	0.15008	0.39495	0.60343	0.41050	0.39815	0.39495	0.39495	0.23813	0.50064	0.25770	0.24216	0.23813	0.23813
90	Female	0.11717	0.38232	0.61204	0.38625	0.38232	0.39202	0.38232	0.24741	0.52731	0.25220	0.24741	0.25923	0.24741
91	Male	0.16705	0.43961	0.63270	0.45401	0.44258	0.43961	0.43961	0.26505	0.51829	0.28394	0.26894	0.26505	0.26505
91	Female	0.13299	0.43394	0.64447	0.43754	0.43394	0.44283	0.43394	0.28081	0.54829	0.28539	0.28081	0.29211	0.28081
92	Male	0.18446	0.48543	0.66273	0.49865	0.48815	0.48543	0.48543	0.29268	0.53640	0.31085	0.29642	0.29268	0.29268
92	Female	0.14985	0.48895	0.67902	0.49220	0.48895	0.49698	0.48895	0.31641	0.57065	0.32076	0.31641	0.32715	0.31641
93	Male	0.20160	0.53054	0.69230	0.54260	0.53302	0.53054	0.53054	0.31987	0.55422	0.33735	0.32347	0.31987	0.31987
93	Female	0.16781	0.54755	0.71583	0.55043	0.54755	0.55466	0.54755	0.35433	0.59447	0.35845	0.35433	0.36448	0.35433
94	Male	0.21751	0.57241	0.71974	0.58339	0.57467	0.57241	0.57241	0.34512	0.57077	0.36194	0.34858	0.34512	0.34512
94	Female	0.18700	0.61017	0.75515	0.61265	0.61017	0.61629	0.61017	0.39485	0.61992	0.39871	0.39485	0.40436	0.39485
95	Male	0.22528	0.59285	0.73314	0.60331	0.59501	0.59285	0.59285	0.35744	0.57885	0.37395	0.36084	0.35744	0.35744
95	Female	0.19743	0.64420	0.77653	0.64647	0.64420	0.64979	0.64420	0.41688	0.63375	0.42059	0.41688	0.42604	0.41688
96	Male	0.24431	0.64293	0.76597	0.65211	0.64482	0.64293	0.64293	0.38764	0.59864	0.40337	0.39088	0.38764	0.38764
96	Female	0.22285	0.72714	0.82862	0.72888	0.72714	0.73143	0.72714	0.47055	0.66746	0.47392	0.47055	0.47887	0.47055
97	Male	0.26334	0.69301	0.79879	0.70090	0.69464	0.69301	0.69301	0.41783	0.61843	0.43279	0.42091	0.41783	0.41783
97	Female	0.23874	0.77899	0.86119	0.78040	0.77899	0.78246	0.77899	0.50410	0.68854	0.50726	0.50410	0.51190	0.50410

Age	Sex	General population	Dialysis	Dialysis with cancer					Transplant	Transplant with cancer				
				0-1 years	1-2 years	2-3 years	3-4 years	4+ years		0-1 years	1-2 years	2-3 years	3-4 years	4+ years
98	Male	0.28237	0.74309	0.83161	0.74969	0.74445	0.74309	0.74309	0.44803	0.63822	0.46221	0.45095	0.44803	0.44803
98	Female	0.25276	0.82474	0.88992	0.82585	0.82474	0.82749	0.82474	0.53371	0.70713	0.53668	0.53371	0.54103	0.53371
99	Male	0.30140	0.79317	0.86444	0.79849	0.79427	0.79317	0.79317	0.47822	0.65801	0.49163	0.48098	0.47822	0.47822
99	Female	0.26774	0.87362	0.92062	0.87442	0.87362	0.87560	0.87362	0.56534	0.72700	0.56811	0.56534	0.57217	0.56534
100	Male	0.32043	0.84325	0.89726	0.84728	0.84408	0.84325	0.84325	0.50841	0.67780	0.52105	0.51101	0.50841	0.50841
100	Female	0.28385	0.92618	0.95364	0.92665	0.92618	0.92734	0.92618	0.59935	0.74836	0.60191	0.59935	0.60565	0.59935

Based on life tables from the Australian Bureau of Statistics (ABS) [27], standardized mortality ratios (SMRs) for dialysis and transplant estimated from ANZDATA annual reports [9], and relative survival with cancer derived from Australian Institute of Health and welfare (AIHW) cancer data [30]

Annual incidence rates of cancer among dialysis patients stratified by 5-year age group and sex are presented in Table 5.4 (reproduced from Supplementary Table 7 in Hedley et al., 2023 [1].

Table 5.4: Annual incidence rates of cancer for dialysis patients compared with the general population, by 5-year age group and sex

Age	General population		Dialysis	
	Female	Male	Female	Male
0-4	0.00066	0.00073	0.00105	0.00116
5-9	0.00038	0.00046	0.00061	0.00073
10-14	0.00050	0.00051	0.00079	0.00081
15-19	0.00085	0.00085	0.00136	0.00135
20-24	0.00117	0.00110	0.00187	0.00176
25-29	0.00190	0.00154	0.00303	0.00245
30-34	0.00324	0.00215	0.00518	0.00342
35-39	0.00472	0.00306	0.00753	0.00489
40-44	0.00747	0.00485	0.01193	0.00774
45-49	0.01115	0.00801	0.01780	0.01280
50-54	0.01517	0.01410	0.02423	0.02251
55-59	0.01895	0.02333	0.03026	0.03725
60-64	0.02523	0.03597	0.04028	0.05744
65-69	0.03309	0.05103	0.05283	0.08148
70-74	0.04134	0.06377	0.06600	0.10182
75-79	0.04696	0.07609	0.07497	0.12149
80-84	0.05276	0.08652	0.08424	0.13814
85-89	0.05699	0.09294	0.09100	0.14839
90+	0.05295	0.09149	0.08455	0.14607

Based on cancer data from the Australian Institute of Health and Welfare (AIHW) [30] and incidence rate ratio (IRR) of 1.60 estimated from AIHW cancer data and Wong et al., 2016 [31]

The utility values by cancer site and stage are summarized in Table 5.5 (reproduced from Supplementary Table 10 in Hedley et al., 2023 [1].

Calculations of all costs were performed in Microsoft Excel in a spreadsheet titled 'Cost Calculations' which is available here:

https://github.com/james-hedley/PBM_economic_evaluation [48].

Table 5.5: Utility values for cancer by site and stage at diagnosis

Cancer site	Incidence (2011)	Proportion	Utility	Lower	Upper
Stage I					
Breast	6,110	0.10	0.73	0.56	0.90
Colorectal	3,098	0.05	0.71	0.64	0.77
Lung	1,183	0.02	0.73	0.59	0.86
Melanoma	8,730	0.14	0.69	0.58	0.80
Prostate	7,186	0.11	0.87	-	-
Total	26,307	0.42	0.75	0.58	0.83
Stage II					
Breast	4,936	0.08	0.64	0.48	0.79
Colorectal	3,399	0.05	0.64	0.56	0.72
Lung	662	0.01	0.69	0.56	0.81
Melanoma	1,577	0.02	0.69	0.58	0.80
Prostate	9,245	0.15	0.87	-	-
Total	19,819	0.31	0.75	0.53	0.77
Stage III					
Breast	1,721	0.03	0.61	0.45	0.77
Colorectal	3,299	0.05	0.64	0.56	0.72
Lung	1,131	0.02	0.58	0.27	0.89
Melanoma	331	0.01	0.62	0.54	0.70
Prostate	2,246	0.04	0.55	-	-
Total	8,728	0.14	0.60	0.48	0.76
Stage IV					
Breast	660	0.01	0.61	0.35	0.86
Colorectal	2,474	0.04	0.42	0.30	0.53
Lung	4,273	0.07	0.75	0.66	0.84
Melanoma	233	0.00	0.66	0.58	0.80
Prostate	836	0.01	0.55	-	-
Total	8,476	0.13	0.62	0.51	0.74
All stages					
Breast	13,427	0.21	0.67	0.51	0.84
Colorectal	12,270	0.19	0.61	0.53	0.69
Lung	7,249	0.11	0.71	0.58	0.85
Melanoma	10,871	0.17	0.69	0.58	0.80
Prostate	19,513	0.31	0.82	-	-
Total	63,330	1.00	0.71	0.54	0.79

Based on cancer data from the Australian Institute of Health and Welfare (AIHW) [30] and a systematic review by Pourrahmat et al., 2021 [34]

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Chapter 6: Economic evaluation – results and clinical interpretation

6.1 Preface

This chapter presents an economic evaluation of interventions which could increase utilization of kidneys for transplantation from deceased donor with primary brain malignancy. The aim of this study was to establish the cost-effectiveness of each proposed intervention. Details of the statistical modelling used in this economic evaluation are discussed in chapter 4, and details of the economic modelling are discussed in chapter 5 of this thesis. This study is published in *Transplantation Direct* [1].

Due to journal word limits, several discussion points that could not be incorporated in the published version of this study are instead included here.

6.1.1 Impact on living donor transplantation

In our economic modelling we found that increasing the number of kidneys available from deceased donors slightly reduced the number of living donor transplants performed. This is because some patients who are waitlisted for a deceased donor kidney may eventually find a suitable living donor instead. If such a patient were to be offered a deceased donor kidney earlier, due to the increase in kidneys available from donors with primary brain malignancy, then they may accept this before their living donor becomes available, thus reducing the number of living donor transplants performed.

On the surface this may seem like a negative consequence of our proposed interventions, since it is well established that living donor transplants result in better recipient outcomes compared to deceased donor transplants [2]. However, these patients may experience better outcomes over the course of their lifetimes by potentially having a suitable living donor

available for a subsequent transplant later in life. In general, patients would likely be better-off accepting a deceased donor kidney while they are younger and saving their living donor for potential future use when they (the patient) are older and less likely to be offered a deceased donor kidney. Furthermore, there may be benefits to other family members with kidney failure who could accept a kidney from this living donor in future, potentially avoiding the need to be waitlisted for a deceased donor kidney.

Our economic evaluation did not capture the potential downstream benefits of having more living donors available later in life, hence our results may underestimate the overall benefits and cost-savings of increasing utilization of kidneys from deceased donors with PBM.

6.1.2 Impact on individual patients

A major advantage of performing an individual-level simulation for an economic evaluation is that equity concerns can be addressed. Although our results clearly showed that any intervention that increases utilization of deceased donors with PBM improves health outcomes and is cost-saving at the population level, we were also able to compare specific subgroups of patients. We found that while some subgroups benefitted more than others (e.g., younger patients were more likely to have improved health outcomes than older patients), we also found that no subgroup was worse-off overall. This means that the proposed interventions could result in potential inequities, but that even the patients who receive the least benefit would still be better-off. Therefore, the potential for inequity should not affect the decision to adopt any of the proposed interventions.

Although being performed at the individual patient level, the economic model did not account for individual patients having different risk tolerance thresholds. Different risk thresholds could arise due to personal preferences, or they could be due to different individual circumstances. Some patients may understand that their individual characteristics such as age, blood group, or time already spent on dialysis mean they will likely be offered a deceased donor kidney soon. Such an individual would have little incentive to accept the risk associated with a kidney from a donor with PBM if they would likely receive a better offer in the near future. Conversely, someone who is unlikely to receive a deceased donor kidney before dying (e.g., due to older age) would have a much greater incentive to accept a risk of cancer transmission if it means they receive a transplant.

6.1.3 Future work

Future work could build on the results of this economic evaluation by developing a risk calculator to help patients decide whether their individual characteristics mean they would be better off accepting a kidney from a deceased donor with PBM (and therefore with a risk of cancer transmission), or if they should remain on dialysis and continue to wait for a better donor kidney to become available.

It would also be useful to explore how the risk of cancer transmission could be effectively communicated to patients in order to gain informed consent prior to transplantation. Many people have difficulties understanding risks, especially when they are small [3,4]. In the context of organ donation, a patient may instinctively avoid a donor kidney if there is a chance of cancer transmission, without fully considering the actual risk of transmission occurring and the consequences of not receiving a transplant. Future research could explore

alternative ways of presenting risk information such as a percentage vs. a ratio (e.g., 5% vs. 1/20), or as a chance of a negative outcome vs. a positive outcome (e.g., 5% chance of cancer vs. 95% chance of no cancer).

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6.2 Abstract

Background: Kidneys from potential deceased donors with brain cancer are often foregone due to concerns of cancer transmission risk to recipients. There may be uncertainty around donors' medical history and their absolute transmission risk, or risk-averse decision-making among clinicians. However, brain cancer transmissions are rare and prolonging waiting time for recipients is harmful.

Methods: We assessed the cost-effectiveness of increasing utilization of potential deceased donors with brain cancer using a Markov model simulation of 1,500 patients waitlisted for a kidney transplant, based on linked transplant registry data and with a payer perspective (Australian government). We estimated costs and quality-adjusted life-years (QALYs) for three interventions: decision support for clinicians in assessing donor risk; improved cancer classification accuracy with real-time data-linkage to hospital records and cancer registries; and increased risk-tolerance to allow intermediate-risk donors (up to 6.4% potential transmission risk).

Results: Compared with current practice, decision support provided 0.3% more donors with an average transmission risk of 2%. Real-time data linkage provided 0.6% more donors (1.1% average transmission risk) and increasing risk tolerance (accepting intermediate-risk 6.4%) provided 2.1% more donors (4.9% average transmission risk). Interventions were dominant (improved QALYs and saved costs) in 78%, 80%, and 87% of simulations, respectively. The largest benefit was from increasing risk tolerance (mean +18.6 QALYs and AU$2.2m (US$1.6m) cost-savings).

Conclusions: Despite the additional risk of cancer transmission, accepting intermediate-risk donors with brain cancer is likely to increase the number of donor kidneys available for transplant, improve patient outcomes, and reduce overall healthcare expenditure.

6.3 Introduction

Kidney transplantation is the optimal treatment for kidney failure [1-3] and is cost-effective, typically resulting in cost savings compared with dialysis [4]. However, transplantation rates are limited by the global shortage of organs available for transplant [3,5]. Increasing the pool of donor organs available for transplant is an important objective internationally [6-8], and in Australia [9].

In Australia, potential organ donors are referred to state and territory donor services for detailed medical suitability assessment by a donation specialist. Next-of-kin consent is often sought simultaneously. If organs are considered unsuitable for transplantation (e.g., due to risk of infection or cancer transmission to a recipient), the potential donor may be declined. Primary brain malignancies (PBMs) have a lower transmission risk (<6.4%) than other similar grade cancers [10-12]. Despite this, classification of PBMs is complex and can lead to uncertainty for clinicians deciding whether to proceed with a potential donor. This is particularly challenging if detailed clinical information is lacking in the time-critical setting of donation decision making. A recent study demonstrated that only 74% of perceived brain cancers among potential donors could be verified as malignant in linked medical records [13]. Furthermore, estimates of PBM transmission risk in clinical practice guidelines[14] are highly variable, and based on studies with no observed transmissions [11,12]. These guidelines are similar to those used in US[15], UK[16], and EU[17] and recommend accepting donors with a low risk of transmission (<2%), and permit donors with an intermediate risk of transmission (6.4%) on a case-by-case basis. A summary of brain cancer transmission risk classifications is presented in Table 6.S1. However, we know many potential donors with low and intermediate risk brain cancers are foregone. A recent study found that in New South Wales

(NSW), Australia, 24% of potential deceased donors with a primary brain tumor were declined due to a perceived risk of cancer transmission [18].

Reducing risk for patients is important but must be balanced against the adverse consequences of prolonging time spent waiting for a transplant. Potential donors with PBM are typically younger and otherwise healthier than other donors [19], so are excellent organ donation candidates (apart from their PBM). In Australia data is collected from all potential donors [20], presenting an ideal opportunity to study donors foregone. It may be unclear how many potential donors with PBM are foregone internationally because reporting typically focusses on actual donors, and neglects those who are declined or not contemplated [21,22]. In NSW, the largest state in Australia, 5% of potential donors are declined due to perceived history of PBM. However, only 74% of potential donors reported to have PBM when referred to donation services had corresponding records in the NSW cancer registry. The remaining 26% of these potential donors either never had PBM, or had a benign tumor and could have safely donated [13]. These potential missed opportunities for donation may be even higher in the US, where 1.1% of deceased donors reportedly had a brain tumor at the time of donation but only 44% could be verified in cancer registries [23].

The potential impact of policies to increase acceptance of donors with cancer has not been explored [13]. A recent systematic review identified economic evaluations surrounding kidney donation and allocation policies [24]. Many such policies have been found to be cost-effective, including developing donation protocols and teams with clearly defined responsibilities within hospitals [25-27], accepting donation after circulatory death (DCD) donors [28,29], accepting expanded criteria donors [30], adopting an opt-out model of consent [31], and accepting donors with potential hepatitis C infection [32-34]. In this study we sought to determine the cost-

effectiveness of increasing utilization of kidneys from potential deceased donors with PBM in the Australian setting, and to explore how individual patients would be impacted.

6.4 Methods

6.4.1 Model Structure

We developed a Markov model patient-level simulation, in which individual patients transition between health states (e.g., waitlist, transplanted, dead) at discrete time intervals (cycles) with different probabilities under alternative scenarios. Markov models are commonly used in economic evaluations for kidney transplantation [24] to capture important aspects of kidney failure at the cohort-level (e.g. the proportion of patients receiving a transplant vs. remaining on dialysis). We performed a patient-level simulation to additionally capture variability in characteristics and health outcomes among individual patients. We simulated a cohort of 1,500 people with kidney failure waiting for a deceased donor kidney transplant in Australia (the approximate number on the waitlist during 2021 [35]). The modelled time-horizon was 25-years to capture outcomes over the lifetime for a typical person with kidney failure [36], as is widely recommended for economic evaluations [37]. We assumed patients would transition between health states in discrete time intervals of 3-months, and we applied a half-cycle correction to capture potential transitions within each interval [38]. To account for variability of our results due to randomness, we repeated our simulation 10,000 times ensuring estimated proportions had a 95%CI of at most ±1%. We adopted a payer perspective (i.e., Australian government), and discounted costs and quality-adjusted life-years (QALYs) 5% annually following Australian guidelines for economic evaluations [38,39]. The model was constructed using R software [40-42]. Our economic evaluation followed the consolidated health economic reporting standards (CHEERS) [43]. Our cost

calculations and R code are available here:

https://github.com/james-hedley/PBM_economic_evaluation.

6.4.2 Patient and donor characteristics

We simulated characteristics for each patient upon entering the model, which determined their probabilities of transitioning between health states. Patient-level characteristics were age, sex, blood group, number of previous kidney transplants, and number of comorbidities (chronic lung disease, coronary artery disease, peripheral vascular disease, cerebrovascular disease, diabetes, hepatitis C, and history of cancer). If a patient received a kidney transplant, we also simulated donor characteristics: presence of PBM, donor type (living, DCD, donation after brain death (DBD), or DBD expanded criteria [14]), age, sex, and Australian kidney donor profile index (KDPI) [44].

Distributions of characteristics were informed by data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) and Australia and New Zealand Organ Donor Registry (ANZOD). Data was provided for the Maximising Organ Donor Utility System-wide (MODUS) study [45] which was approved by the University of Sydney Human Research Ethics Committee (project number 2020/828).

6.4.3 Health states and transitions

We included five main health states: on waitlist, off waitlist, functioning transplant, transplant (graft) failure, and death. We separated kidney transplants by donor type (DCD, DBD, or living) and separated all deceased donor transplant patients (functioning and failed) by their cancer status (none, *de-novo*, or donor-transmitted). Since some transmitted cancers may be misattributed to the recipient as *de-novo*, we included all recipient cancer

sites in our model, not just transmitted PBMs. The model structure is presented in Figure 6.1.

Details of how patients transition between health states are provided in Appendix 1. Briefly, patients entered the model on waitlist and were then either removed due to *de-novo* cancer, received a transplant, or died. Once transplanted, the transplant could fail, or the patient could develop *de-novo* cancer. If they received a kidney from a deceased donor with PBM, there was a chance of cancer transmission. If transmission occurred, the patient would be diagnosed after nine months (see Appendix 1 for explanation), have their kidney removed, and remain in the transplant failure with cancer health state until death. Although it may be possible to treat a transmitted cancer without removing the transplanted kidney, our assumption that all patients would undergo nephrectomy was conservative (i.e., favored current practice), and was consistent with available case-reports (Appendix 1).

6.4.4 Comparators

We considered three interventions that have previously been proposed to increase utilization of organs from deceased donors with cancer [13], and compared them with current practice (i.e., individual clinicians deciding which potential donors with PBM to accept or decline). Comparators were: 1) decision support for clinicians in accurately estimating absolute donor risk for cancer transmission; 2) improved clinical information with greater accuracy through real-time data-linkage to hospital records and cancer registries to improve classification of potential donor cancer type and hence transmission risk; and 3) increased risk-tolerance to allow use of donors with intermediate-risk PBM (estimated transmission risk 6.4%) [13,14]. More detail about these comparators is provided in Appendix 2.

6.4.5 Model inputs

Transition probabilities between health states were based on Australian life tables [46], Australian Institute for Health and Welfare cancer data [47], ANZDATA annual reports [48,49], and time-to-event analysis of ANZDATA and ANZOD data. Utility values (QALY weights) for each health state were based on quality of life studies in patients with kidney failure [50,51] and cancer [52]. Costs in 2021 Australian dollars were based on National Hospitals Cost Data Collection [53], Pharmaceutical Benefits Scheme [54], Medicare Benefits Schedule [55], and previous costing studies [56-58]. Details of the derivation of all transition probabilities, utilities, and costs are reported in Appendix 2.

6.4.6 Economic evaluation

We assessed cost-effectiveness by comparing incremental costs with incremental QALYs. Our willingness-to-pay (WTP) threshold was $28,000 per QALY [59,60], which is more conservative than the typical $50,000 threshold [61] (see Appendix 2). We calculated 95% confidence intervals (95%CI) for costs and QALYs based on the 2.5th and 97.5th percentiles across all simulations. We also compared interventions by the number of deceased and living donor transplants, life-years spent with transplant, and cancer transmission rate. To account for variability across patients we reported the proportion who would have decreased, increased, or unchanged QALYs.

6.4.7 Uncertainty analyses

We performed a probabilistic sensitivity analysis to assess uncertainty in model parameters, a worst-case scenario where transmission resulted in immediate death, and a threshold analysis to determine the transmission risk at which increased risk tolerance would no longer be cost-effective. Further detail about uncertainty analyses is provided in Appendix 2.

6.5 Results

6.5.1 Patient and donor characteristics

The typical waitlisted patient was a 50-year-old male with blood group O, no prior transplants, and one comorbidity. The typical deceased donor was a 37-year-old male DBD donor without PBM and with an Australian KDPI of 33.7. Distributions and parameters for patient characteristics are presented in Table 6.S2, and for donor characteristics in Table 6.S3.

6.5.2 Impact of proposed interventions

Among 172 potential donors declined due to cancer [13], with decision support one additional donor with low-risk PBM (2%) would have been accepted, increasing overall donation 0.3%. With real-time data-linkage two additional donors would have been accepted: one low-risk (2%) and one not contraindicated (0.1%). Overall donation would increase 0.6%, and these new donors would have an average transmission risk of 1.1%. With increased risk tolerance, seven additional donors would have been accepted including one low-risk (2%), one not contraindicated (0.1%), and five intermediate-risk (6.4%). Overall donation would increase 2.1%, and these new donors would have an average transmission risk of 4.9%.

6.5.3 Model inputs

For a typical waitlisted patient (50 year-old male, blood group O, no previous transplants, and one comorbidity), the probability of receiving a transplant within the first year was 38.6% from a deceased donor, and 36.9% from a living donor. After receiving a deceased donor transplant, the probability of developing cancer within the first year was 0.2%. Without developing cancer, the probability of transplant failure within the first year was 1.4%. If the recipient did develop cancer, the probability of transplant failure within the first

year was 13.5%. Incidence rates and model parameters used to calculate transition probabilities are presented in Tables S4-S9.

We applied utilities to each health state to reflect relative quality of life. Patients on dialysis had utility 0.73 (0.52 with *de-novo* cancer or 0.45 with transmitted cancer if their transplant failed and they returned to dialysis). Transplanted patients had utility 0.83 (0.59 with *de-novo* cancer or 0.51 with transmitted cancer). Calculation of utility values for cancer is presented in Table 6.S10.

The annual cost of dialysis was $78,845, whereas a deceased donor transplant cost $78,836 in the first year but only $3,949 annually thereafter. In the first year after cancer diagnosis, *de-novo* cancers cost $45,425 while transmitted cancers cost $48,018 plus $10,478 if nephrectomy was required. All costs associated with each modelled health state (based on nationally reported prices and previous costing studies) are summarized in Appendix 2.

6.5.4 Economic evaluation

Among 1,500 simulated patients entering the waitlist under current practice, on average over 10,000 simulations there were 1,135 or 75.7% (95% CI 73.5 – 88.7%) who received a deceased donor transplant and 112 or 7.5% (95% CI 6.2 – 8.9%) who received a living donor transplant. On average, all proposed interventions resulted in increased QALYs and cost savings (i.e., dominant) compared with current practice. Decision support with increased risk tolerance was the most likely to be cost-effective (dominant in 87%, <$28k/QALY gained in 88%, and <$50k/QALY gained in 89% of simulations). Under this intervention, health outcomes would improve (+18.8 QALYs, 95%CI -9.5 to 51.1) and healthcare expenditure would reduce by $2.2m (95%CI $121k higher to $4.6m lower). Most patients would be

unaffected; however, a small proportion (1.2%) would benefit (mean +1.5 QALYs) while an even smaller proportion (0.2%) would have worse outcomes (mean -3.4 QALYs). The overall cost-effectiveness of each intervention is presented in Figure 6.2, and all results from the economic evaluation are summarized in Table 6.1. The cumulative average incremental costs and QALYs after each simulation compared to the results after all 10,000 simulations quickly approached zero, demonstrating that 10,000 simulations were sufficient (Figure 6.S1).

Overall, patients in every subgroup were more likely to benefit than be harmed, but benefits were not shared evenly. Older patients were least likely to benefit (age 65+ vs. 0-44, relative risk ratio RRR 0.56, 95%CI 0.54 – 0.59, p<0.001). Characteristics for all 15 million simulated patients (1,500 patients x 10,000 simulations) and their probability of having higher vs. lower QALYs under decision support with increased risk tolerance is summarized in Table 6.2.

6.5.5 Uncertainty analyses

Incremental costs and QALYs from probabilistic sensitivity analysis were similar to the base-case, hence results were robust to uncertainty in model parameters. Results were most sensitive to the probability of deceased donor transplant and the probability of deceased donor transplant failure. All interventions remained dominant even in the worst-case scenario with immediate death after cancer transmission (increased risk tolerance +15.7 QALYs and $2.7m cost-savings). Decision support with increased risk tolerance would improve health outcomes until the average transmission risk for new donors reaches 20% and would reduce costs until the average transmission risk reaches 32% (Figure 6.3). The

cost-effectiveness from each simulation of the sensitivity analysis is presented in Figure 6.S2, and the marginal impact of parameter changes is presented in Figure 6.S3.

6.6 Discussion

We found that despite the increased transmission risk to recipients, any increase in donation from donors with PBM would improve patient outcomes (QALYs) and save money. Our conclusions were robust to sensitivity analysis, and even if the risk of transmission were four times greater (20%), accepting intermediate-risk donors would remain cost-effective.

Our findings were consistent with results from previous economic evaluations of improvements to kidney donation policies [24]. Economic evaluations typically focus on average outcomes across the population, whereas our simulation of individual patients allowed us to explore variability between patients. We found that a small proportion of patients (0.19%) would experience cancer transmission and be worse-off than if they had remained on dialysis. A much larger proportion (1.23%) would be better-off since most transplants from donors with PBM do not result in transmission. Most patients, however, would be unaffected. Real-time data-linkage resulted in the smallest average QALYs lost among those worse-off while decision support alone resulted in the largest average QALYs gained among those better-off. However, when considering the proportion of patients better-off, increase risk tolerance was clearly the most beneficial intervention. Benefits were not shared evenly among all patient subgroups, but all patients were much more likely to benefit than be harmed, hence the potential for inequity should not discourage adoption of the proposed interventions.

In Australia, organ transplantation is regulated though guidelines rather than legislation. Ethical guidelines for transplantation state that the "expected benefit to the recipient must outweigh any expected risk" [62], which in the context of our results demonstrating net health benefits to patients, could be interpreted as supportive of accepting kidneys from deceased donors with brain cancer. Similarly, the good medical practice code of conduct promotes "making patient safety your first priority" [63], which may also be considered supportive of accepting a kidney transplant with a cancer transmission risk since expected survival is greater than remaining on dialysis. These principles of prioritizing patient health outcomes and safety are reflected in medical guidelines internationally [64-66].

A major strength of our study is our use of data for all potential donors from NSW [13], which has a centralized donation service. This allowed us to capture missed opportunities for donation from donors with PBM that may not have been reported in other jurisdictions. Furthermore, our use of national transplant registry data to estimate patient and donor characteristics and transition probabilities provides confidence that our findings are applicable to the Australian kidney waitlist. Due to variability in healthcare systems, it is unclear whether the magnitude of cost-savings we report would be generalizable to other jurisdictions, but the direction of the effect is likely to be consistent. However, underutilization of potential deceased donors with PBM is an issue internationally [67], and our findings of improved health outcomes may therefore be applicable to other countries. We found that accepting intermediate risk PBM donors (6.4% transmission risk) increased donation by 2.1%, which could mean an additional 17 kidneys transplanted annually in Australia [68], 49 in the UK [21], 90 in the Eurotransplant network [69], and 582 in the US [70].

Our economic model was comprehensive and incorporated a wide range of benefits of increasing kidney donation from donors with PBM. For example, we considered not only the increase in the number of donors available for transplant, but also the improved quality of these donors in terms of their characteristics such as age and comorbidities [19]. A limitation of our model is that it does not account for a dynamic waitlist, where people may be temporarily made inactive for medical reasons, and where a patient being transplanted increases the chances of receiving a transplant for those remaining waiting. We do not expect that the effect of waitlist dynamics would substantially change our results or conclusions. Our study is also limited to assessing the impact of increasing utilization of donors with only one type of cancer (PBM) and donation of only one organ (kidneys). It is unclear whether accepting more donors with other types of cancer would be beneficial, but we expect that increasing utilization of other organs (e.g., liver, heart, and lungs) would be even more cost-effective since these recipients often have no alternative treatment.

Our study is limited to assessing the impact of several proposed interventions, without accounting for the potential administrative costs associated with their implementation. A decision support tool for donation specialists such as an app would incur set-up and maintenance costs, as would establishing real-time access to cancer registry or hospital admissions data. While increasing risk tolerance would theoretically not have any direct cost, it would require additional patient education and informed consent, and increased capacity for shared decision making between clinicians and patients. It would also require a change in donation specialists' attitudes, and behavior change is difficult to achieve. Individual clinicians may wish to avoid the psychological consequence of an active decision which may inadvertently bring harm to their own patient, even with the knowledge that inaction (i.e., declining a donor) will likely harm their patient more. Furthermore, if a

recipient of a transmitted cancer were to seek compensation, the potential fees to defend or settle a case could exceed the overall system-wide cost-savings from increasing donation. Ensuring that recipients are fully informed of the potential harms involved and that decision making is shared between clinicians and their patients could help mitigate this risk. However, if our analysis were expanded to include potential donors with other cancers (also with low but non-zero risk of transmission), or other organs, the overall impact of our proposed interventions would likely increase with virtually no additional implementation costs.

The magnitude of health benefits and cost-savings realized relies on our assumption that all additional donors would proceed to transplantation, which may be an overestimate. However, the direction of our findings is independent of the number of new donors available. Even with changes to the assumed increase in donation under each intervention, or to the incidence or prevalence of brain cancers in the potential donor population, our conclusion that increasing utilization of kidneys from donors with brain cancer remains unchanged.

We have demonstrated that increasing utilization of kidneys from deceased donors with PBM would benefit people waiting for a kidney transplant while also reducing healthcare expenditure. Although the overall impacts are relatively minor, a small proportion of patients stand to benefit greatly whilst freeing up sorely needed healthcare funding. Our results provide a framework for determining whether the benefits of the proposed interventions (in terms of cost-savings and increased QALYs) outweigh the costs of implementation.

6.7 Conclusions

We have shown that any increase in utilization of kidneys from deceased donors with PBM both improves health outcomes for patients waiting for a kidney transplant and reduces healthcare costs. The greatest benefit was from increasing clinician risk tolerance to accept donors with intermediate-risk PBMs, and policy makers should consider this as a strategy to increase rates of transplantation.

6.8 Acknowledgements

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6.10 Tables

Table 6.1: Results of the economic evaluation for three interventions to increase utilization of deceased kidney donors with brain cancer

Outcome	Current practice	Decision support	Decision support + real-time data-linkage	Decision support + increased risk tolerance
Cost-effectiveness				
Total QALYs	12,612.6	12,615.9	12,619.4	12,631.5
Total costs	$408,257,368	$407,907,806	$407,544,457	$406,097,633
Incremental QALYs	-	3.3	6.8	18.8
Incremental QALYs 95% CI	-	(-7.0, 17.3)	(-6.8, 25.4)	(-9.5, 51.1)
Incremental costs	-	-$349,563	-$712,912	-$2,159,736
Incremental costs 95% CI	-	(-$1,387,484, $521,979)	(-$2,093,160, $414,348)	(-$4,607,211, $120,887)
Proportion dominant	-	78%	80%	87%
Proportion cost-effective	-	82%	84%	88%
Individual patients				
Proportion worse-off	-	0.02%	0.04%	0.19%
Mean QALYs among worse-off	-	-2.99	-2.80	-3.40
Proportion unaffected	-	99.8%	99.6%	98.6%
Proportion better-off	-	0.18%	0.37%	1.23%
Mean QALYs among better-off	-	1.55	1.53	1.53
Transplants and transmissions				
Change in living donor transplants	-	-0.2%	-0.4%	-1.2%
Change in life-years with living donor transplant	-	-3.2	-6.4	-22.2
Change in deceased donor transplants	-	0.1%	0.2%	0.5%
Change in life-years with deceased donor transplant	-	16.0	32.5	99.4
Additional cancer transmissions (per 100,000 patients)	-	4.2	4.4	70.1

QALYs, quality-adjusted life-years; 95%CI, 95% confidence interval

Table 6.2: Characteristics of simulated patients and comparison of those with lower vs. higher quality-adjusted life-years (QALYs) under decision support with increased risk tolerance

		Lower QALYs		Higher QALYs			
Characteristic	**Simulated patients, N (column %)**	N (column %)	Row %	N (column %)	Row %	**RRR (95% CI)**	**p-value**
Overall	15,000,000 (100)	28,121 (100)	0.19	184,999 (100)	1.23	-	
Age, mean (SD)	49.1 (14.59)	50.4 (15.25)		47.6 (14.07)			<0.001
0-44	5,646,864 (38)	9,896 (35)	0.18	75,960 (41)	1.35	ref	
45-54	4,023,930 (27)	7,073 (25)	0.18	51,299 (28)	1.27	0.95 (0.92, 0.98)	
55-64	3,150,066 (21)	6,168 (22)	0.20	36,745 (20)	1.17	0.78 (0.76, 0.81)	
65+	2,179,140 (15)	4,986 (18)	0.23	21,243 (11)	0.97	0.56 (0.54, 0.59)	
Sex							<0.001
Male	5,505,593 (37)	9,926 (35)	0.18	67,799 (37)	1.23	ref	
Female	9,494,407 (63)	18,197 (65)	0.19	117,448 (63)	1.24	1.04 (1.01, 1.06)	
Blood group							<0.001
O	6,745,358 (45)	12,154 (43)	0.18	81,594 (44)	1.21	ref	
A	5,565,829 (37)	11,065 (39)	0.20	71,198 (38)	1.28	0.96 (0.94, 0.99)	
B	2,011,989 (13)	3,662 (13)	0.18	23,716 (13)	1.18	0.96 (0.93, 1.00)	
AB	676,824 (5)	1,242 (4)	0.18	8,739 (5)	1.29	1.05 (0.99, 1.12)	
Previous transplants							0.002
0	14,664,378 (98)	27,447 (98)	0.19	180,920 (98)	1.23	ref	
1+	335,622 (2)	676 (2)	0.20	4,327 (2)	1.29	0.89 (0.82, 0.96)	
Comorbidities, mean (SD)	0.8 (0.99)	0.9 (1.03)		0.8 (0.96)			<0.001
0	6,890,415 (46)	12,292 (44)	0.18	87,013 (47)	1.26	ref	
1	4,993,441 (33)	9,456 (34)	0.19	61,502 (33)	1.23	0.97 (0.94, 1.00)	
2+	3,116,144 (21)	6,375 (23)	0.20	36,732 (20)	1.18	0.96 (0.92, 0.99)	

QALYs, quality-adjusted life-years; RRR, (adjusted) relative risk ratio; 95%CI, 95% confidence interval; SD, standard deviation

[a] 1,500 patients were simulated 10,000 times, hence there were 15 million simulated patients in total

Rates of lower vs. higher QALYs show whether a subgroup of patients is more likely to have improved or reduced health outcomes under the intervention. Relative risk ratio (RRR) compares whether a subgroup is more likely (RRR > 1) or less likely (RRR < 1) to have better health outcomes compared with a reference group. For example, those aged 65+ are more likely to have higher QALYs than lower QALYs under the intervention (0.97% vs. 0.23%). However, the benefit is 44% less than would be expected in those aged 0-44 (RRR 0.56, 95%CI 0.54 - 0.59, p<0.001). These patients are likely to benefit from the intervention, but they receive a less than equitable share of the total benefits.

6.11 Figures

Figure 6.1: Structure of the Markov model used to simulate individual patients

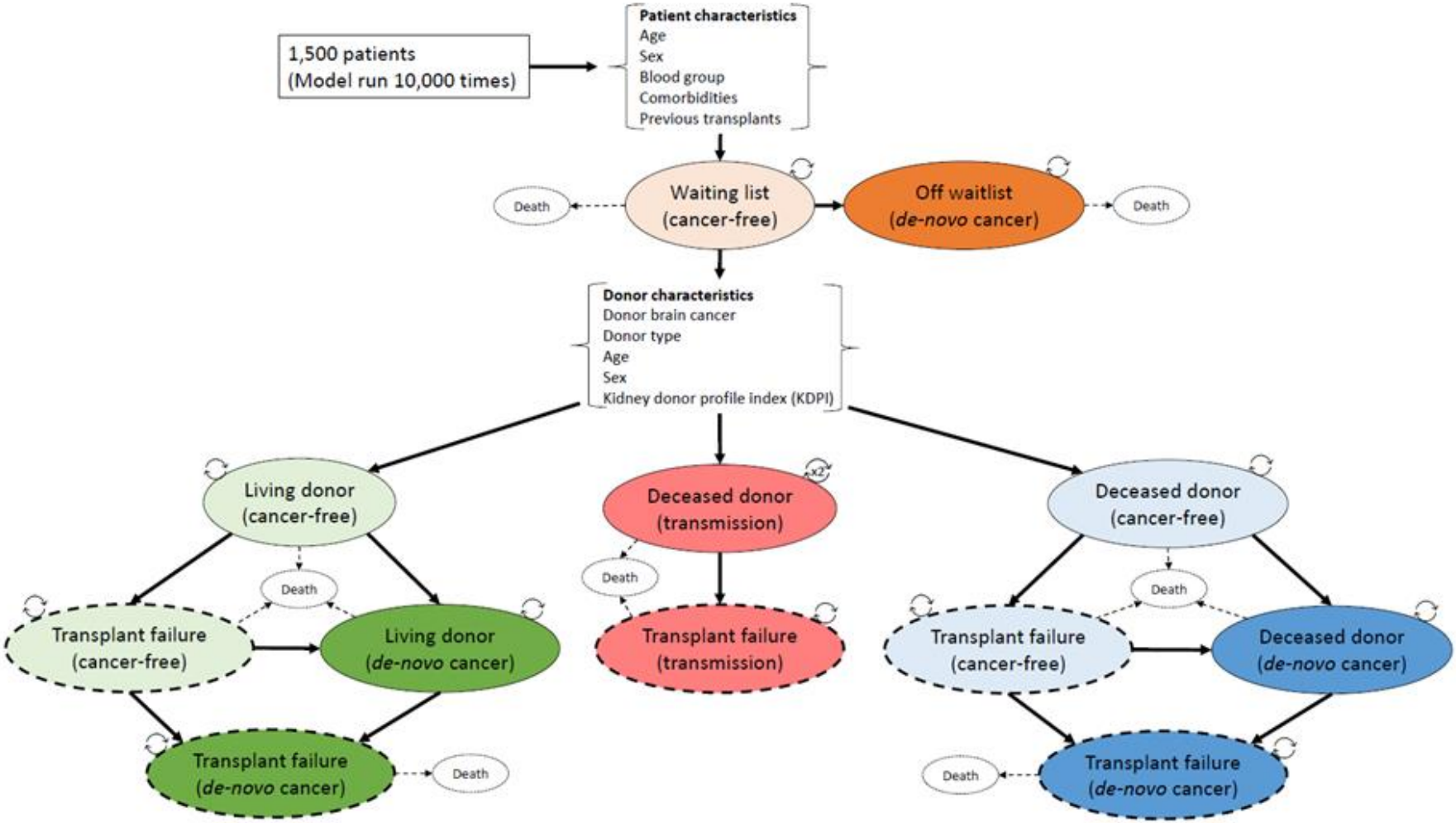


Figure 6.2: Incremental costs and quality-adjusted life-years (QALYs) gained compared with current practice from 10,000 simulations of each intervention

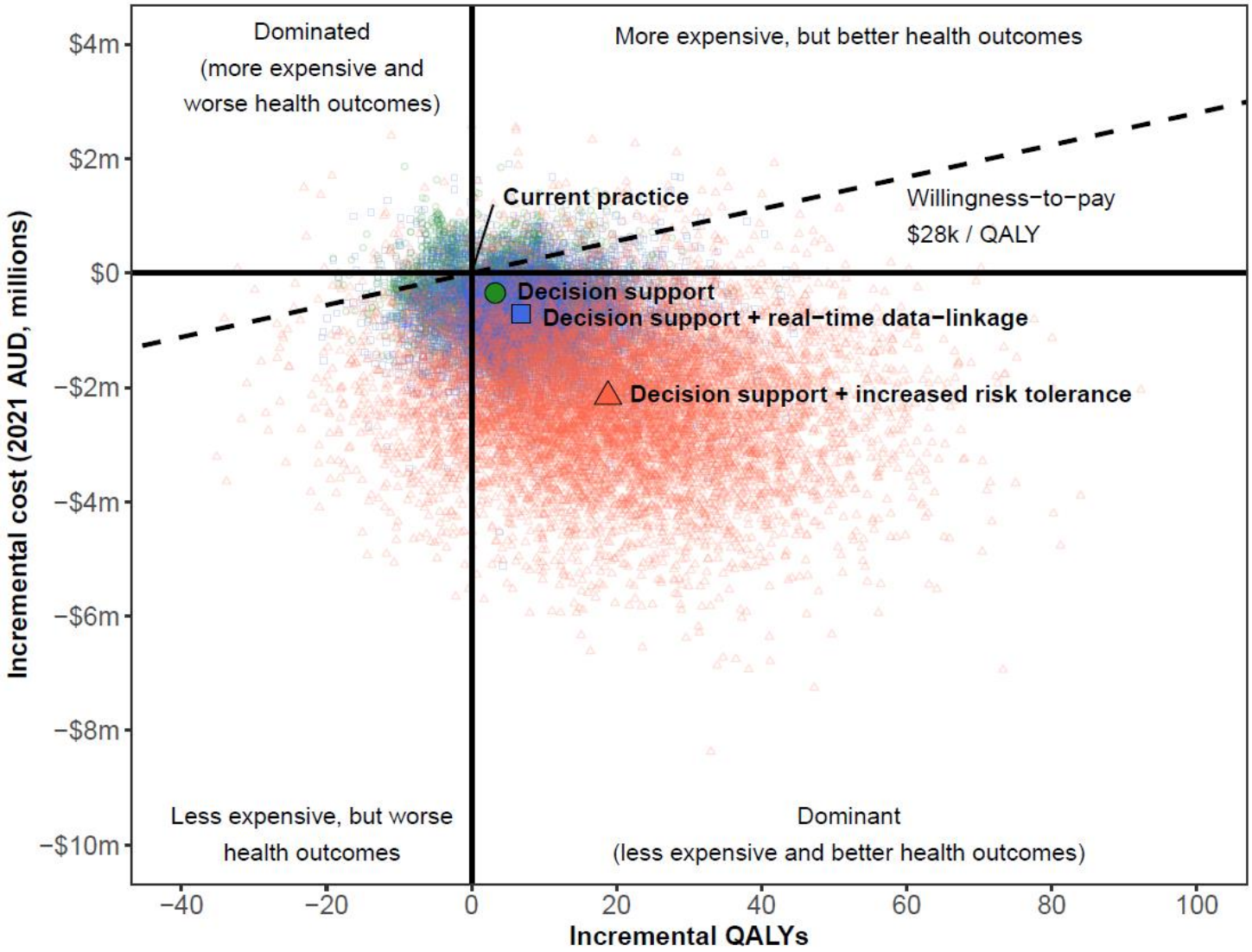
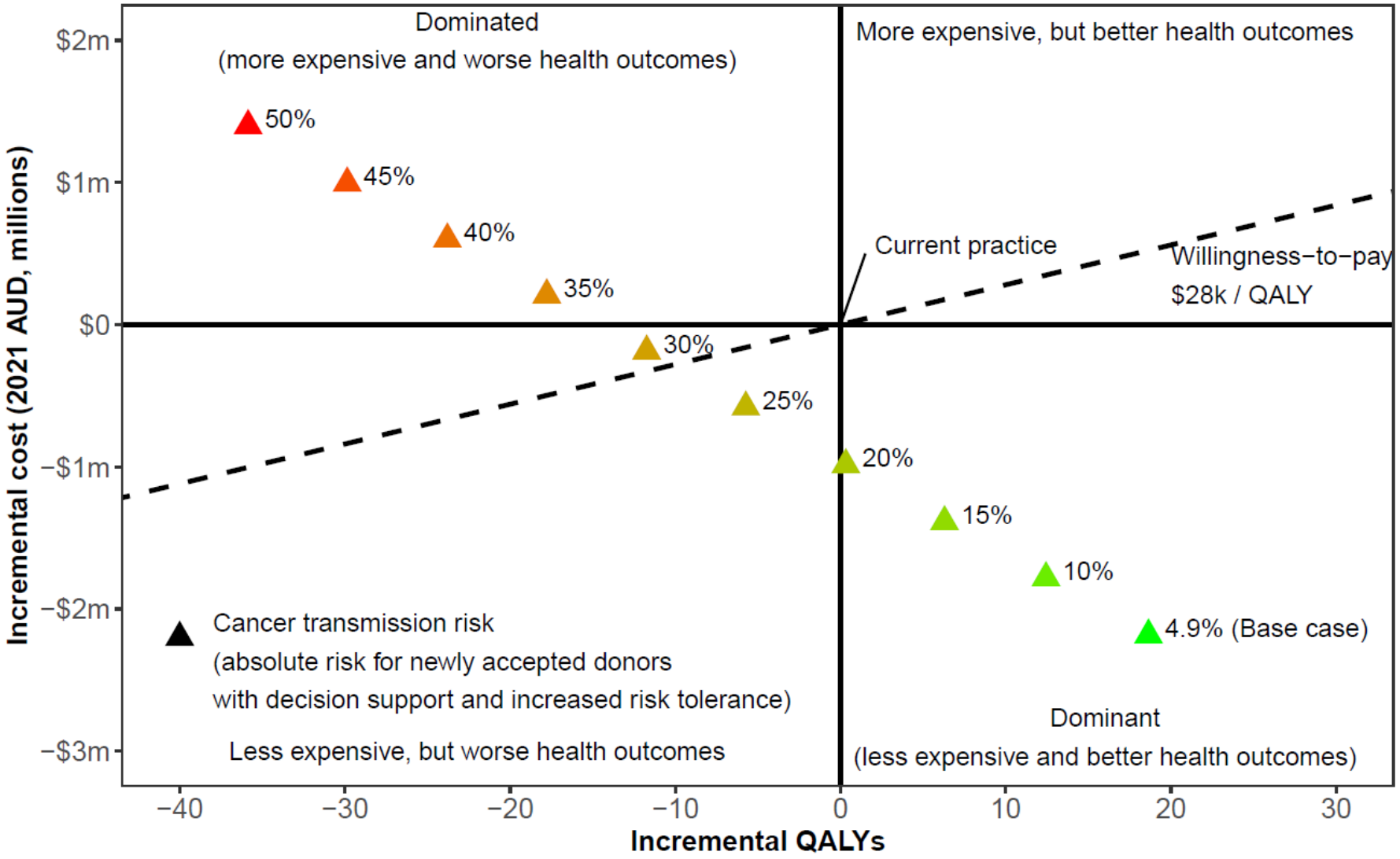


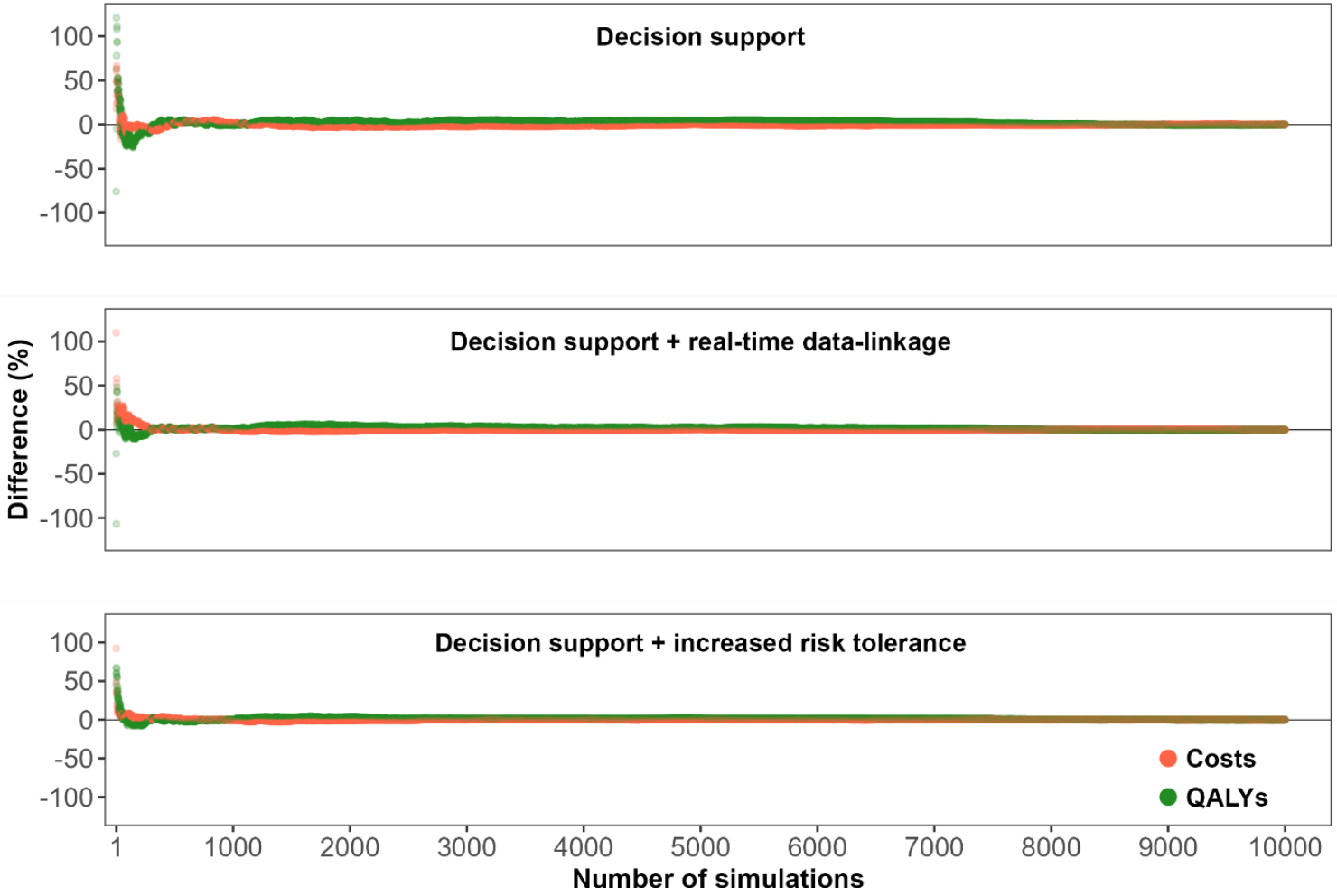
Figure 6.3: Threshold analysis - incremental costs and quality-adjusted life-years (QALYs) gained from 10,000 simulations of decision support with increased risk tolerance, with alternative transmission risks



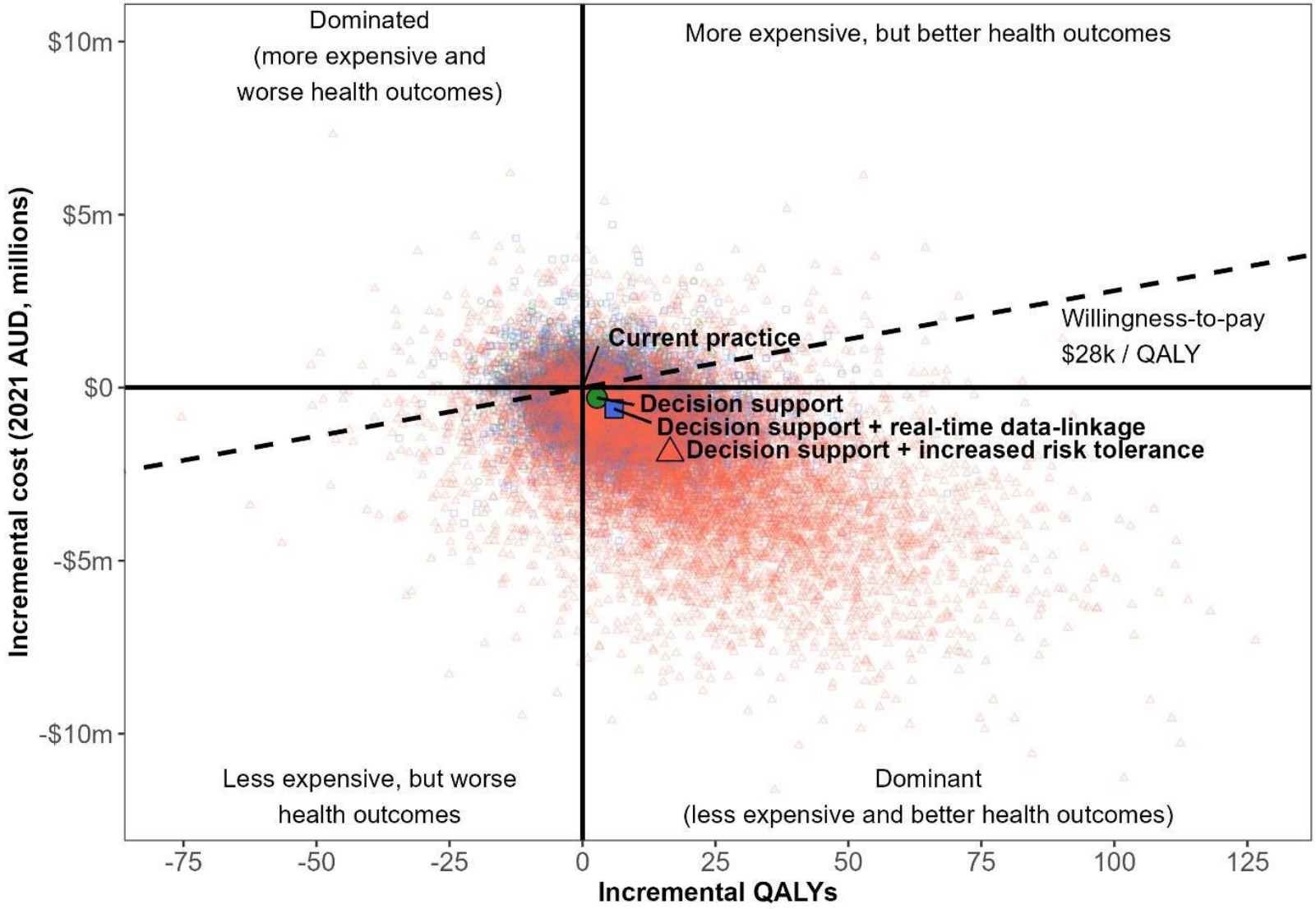
6.12 Supplementary material

6.12.1 Supplementary Figures

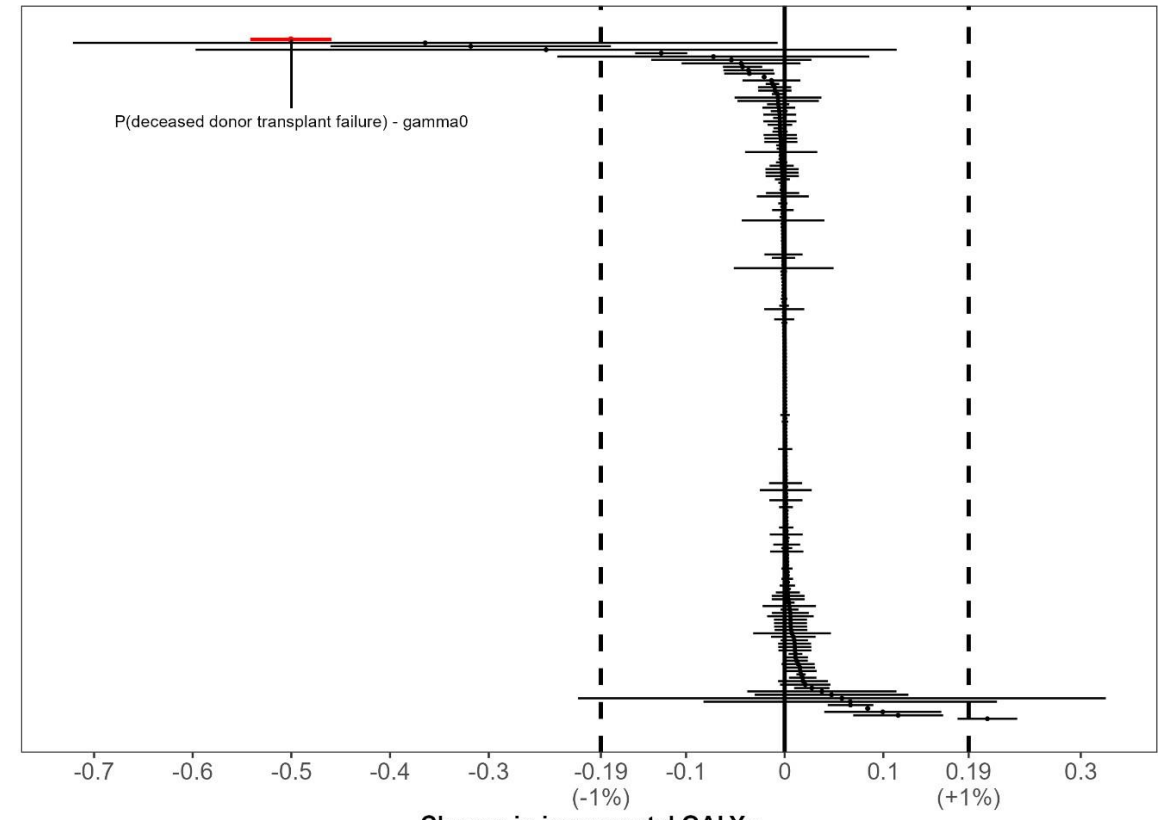
Supplementary Figure 6.S1: Proportional difference between cumulative average incremental costs and quality-adjusted life-years (QALYs) gained compared with current practice, and their final values under each intervention

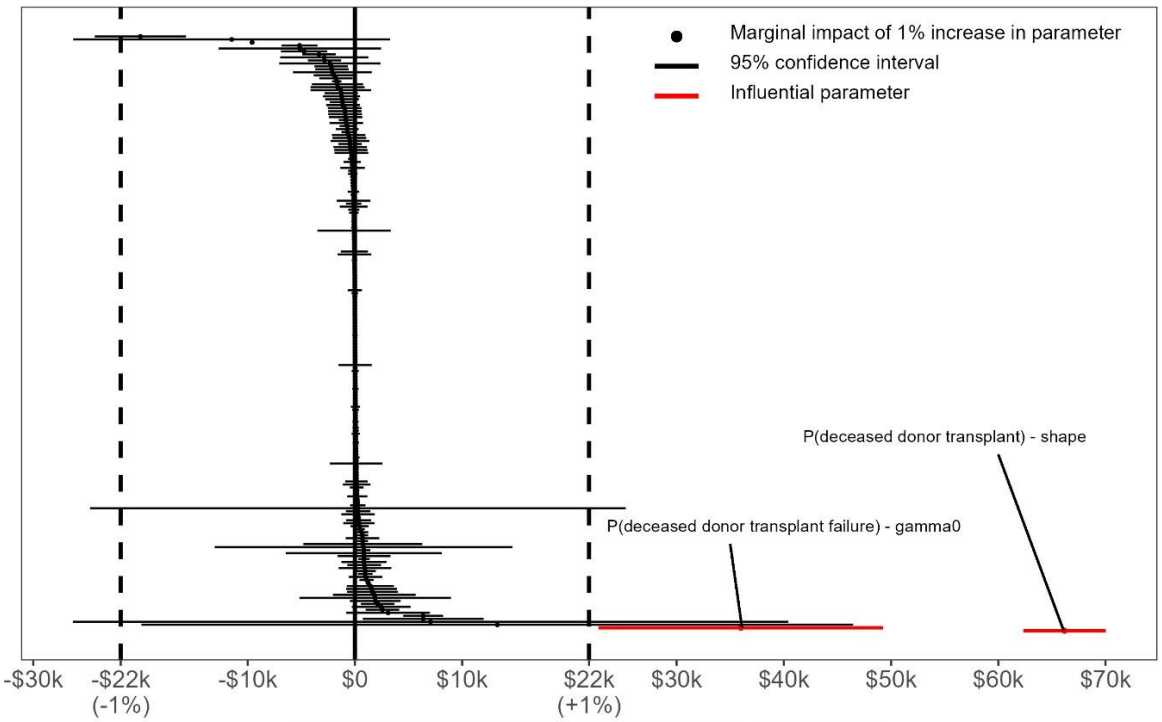


Supplementary Figure 6.S2: Incremental costs and quality-adjusted life-years (QALYs) gained from 10,000 probabilistic sensitivity analysis simulations of each intervention



Supplementary Figure 6.S3: Marginal change in incremental costs and quality-adjusted life-years (QALYs) from a 1% increase in each parameter





Based on a linear regression of the results from 10,000 probabilistic sensitivity analysis simulations.
Each point represents a model paramater. Dashed lines represent a 1% change in incremental costs or QALYs (in the decison support + increased risk tolerance scenario). Parameters with a 95% CI that lies outside the dashed lines may be considered influential, i.e. the model is sensitive to changes in these parameters (highlighted in red and labeled).

6.12.2 Supplementary Tables

Supplementary Table 6.S1: Current classification of transmission risk from deceased donor brain cancers in Australia

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[a] – 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, C19MCaltered
- CNS embryonal tumour, NOS
- CNS embryonal tumour with rhabdoid features
- Medulloepithelioma
- Ependymoblastoma
- 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

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

Reproduced from Table M1 of TSANZ Clinical Guidelines for Organ Transplantation from Deceased Donors [1]

Supplementary Table 6.S2: Distributions and parameters used to simulate patient characteristics

Parameter, mean (SE)	**Number of previous transplants**	**Blood group**			**Female**	**Age at waitlisting**	**Number of comorbidities**
		A	B	AB			
Distribution	Poisson		Multinomial		Binomial	Normal	Poisson
Standard deviation (σ)	-	-	-	-	-	14.51	-
Intercept	-3.79 (0.07)	-0.19 (0.02)	-1.21 (0.03)	-2.32 (0.06)	-0.53 (0.03)	50.21 (0.27)	-1.57 (0.06)
Number of previous transplants	-	0.03 (0.16)	-0.08 (0.24)	0.68 (0.27)	0.20 (0.15)	-8.62 (1.06)	-0.08 (0.09)
Blood group A	-	-	-	-	-0.02 (0.05)	0.40 (0.35)	-0.04 (0.03)
Blood group B	-	-	-	-	-0.06 (0.07)	-0.25 (0.50)	-0.03 (0.04)
Blood group AB	-	-	-	-	-0.19 (0.12)	0.31 (0.79)	-0.13 (0.06)
Female	-	-	-	-	-	-1.54 (0.33)	-0.22 (0.03)
Age at waitlisting	-	-	-	-	-	-	0.03 (0.001)

SE, standard error

Supplementary Table 6.S3: Distributions and parameters used to simulate donor characteristics

Parameter, mean (SE)	**Primary brain malignancy**	**Deceased donor type**		**Donor female**	**Donor age**	**KDPI**
		DBD SCD	DBD ECD			
Distribution	Binomial	Multinomial		Binomial	Normal	Logit-normal
Standard deviation (σ)	-	-	-	-	13.48	0.91
Intercept	-8.08 (0.76)	2.70 (0.11)	-0.20 (0.14)	-0.46 (0.05)	35.85 (0.33)	-2.70 (0.05)
Number of previous transplants	-0.26 (0.26)	0.15 (0.06)	0.13 (0.07)	0.03 (0.03)	-0.74 (0.22)	-0.04 (0.02)
Blood group A	-0.13 (0.22)	-0.05 (0.05)	-0.11 (0.07)	-0.01 (0.03)	0.06 (0.21)	-0.08 (0.02)
Blood group B	-0.01 (0.31)	0.17 (0.08)	-0.01 (0.10)	-0.08 (0.05)	-0.41 (0.31)	-0.01 (0.03)
Blood group AB	0.08 (0.44)	0.17 (0.12)	-0.22 (0.15)	-0.02 (0.07)	-0.83 (0.47)	-0.08 (0.04)
Female	0.27 (0.20)	0.03 (0.05)	-0.09 (0.06)	-0.15 (0.03)	0.09 (0.20)	0.01 (0.02)
Number of comorbidities	-0.16 (0.12)	-0.13 (0.02)	-0.07 (0.03)	0.07 (0.02)	0.66 (0.11)	-0.03 (0.01)
Age at transplant	-0.01 (0.01)	-0.03 (0.002)	0.01 (0.003)	0.01 (0.001)	0.19 (0.01)	0.0002 (0.0007)
Deceased donor	3.58 (0.72)	-	-	-	-	-
Donor primary brain malignancy	-	0.36 (0.29)	-0.97 (0.49)	0.13 (0.20)	-0.66 (1.34)	0.16 (0.11)
DCD donor	-	-	-	-0.50 (0.05)	-0.75 (0.35)	-
DBD standard criteria donor	-	-	-	-0.09 (0.03)	-9.11 (0.22)	-0.45 (0.02)
DBD expanded criteria donor	-	-	-	0.12 (0.05)	17.73 (0.33)	0.40 (0.03)
Donor female	-	-	-	-	3.36 (0.19)	0.29 (0.02)
Donor age	-	-	-	-	-	0.07 (0.0007)

SE, standard error; DCD, donation after circulatory death; DBD, donation after brain death; SCD, standard criteria donor; ECD, expanded criteria donor; KPDI, kidney donor profile index

Supplementary Table 6.S4: Standardized mortality ratios (SMRs) for patients with kidney failure, by age and sex

Age	Female		Male	
	Dialysis	Transplant	Dialysis	Transplant
25	143.1	9.0	61.6	-
35	63.9	4.1	38.0	3.1
45	52.5	4.2	23.8	3.3
55	26.6	4.5	16.1	2.9
65	15.5	3.8	9.9	2.5
75	6.8	1.8	5.3	1.9
85	3.3	2.1	2.6	1.6

Estimated from ANZDATA annual reports [2]

Supplementary Table 6.S5: Average relative survival with cancer by 5-year age group, sex, and years after diagnosis

	Average relative survival compared with the general population, %									
	Females					***Males***				
Age group	0-1 years	1-2 years	2-3 years	3-4 years	4+ years	0-1 years	1-2 years	2-3 years	3-4 years	4+ years
0-4	98.5	97.4	97.0	96.8	96.6	97.5	96.8	96.4	96.0	95.9
5-9	98.9	98.5	98.4	98.3	98.3	98.7	98.0	97.7	97.5	97.4
10-14	98.5	97.7	97.3	96.7	96.5	99.0	98.1	97.3	97.3	97.3
15-19	98.6	97.5	96.8	96.0	95.6	98.8	97.2	96.6	95.7	95.8
20-24	98.9	97.6	97.2	96.8	96.2	98.4	96.7	96.1	95.5	95.0
25-29	98.4	97.1	96.7	95.9	95.5	97.8	96.2	95.7	95.1	94.6
30-34	97.4	94.9	95.2	94.5	94.0	96.1	95.0	94.9	94.9	94.5
35-39	96.1	93.8	92.9	92.9	92.3	95.5	92.9	92.5	92.9	92.6
40-44	94.4	90.7	89.2	89.1	88.5	92.8	88.5	86.2	85.5	85.0
45-49	92.0	88.5	86.7	84.8	84.2	89.7	85.9	83.2	81.9	80.7
50-54	89.9	85.1	83.5	82.2	81.0	88.0	81.2	78.9	77.6	77.1
55-59	87.6	82.0	79.2	78.5	77.1	84.6	79.1	76.8	75.9	74.2
60-64	86.8	80.8	77.1	75.3	75.1	83.3	76.5	72.8	70.3	68.0
65-69	84.1	77.7	73.2	72.0	70.4	79.9	72.8	69.7	67.3	67.6
70-74	81.5	74.7	71.4	71.6	70.3	77.6	72.7	68.7	66.5	64.5
75-79	77.3	71.2	70.6	68.3	66.2	75.3	68.8	65.5	63.3	61.3
80-84	72.3	68.3	66.6	65.9	65.3	71.5	66.8	64.0	65.2	64.8
85+	62.8	62.4	62.6	61.6	64.2	65.5	63.9	63.5	63.8	67.5

Derived from cancer data from the Australian Institute of Health and Welfare (AIHW) [3]

Supplementary Table 6.S6: Annual mortality rates by age, sex, treatment, and years since cancer diagnosis

Age	Sex	General population	Dialysis	Dialysis with cancer					Transplant	Transplant with cancer				
				0-1 years	1-2 years	2-3 years	3-4 years	4+ years		0-1 years	1-2 years	2-3 years	3-4 years	4+ years
0	Male	0.00364	0.22436	0.24412	0.22925	0.22788	0.22717	0.22587	0.01761	0.04264	0.02380	0.02206	0.02117	0.01952
0	Female	0.00297	0.42496	0.43363	0.43130	0.42759	0.42622	0.42601	0.02676	0.04142	0.03748	0.03121	0.02888	0.02852
1	Male	0.00025	0.01541	0.04050	0.02162	0.01987	0.01898	0.01733	0.00121	0.02666	0.00751	0.00574	0.00483	0.00315
1	Female	0.00024	0.03434	0.04889	0.04498	0.03875	0.03644	0.03609	0.00216	0.01720	0.01315	0.00672	0.00433	0.00397
2	Male	0.00014	0.00863	0.03389	0.01488	0.01312	0.01222	0.01056	0.00068	0.02614	0.00698	0.00521	0.00430	0.00262
2	Female	0.00012	0.01717	0.03198	0.02800	0.02166	0.01931	0.01895	0.00108	0.01613	0.01208	0.00565	0.00325	0.00289
3	Male	0.00012	0.00740	0.03269	0.01366	0.01190	0.01099	0.00933	0.00058	0.02604	0.00688	0.00511	0.00420	0.00253
3	Female	0.00010	0.01431	0.02916	0.02517	0.01881	0.01645	0.01609	0.00090	0.01596	0.01191	0.00547	0.00307	0.00271
4	Male	0.00010	0.00616	0.03148	0.01243	0.01067	0.00976	0.00810	0.00048	0.02595	0.00679	0.00502	0.00411	0.00243
4	Female	0.00008	0.01145	0.02634	0.02234	0.01597	0.01360	0.01324	0.00072	0.01578	0.01173	0.00529	0.00289	0.00253
5	Male	0.00009	0.00555	0.01832	0.01288	0.00878	0.00705	0.00649	0.00044	0.01327	0.00780	0.00369	0.00195	0.00139
5	Female	0.00007	0.01002	0.02104	0.01425	0.01072	0.01117	0.01002	0.00063	0.01176	0.00491	0.00134	0.00180	0.00063
6	Male	0.00008	0.00493	0.01771	0.01226	0.00817	0.00644	0.00588	0.00039	0.01322	0.00775	0.00364	0.00190	0.00134
6	Female	0.00006	0.00859	0.01963	0.01283	0.00929	0.00974	0.00859	0.00054	0.01167	0.00482	0.00125	0.00171	0.00054
7	Male	0.00007	0.00431	0.01710	0.01165	0.00755	0.00582	0.00526	0.00034	0.01317	0.00771	0.00359	0.00185	0.00129
7	Female	0.00006	0.00859	0.01963	0.01283	0.00929	0.00974	0.00859	0.00054	0.01167	0.00482	0.00125	0.00171	0.00054
8	Male	0.00007	0.00431	0.01710	0.01165	0.00755	0.00582	0.00526	0.00034	0.01317	0.00771	0.00359	0.00185	0.00129
8	Female	0.00006	0.00859	0.01963	0.01283	0.00929	0.00974	0.00859	0.00054	0.01167	0.00482	0.00125	0.00171	0.00054
9	Male	0.00007	0.00431	0.01710	0.01165	0.00755	0.00582	0.00526	0.00034	0.01317	0.00771	0.00359	0.00185	0.00129
9	Female	0.00006	0.00859	0.01963	0.01283	0.00929	0.00974	0.00859	0.00054	0.01167	0.00482	0.00125	0.00171	0.00054
10	Male	0.00007	0.00431	0.01421	0.01351	0.01196	0.00452	0.00483	0.00034	0.01028	0.00957	0.00802	0.00055	0.00086
10	Female	0.00006	0.00859	0.02301	0.01667	0.01353	0.01379	0.01065	0.00054	0.01508	0.00870	0.00553	0.00579	0.00262
11	Male	0.00008	0.00493	0.01482	0.01412	0.01258	0.00514	0.00545	0.00039	0.01033	0.00962	0.00807	0.00060	0.00091
11	Female	0.00007	0.01002	0.02442	0.01809	0.01496	0.01522	0.01208	0.00063	0.01517	0.00879	0.00562	0.00588	0.00271
12	Male	0.00010	0.00616	0.01604	0.01534	0.01380	0.00637	0.00668	0.00048	0.01042	0.00972	0.00816	0.00069	0.00100
12	Female	0.00009	0.01288	0.02724	0.02093	0.01780	0.01806	0.01493	0.00081	0.01535	0.00896	0.00580	0.00606	0.00289
13	Male	0.00013	0.00801	0.01788	0.01718	0.01563	0.00822	0.00853	0.00063	0.01056	0.00986	0.00831	0.00084	0.00115
13	Female	0.00011	0.01574	0.03006	0.02377	0.02065	0.02091	0.01779	0.00099	0.01552	0.00914	0.00598	0.00624	0.00307
14	Male	0.00017	0.01048	0.02032	0.01962	0.01808	0.01068	0.01099	0.00082	0.01076	0.01005	0.00850	0.00103	0.00134
14	Female	0.00013	0.01860	0.03288	0.02661	0.02350	0.02376	0.02064	0.00117	0.01570	0.00932	0.00615	0.00642	0.00325

Age	Sex	General population	Dialysis	Dialysis with cancer					Transplant	Transplant with cancer				
				0-1 years	1-2 years	2-3 years	3-4 years	4+ years		0-1 years	1-2 years	2-3 years	3-4 years	4+ years
15	Male	0.00024	0.01479	0.02633	0.03123	0.02017	0.02475	0.01479	0.00116	0.01286	0.01783	0.00661	0.01126	0.00116
15	Female	0.00016	0.02289	0.03667	0.03355	0.03042	0.03096	0.02659	0.00144	0.01552	0.01233	0.00913	0.00968	0.00522
16	Male	0.00031	0.01911	0.03059	0.03548	0.02446	0.02902	0.01911	0.00150	0.01319	0.01816	0.00695	0.01159	0.00150
16	Female	0.00018	0.02576	0.03949	0.03638	0.03326	0.03380	0.02944	0.00162	0.01569	0.01251	0.00931	0.00986	0.00540
17	Male	0.00040	0.02466	0.03608	0.04093	0.02998	0.03451	0.02466	0.00193	0.01362	0.01859	0.00738	0.01202	0.00193
17	Female	0.00020	0.02862	0.04231	0.03921	0.03609	0.03663	0.03229	0.00180	0.01587	0.01269	0.00949	0.01004	0.00558
18	Male	0.00048	0.02959	0.04095	0.04578	0.03488	0.03939	0.02959	0.00232	0.01400	0.01897	0.00777	0.01240	0.00232
18	Female	0.00022	0.03148	0.04513	0.04204	0.03893	0.03947	0.03514	0.00198	0.01605	0.01287	0.00966	0.01022	0.00576
19	Male	0.00054	0.03328	0.04460	0.04942	0.03856	0.04305	0.03328	0.00261	0.01429	0.01926	0.00806	0.01269	0.00261
19	Female	0.00023	0.03291	0.04654	0.04346	0.04035	0.04089	0.03657	0.00207	0.01614	0.01296	0.00975	0.01031	0.00585
20	Male	0.00058	0.03575	0.05072	0.05246	0.04167	0.04201	0.04086	0.00281	0.01828	0.02008	0.00893	0.00928	0.00809
20	Female	0.00024	0.03434	0.04453	0.04722	0.03892	0.03806	0.03989	0.00216	0.01269	0.01547	0.00689	0.00600	0.00790
21	Male	0.00060	0.03698	0.05193	0.05367	0.04290	0.04324	0.04208	0.00290	0.01838	0.02018	0.00903	0.00938	0.00818
21	Female	0.00024	0.03434	0.04453	0.04722	0.03892	0.03806	0.03989	0.00216	0.01269	0.01547	0.00689	0.00600	0.00790
22	Male	0.00062	0.03822	0.05314	0.05488	0.04412	0.04446	0.04331	0.00300	0.01847	0.02027	0.00912	0.00948	0.00828
22	Female	0.00024	0.03434	0.04453	0.04722	0.03892	0.03806	0.03989	0.00216	0.01269	0.01547	0.00689	0.00600	0.00790
23	Male	0.00063	0.03883	0.05375	0.05549	0.04474	0.04508	0.04392	0.00305	0.01852	0.02032	0.00917	0.00952	0.00833
23	Female	0.00024	0.03434	0.04453	0.04722	0.03892	0.03806	0.03989	0.00216	0.01269	0.01547	0.00689	0.00600	0.00790
24	Male	0.00064	0.03945	0.05436	0.05609	0.04535	0.04569	0.04453	0.00310	0.01857	0.02037	0.00922	0.00957	0.00837
24	Female	0.00024	0.03434	0.04453	0.04722	0.03892	0.03806	0.03989	0.00216	0.01269	0.01547	0.00689	0.00600	0.00790
25	Male	0.00065	0.04006	0.06145	0.05573	0.04482	0.04565	0.04556	0.00314	0.02535	0.01941	0.00809	0.00894	0.00885
25	Female	0.00024	0.03434	0.04961	0.04723	0.03867	0.04181	0.03859	0.00216	0.01794	0.01548	0.00664	0.00988	0.00655
26	Male	0.00066	0.04068	0.06205	0.05634	0.04544	0.04626	0.04618	0.00319	0.02540	0.01946	0.00813	0.00899	0.00890
26	Female	0.00026	0.03720	0.05242	0.05005	0.04152	0.04465	0.04144	0.00234	0.01811	0.01566	0.00682	0.01006	0.00673
27	Male	0.00067	0.04130	0.06265	0.05694	0.04605	0.04687	0.04679	0.00324	0.02544	0.01951	0.00818	0.00904	0.00895
27	Female	0.00027	0.03863	0.05383	0.05147	0.04295	0.04607	0.04286	0.00243	0.01820	0.01575	0.00691	0.01015	0.00682
28	Male	0.00069	0.04253	0.06386	0.05816	0.04728	0.04810	0.04801	0.00334	0.02554	0.01960	0.00828	0.00913	0.00905
28	Female	0.00028	0.04006	0.05524	0.05288	0.04437	0.04749	0.04429	0.00252	0.01829	0.01584	0.00700	0.01024	0.00691
29	Male	0.00072	0.04438	0.06567	0.05997	0.04912	0.04994	0.04985	0.00348	0.02568	0.01975	0.00842	0.00928	0.00919
29	Female	0.00028	0.04006	0.05524	0.05288	0.04437	0.04749	0.04429	0.00252	0.01829	0.01584	0.00700	0.01024	0.00691
30	Male	0.00075	0.02850	0.06674	0.03942	0.02915	0.02854	0.03269	0.00230	0.04157	0.01351	0.00297	0.00235	0.00661
30	Female	0.00030	0.01917	0.04468	0.04420	0.01917	0.02588	0.02428	0.00122	0.02721	0.02672	0.00122	0.00807	0.00644
31	Male	0.00079	0.03002	0.06820	0.04092	0.03067	0.03006	0.03421	0.00242	0.04169	0.01364	0.00309	0.00247	0.00673
31	Female	0.00033	0.02108	0.04655	0.04607	0.02108	0.02779	0.02619	0.00135	0.02733	0.02684	0.00135	0.00819	0.00656

Age	Sex	General population	Dialysis	Dialysis with cancer					Transplant	Transplant with cancer				
				0-1 years	1-2 years	2-3 years	3-4 years	4+ years		0-1 years	1-2 years	2-3 years	3-4 years	4+ years
32	Male	0.00083	0.03154	0.06966	0.04242	0.03219	0.03158	0.03572	0.00255	0.04181	0.01376	0.00322	0.00259	0.00686
32	Female	0.00037	0.02364	0.04904	0.04856	0.02364	0.03033	0.02873	0.00151	0.02749	0.02700	0.00151	0.00835	0.00672
33	Male	0.00088	0.03344	0.07148	0.04430	0.03409	0.03348	0.03761	0.00270	0.04196	0.01391	0.00337	0.00275	0.00701
33	Female	0.00041	0.02619	0.05153	0.05105	0.02619	0.03286	0.03127	0.00167	0.02764	0.02716	0.00167	0.00851	0.00688
34	Male	0.00094	0.03572	0.07367	0.04655	0.03636	0.03576	0.03988	0.00288	0.04213	0.01409	0.00355	0.00293	0.00719
34	Female	0.00045	0.02875	0.05401	0.05354	0.02875	0.03540	0.03382	0.00184	0.02780	0.02732	0.00184	0.00868	0.00704
35	Male	0.00100	0.03800	0.08123	0.06385	0.04230	0.03800	0.04182	0.00307	0.04787	0.02986	0.00753	0.00307	0.00703
35	Female	0.00050	0.03194	0.07010	0.05457	0.04129	0.03194	0.03815	0.00204	0.04137	0.02537	0.01167	0.00204	0.00844
36	Male	0.00107	0.04066	0.08377	0.06644	0.04495	0.04066	0.04447	0.00328	0.04808	0.03007	0.00774	0.00328	0.00725
36	Female	0.00054	0.03450	0.07255	0.05707	0.04382	0.03450	0.04069	0.00220	0.04153	0.02553	0.01184	0.00220	0.00860
37	Male	0.00114	0.04331	0.08631	0.06903	0.04760	0.04331	0.04712	0.00350	0.04828	0.03028	0.00796	0.00350	0.00746
37	Female	0.00058	0.03705	0.07500	0.05956	0.04635	0.03705	0.04323	0.00237	0.04169	0.02569	0.01200	0.00237	0.00877
38	Male	0.00121	0.04597	0.08885	0.07161	0.05024	0.04597	0.04977	0.00371	0.04849	0.03049	0.00817	0.00371	0.00767
38	Female	0.00064	0.04089	0.07869	0.06330	0.05014	0.04089	0.04704	0.00261	0.04192	0.02593	0.01224	0.00261	0.00901
39	Male	0.00129	0.04901	0.09175	0.07457	0.05327	0.04901	0.05280	0.00396	0.04872	0.03073	0.00842	0.00396	0.00792
39	Female	0.00070	0.04472	0.08237	0.06705	0.05394	0.04472	0.05085	0.00286	0.04216	0.02616	0.01248	0.00286	0.00925
40	Male	0.00138	0.03291	0.10214	0.07824	0.05744	0.04119	0.03904	0.00452	0.07579	0.05119	0.02978	0.01305	0.01083
40	Female	0.00076	0.03987	0.09400	0.07715	0.05607	0.04080	0.04602	0.00317	0.05938	0.04188	0.01999	0.00414	0.00956
41	Male	0.00147	0.03505	0.10414	0.08029	0.05953	0.04332	0.04117	0.00482	0.07607	0.05147	0.03007	0.01335	0.01113
41	Female	0.00082	0.04302	0.09697	0.08018	0.05916	0.04394	0.04915	0.00342	0.05961	0.04212	0.02024	0.00439	0.00981
42	Male	0.00157	0.03744	0.10635	0.08256	0.06186	0.04569	0.04354	0.00515	0.07637	0.05178	0.03038	0.01367	0.01145
42	Female	0.00090	0.04721	0.10093	0.08421	0.06329	0.04813	0.05332	0.00376	0.05993	0.04244	0.02056	0.00472	0.01015
43	Male	0.00170	0.04054	0.10923	0.08551	0.06488	0.04876	0.04662	0.00557	0.07677	0.05219	0.03080	0.01409	0.01188
43	Female	0.00099	0.05193	0.10539	0.08875	0.06793	0.05285	0.05801	0.00413	0.06028	0.04281	0.02093	0.00510	0.01052
44	Male	0.00184	0.04388	0.11233	0.08870	0.06813	0.05207	0.04994	0.00603	0.07719	0.05263	0.03125	0.01455	0.01233
44	Female	0.00107	0.05613	0.10935	0.09278	0.07205	0.05704	0.06218	0.00447	0.06060	0.04313	0.02126	0.00543	0.01085
45	Male	0.00200	0.04769	0.14588	0.08839	0.07724	0.06244	0.06205	0.00655	0.10898	0.04901	0.03738	0.02194	0.02153
45	Female	0.00116	0.06085	0.13620	0.09622	0.07999	0.08107	0.06811	0.00484	0.08469	0.04233	0.02513	0.02627	0.01254
46	Male	0.00217	0.05174	0.14951	0.09227	0.08116	0.06643	0.06604	0.00711	0.10948	0.04955	0.03792	0.02249	0.02208
46	Female	0.00125	0.06557	0.14054	0.10077	0.08462	0.08569	0.07280	0.00522	0.08503	0.04269	0.02549	0.02664	0.01291
47	Male	0.00233	0.05556	0.15293	0.09592	0.08486	0.07019	0.06980	0.00764	0.10995	0.05005	0.03843	0.02301	0.02260
47	Female	0.00136	0.07134	0.14585	0.10632	0.09027	0.09134	0.07852	0.00568	0.08545	0.04313	0.02594	0.02709	0.01337
48	Male	0.00250	0.05961	0.15657	0.09981	0.08879	0.07418	0.07379	0.00819	0.11045	0.05058	0.03897	0.02355	0.02315
48	Female	0.00148	0.07764	0.15164	0.11238	0.09644	0.09750	0.08477	0.00618	0.08591	0.04361	0.02643	0.02758	0.01386

Age	Sex	General population	Dialysis	Dialysis with cancer					Transplant	Transplant with cancer				
				0-1 years	1-2 years	2-3 years	3-4 years	4+ years		0-1 years	1-2 years	2-3 years	3-4 years	4+ years
49	Male	0.00268	0.06391	0.16042	0.10391	0.09295	0.07840	0.07802	0.00878	0.11098	0.05115	0.03954	0.02413	0.02373
49	Female	0.00162	0.08498	0.15840	0.11945	0.10363	0.10468	0.09206	0.00676	0.08645	0.04417	0.02701	0.02815	0.01444
50	Male	0.00287	0.04614	0.16033	0.12051	0.07288	0.06139	0.05259	0.00843	0.12713	0.08574	0.03622	0.02428	0.01513
50	Female	0.00176	0.04673	0.14265	0.09752	0.06540	0.06165	0.06048	0.00785	0.10767	0.06071	0.02727	0.02338	0.02215
51	Male	0.00309	0.04968	0.16344	0.12378	0.07632	0.06487	0.05610	0.00907	0.12770	0.08634	0.03685	0.02491	0.01577
51	Female	0.00191	0.05071	0.14623	0.10129	0.06930	0.06557	0.06440	0.00852	0.10828	0.06134	0.02793	0.02404	0.02281
52	Male	0.00334	0.05370	0.16698	0.12748	0.08022	0.06882	0.06009	0.00981	0.12834	0.08701	0.03757	0.02563	0.01650
52	Female	0.00207	0.05496	0.15005	0.10531	0.07347	0.06976	0.06859	0.00923	0.10892	0.06202	0.02863	0.02474	0.02352
53	Male	0.00363	0.05836	0.17108	0.13178	0.08476	0.07341	0.06472	0.01066	0.12909	0.08780	0.03839	0.02647	0.01734
53	Female	0.00225	0.05974	0.15435	0.10984	0.07815	0.07446	0.07330	0.01003	0.10964	0.06278	0.02941	0.02553	0.02431
54	Male	0.00396	0.06366	0.17575	0.13667	0.08991	0.07863	0.06999	0.01163	0.12995	0.08869	0.03934	0.02742	0.01831
54	Female	0.00244	0.06479	0.15888	0.11461	0.08310	0.07943	0.07827	0.01088	0.11040	0.06358	0.03025	0.02636	0.02514
55	Male	0.00432	0.06945	0.21239	0.13006	0.09698	0.07976	0.09115	0.01268	0.16434	0.07699	0.04189	0.02362	0.03571
55	Female	0.00264	0.07010	0.18535	0.12912	0.10214	0.07899	0.08653	0.01177	0.13426	0.07449	0.04583	0.02122	0.02923
56	Male	0.00472	0.07588	0.21784	0.13608	0.10322	0.08612	0.09744	0.01386	0.16534	0.07809	0.04303	0.02478	0.03686
56	Female	0.00285	0.07567	0.19024	0.13434	0.10753	0.08451	0.09200	0.01271	0.13508	0.07537	0.04673	0.02215	0.03015
57	Male	0.00515	0.08280	0.22369	0.14254	0.10993	0.09296	0.10419	0.01512	0.16641	0.07927	0.04425	0.02603	0.03809
57	Female	0.00308	0.08178	0.19559	0.14006	0.11342	0.09056	0.09800	0.01373	0.13598	0.07633	0.04772	0.02316	0.03116
58	Male	0.00562	0.09035	0.23008	0.14960	0.11726	0.10043	0.11157	0.01650	0.16758	0.08056	0.04559	0.02740	0.03944
58	Female	0.00336	0.08921	0.20210	0.14702	0.12060	0.09792	0.10531	0.01498	0.13707	0.07750	0.04893	0.02440	0.03238
59	Male	0.00614	0.09871	0.23716	0.15742	0.12537	0.10870	0.11973	0.01803	0.16887	0.08199	0.04708	0.02891	0.04093
59	Female	0.00364	0.09665	0.20861	0.15398	0.12778	0.10529	0.11261	0.01623	0.13816	0.07867	0.05013	0.02564	0.03361
60	Male	0.00669	0.06630	0.22192	0.14322	0.11059	0.09898	0.09674	0.01684	0.18070	0.09784	0.06348	0.05125	0.04889
60	Female	0.00397	0.06158	0.18535	0.12613	0.10550	0.08353	0.06334	0.01518	0.14506	0.08292	0.06127	0.03822	0.01702
61	Male	0.00728	0.07215	0.22679	0.14859	0.11616	0.10462	0.10239	0.01833	0.18194	0.09920	0.06490	0.05268	0.05033
61	Female	0.00432	0.06701	0.19006	0.13118	0.11067	0.08883	0.06876	0.01651	0.14623	0.08416	0.06254	0.03952	0.01836
62	Male	0.00791	0.07839	0.23199	0.15432	0.12211	0.11065	0.10843	0.01991	0.18326	0.10066	0.06641	0.05421	0.05186
62	Female	0.00466	0.07228	0.19464	0.13609	0.11570	0.09398	0.07402	0.01781	0.14735	0.08537	0.06378	0.04079	0.01965
63	Male	0.00856	0.08483	0.23736	0.16023	0.12825	0.11686	0.11466	0.02155	0.18462	0.10216	0.06797	0.05579	0.05344
63	Female	0.00499	0.07740	0.19908	0.14086	0.12058	0.09898	0.07913	0.01907	0.14845	0.08655	0.06499	0.04202	0.02091
64	Male	0.00925	0.09167	0.24306	0.16650	0.13476	0.12346	0.12128	0.02329	0.18607	0.10375	0.06962	0.05747	0.05513
64	Female	0.00536	0.08314	0.20406	0.14620	0.12605	0.10459	0.08486	0.02049	0.14968	0.08786	0.06633	0.04341	0.02233
65	Male	0.01000	0.09910	0.28034	0.17949	0.13722	0.12985	0.09910	0.02518	0.22128	0.11215	0.06642	0.05845	0.02518
65	Female	0.00583	0.09043	0.23495	0.15961	0.14343	0.10543	0.11040	0.02229	0.17764	0.09665	0.07926	0.03841	0.04376

Age	Sex	General population	Dialysis	Dialysis with cancer					Transplant	Transplant with cancer				
				0-1 years	1-2 years	2-3 years	3-4 years	4+ years		0-1 years	1-2 years	2-3 years	3-4 years	4+ years
66	Male	0.01083	0.10733	0.28691	0.18698	0.14510	0.13780	0.10733	0.02726	0.22295	0.11406	0.06842	0.06047	0.02726
66	Female	0.00639	0.09911	0.24226	0.16763	0.15161	0.11397	0.11890	0.02443	0.17944	0.09863	0.08128	0.04051	0.04585
67	Male	0.01176	0.11655	0.29427	0.19537	0.15392	0.14670	0.11655	0.02961	0.22482	0.11619	0.07066	0.06273	0.02961
67	Female	0.00705	0.10935	0.25087	0.17709	0.16125	0.12404	0.12891	0.02695	0.18156	0.10096	0.08365	0.04300	0.04832
68	Male	0.01281	0.12695	0.30259	0.20485	0.16389	0.15675	0.12695	0.03225	0.22694	0.11860	0.07319	0.06528	0.03225
68	Female	0.00779	0.12083	0.26052	0.18770	0.17206	0.13533	0.14014	0.02978	0.18394	0.10357	0.08632	0.04578	0.05109
69	Male	0.01401	0.13884	0.31209	0.21568	0.17528	0.16824	0.13884	0.03527	0.22935	0.12135	0.07609	0.06820	0.03527
69	Female	0.00860	0.13339	0.27109	0.19931	0.18390	0.14768	0.15243	0.03287	0.18654	0.10643	0.08923	0.04882	0.05412
70	Male	0.01539	0.08146	0.28736	0.13966	0.13140	0.11133	0.10861	0.02911	0.24675	0.09063	0.08190	0.06069	0.05781
70	Female	0.00954	0.06490	0.23768	0.14310	0.10574	0.06490	0.08196	0.01727	0.19886	0.09946	0.06020	0.01727	0.03520
71	Male	0.01695	0.08972	0.29377	0.14740	0.13921	0.11932	0.11663	0.03206	0.24904	0.09340	0.08469	0.06354	0.06068
71	Female	0.01061	0.07217	0.24362	0.14977	0.11270	0.07217	0.08910	0.01921	0.20044	0.10123	0.06205	0.01921	0.03711
72	Male	0.01870	0.09898	0.30095	0.15607	0.14797	0.12829	0.12562	0.03538	0.25161	0.09650	0.08782	0.06675	0.06389
72	Female	0.01186	0.08068	0.25055	0.15756	0.12083	0.08068	0.09745	0.02147	0.20228	0.10331	0.06421	0.02147	0.03933
73	Male	0.02068	0.10946	0.30909	0.16589	0.15788	0.13843	0.13579	0.03912	0.25451	0.10001	0.09136	0.07037	0.06752
73	Female	0.01326	0.09020	0.25831	0.16629	0.12994	0.09020	0.10680	0.02401	0.20435	0.10563	0.06664	0.02401	0.04181
74	Male	0.02289	0.12116	0.31816	0.17685	0.16894	0.14974	0.14714	0.04330	0.25775	0.10392	0.09531	0.07441	0.07158
74	Female	0.01481	0.10074	0.26691	0.17595	0.14002	0.10074	0.11715	0.02681	0.20664	0.10820	0.06932	0.02681	0.04457
75	Male	0.02542	0.13455	0.34789	0.20949	0.17598	0.16422	0.16161	0.04809	0.28274	0.13052	0.09365	0.08072	0.07784
75	Female	0.01658	0.11279	0.31402	0.18255	0.12079	0.14176	0.13969	0.03002	0.25003	0.10629	0.03876	0.06169	0.05944
76	Male	0.02835	0.15006	0.35958	0.22366	0.19074	0.17920	0.17663	0.05363	0.28692	0.13558	0.09893	0.08607	0.08321
76	Female	0.01856	0.12625	0.32444	0.19496	0.13413	0.15479	0.15275	0.03360	0.25280	0.10959	0.04232	0.06516	0.06291
77	Male	0.03175	0.16806	0.37314	0.24010	0.20788	0.19658	0.19407	0.06006	0.29176	0.14145	0.10505	0.09228	0.08945
77	Female	0.02081	0.14156	0.33627	0.20906	0.14930	0.16959	0.16760	0.03767	0.25595	0.11334	0.04635	0.06910	0.06686
78	Male	0.03568	0.18886	0.38881	0.25910	0.22769	0.21667	0.21422	0.06750	0.29737	0.14824	0.11213	0.09946	0.09665
78	Female	0.02346	0.15959	0.35021	0.22567	0.16717	0.18703	0.18508	0.04247	0.25966	0.11776	0.05111	0.07374	0.07151
79	Male	0.04014	0.21247	0.40660	0.28066	0.25016	0.23947	0.23709	0.07593	0.30372	0.15595	0.12016	0.10761	0.10482
79	Female	0.02653	0.18047	0.36636	0.24491	0.18786	0.20723	0.20533	0.04803	0.26396	0.12288	0.05661	0.07912	0.07690
80	Male	0.04518	0.11890	0.37005	0.17696	0.15538	0.11890	0.12477	0.07169	0.33630	0.13286	0.11012	0.07169	0.07787
80	Female	0.03016	0.09841	0.34816	0.14868	0.12052	0.10826	0.10614	0.06368	0.32306	0.11589	0.08664	0.07391	0.07171
81	Male	0.05085	0.13382	0.38072	0.19090	0.16968	0.13382	0.13959	0.08068	0.34273	0.14127	0.11875	0.08068	0.08681
81	Female	0.03444	0.11238	0.35826	0.16187	0.13414	0.12207	0.11998	0.07272	0.32959	0.12443	0.09546	0.08285	0.08067
82	Male	0.05727	0.15071	0.39280	0.20668	0.18588	0.15071	0.15637	0.09087	0.35001	0.15078	0.12851	0.09087	0.09693
82	Female	0.03942	0.12862	0.37001	0.17721	0.14999	0.13814	0.13609	0.08324	0.33719	0.13436	0.10572	0.09325	0.09109

Age	Sex	General population	Dialysis	Dialysis with cancer					Transplant	Transplant with cancer				
				0-1 years	1-2 years	2-3 years	3-4 years	4+ years		0-1 years	1-2 years	2-3 years	3-4 years	4+ years
83	Male	0.06458	0.16995	0.40655	0.22465	0.20432	0.16995	0.17548	0.10247	0.35830	0.16161	0.13963	0.10247	0.10845
83	Female	0.04519	0.14745	0.38362	0.19499	0.16836	0.15676	0.15476	0.09542	0.34600	0.14586	0.11760	0.10530	0.10317
84	Male	0.07300	0.19211	0.42239	0.24535	0.22556	0.19211	0.19749	0.11583	0.36785	0.17409	0.15244	0.11583	0.12172
84	Female	0.05200	0.16967	0.39968	0.21597	0.19003	0.17874	0.17679	0.10980	0.35640	0.15944	0.13163	0.11952	0.11743
85	Male	0.08261	0.21740	0.48706	0.23751	0.22154	0.21740	0.21740	0.13107	0.43048	0.15340	0.13567	0.13107	0.13107
85	Female	0.05980	0.19512	0.49447	0.20025	0.19512	0.20777	0.19512	0.12627	0.45123	0.13183	0.12627	0.14000	0.12627
86	Male	0.09340	0.24579	0.50567	0.26517	0.24978	0.24579	0.24579	0.14819	0.44170	0.17008	0.15270	0.14819	0.14819
86	Female	0.06851	0.22354	0.51232	0.22849	0.22354	0.23574	0.22354	0.14466	0.46278	0.15011	0.14466	0.15810	0.14466
87	Male	0.10549	0.27761	0.52652	0.29617	0.28143	0.27761	0.27761	0.16738	0.45427	0.18877	0.17178	0.16738	0.16738
87	Female	0.07849	0.25611	0.53277	0.26084	0.25611	0.26780	0.25611	0.16573	0.47601	0.17105	0.16573	0.17884	0.16573
88	Male	0.11900	0.31316	0.54982	0.33081	0.31680	0.31316	0.31316	0.18881	0.46832	0.20966	0.19310	0.18881	0.18881
88	Female	0.08970	0.29268	0.55575	0.29719	0.29268	0.30380	0.29268	0.18940	0.49088	0.19457	0.18940	0.20214	0.18940
89	Male	0.13397	0.35256	0.57564	0.36919	0.35598	0.35256	0.35256	0.21257	0.48389	0.23280	0.21673	0.21257	0.21257
89	Female	0.10258	0.33471	0.58214	0.33895	0.33471	0.34516	0.33471	0.21660	0.50796	0.22159	0.21660	0.22891	0.21660
90	Male	0.15008	0.39495	0.60343	0.41050	0.39815	0.39495	0.39495	0.23813	0.50064	0.25770	0.24216	0.23813	0.23813
90	Female	0.11717	0.38232	0.61204	0.38625	0.38232	0.39202	0.38232	0.24741	0.52731	0.25220	0.24741	0.25923	0.24741
91	Male	0.16705	0.43961	0.63270	0.45401	0.44258	0.43961	0.43961	0.26505	0.51829	0.28394	0.26894	0.26505	0.26505
91	Female	0.13299	0.43394	0.64447	0.43754	0.43394	0.44283	0.43394	0.28081	0.54829	0.28539	0.28081	0.29211	0.28081
92	Male	0.18446	0.48543	0.66273	0.49865	0.48815	0.48543	0.48543	0.29268	0.53640	0.31085	0.29642	0.29268	0.29268
92	Female	0.14985	0.48895	0.67902	0.49220	0.48895	0.49698	0.48895	0.31641	0.57065	0.32076	0.31641	0.32715	0.31641
93	Male	0.20160	0.53054	0.69230	0.54260	0.53302	0.53054	0.53054	0.31987	0.55422	0.33735	0.32347	0.31987	0.31987
93	Female	0.16781	0.54755	0.71583	0.55043	0.54755	0.55466	0.54755	0.35433	0.59447	0.35845	0.35433	0.36448	0.35433
94	Male	0.21751	0.57241	0.71974	0.58339	0.57467	0.57241	0.57241	0.34512	0.57077	0.36194	0.34858	0.34512	0.34512
94	Female	0.18700	0.61017	0.75515	0.61265	0.61017	0.61629	0.61017	0.39485	0.61992	0.39871	0.39485	0.40436	0.39485
95	Male	0.22528	0.59285	0.73314	0.60331	0.59501	0.59285	0.59285	0.35744	0.57885	0.37395	0.36084	0.35744	0.35744
95	Female	0.19743	0.64420	0.77653	0.64647	0.64420	0.64979	0.64420	0.41688	0.63375	0.42059	0.41688	0.42604	0.41688
96	Male	0.24431	0.64293	0.76597	0.65211	0.64482	0.64293	0.64293	0.38764	0.59864	0.40337	0.39088	0.38764	0.38764
96	Female	0.22285	0.72714	0.82862	0.72888	0.72714	0.73143	0.72714	0.47055	0.66746	0.47392	0.47055	0.47887	0.47055
97	Male	0.26334	0.69301	0.79879	0.70090	0.69464	0.69301	0.69301	0.41783	0.61843	0.43279	0.42091	0.41783	0.41783
97	Female	0.23874	0.77899	0.86119	0.78040	0.77899	0.78246	0.77899	0.50410	0.68854	0.50726	0.50410	0.51190	0.50410
98	Male	0.28237	0.74309	0.83161	0.74969	0.74445	0.74309	0.74309	0.44803	0.63822	0.46221	0.45095	0.44803	0.44803
98	Female	0.25276	0.82474	0.88992	0.82585	0.82474	0.82749	0.82474	0.53371	0.70713	0.53668	0.53371	0.54103	0.53371
99	Male	0.30140	0.79317	0.86444	0.79849	0.79427	0.79317	0.79317	0.47822	0.65801	0.49163	0.48098	0.47822	0.47822
99	Female	0.26774	0.87362	0.92062	0.87442	0.87362	0.87560	0.87362	0.56534	0.72700	0.56811	0.56534	0.57217	0.56534

Age	Sex	General population	Dialysis	Dialysis with cancer					Transplant	Transplant with cancer				
				0-1 years	1-2 years	2-3 years	3-4 years	4+ years		0-1 years	1-2 years	2-3 years	3-4 years	4+ years
100	Male	0.32043	0.84325	0.89726	0.84728	0.84408	0.84325	0.84325	0.50841	0.67780	0.52105	0.51101	0.50841	0.50841
100	Female	0.28385	0.92618	0.95364	0.92665	0.92618	0.92734	0.92618	0.59935	0.74836	0.60191	0.59935	0.60565	0.59935

Based on life tables from the Australian Bureau of Statistics (ABS) [4], standardized mortality ratios (SMRs) for dialysis and transplant estimated from ANZDATA annual reports [2], and relative survival with cancer derived from Australian Institute of Health and welfare (AIHW) cancer data [3]

Supplementary Table 6.S7: Annual incidence rates of cancer for dialysis patients compared with the general population, by 5-year age group and sex

Age	General population		Dialysis	
	Female	Male	Female	Male
0-4	0.00066	0.00073	0.00105	0.00116
5-9	0.00038	0.00046	0.00061	0.00073
10-14	0.00050	0.00051	0.00079	0.00081
15-19	0.00085	0.00085	0.00136	0.00135
20-24	0.00117	0.00110	0.00187	0.00176
25-29	0.00190	0.00154	0.00303	0.00245
30-34	0.00324	0.00215	0.00518	0.00342
35-39	0.00472	0.00306	0.00753	0.00489
40-44	0.00747	0.00485	0.01193	0.00774
45-49	0.01115	0.00801	0.01780	0.01280
50-54	0.01517	0.01410	0.02423	0.02251
55-59	0.01895	0.02333	0.03026	0.03725
60-64	0.02523	0.03597	0.04028	0.05744
65-69	0.03309	0.05103	0.05283	0.08148
70-74	0.04134	0.06377	0.06600	0.10182
75-79	0.04696	0.07609	0.07497	0.12149
80-84	0.05276	0.08652	0.08424	0.13814
85-89	0.05699	0.09294	0.09100	0.14839
90+	0.05295	0.09149	0.08455	0.14607

Based on cancer data from the Australian Institute of Health and Welfare (AIHW) [3] and incidence rate ratio (IRR) of 1.60 estimated from AIHW cancer data and Wong et al., 2016 [5]

Supplementary Table 6.S8: Distributions and parameters used to simulate probabilities of kidney transplant and de-novo cancer after kidney transplant

Parameter, mean (SE)	**Kidney transplant**		***De-novo* cancer after transplant**	
	Deceased donor	Living donor	Deceased donor	Living donor
Distribution	Weibull	Generalized F (stable)	Weibull	Weibull
Shape	0.76 (0.01)	-	0.92 (0.05)	0.99 (0.04)
Scale	0.01 (0.0004)	-	0.000003 (0.000002)	0.00003 (0.00001)
Mu (μ)	-	6.81 (0.55)	-	-
Sigma (σ)	-	2.98 (0.31)	-	-
Q	-	-3.01 (0.93)	-	-
P	-	0.95 (0.65)	-	-
Number of previous transplants	0.29 (0.08)	0.12 (0.32)	0.24 (0.12)	0.08 (0.11)
Blood group A	0.49 (0.03)	-0.33 (0.11)	0.23 (0.13)	-0.09 (0.09)
Blood group B	-0.10 (0.04)	-0.05 (0.15)	0.18 (0.18)	-0.39 (0.16)
Blood group AB	1.05 (0.06)	-0.22 (0.29)	-0.01 (0.28)	-0.20 (0.26)
Female	-0.10 (0.03)	-0.002 (0.10)	-0.08 (0.12)	-0.05 (0.09)
Age at waitlisting	-0.002 (0.001)	0.02 (0.004)	-	-
Number of comorbidities	-0.01 (0.01)	0.29 (0.06)	-0.15 (0.07)	-0.26 (0.09)
Age at transplant	-	-	0.01 (0.005)	-0.001 (0.003)
DBD standard criteria donor	-	-	1.43 (0.31)	-
DBD expanded criteria donor	-	-	1.30 (0.33)	-
Donor female	-	-	-0.24 (0.12)	0.28 (0.09)
Donor age	-	-	-0.01 (0.01)	-0.01 (0.003)
KDPI	-	-	0.02 (0.004)	-

SE, standard error; DCD, donation after circulatory death; DBD, donation after brain death; KDPI, kidney donor profile index

Supplementary Table 6.S9: Distributions and parameters used to simulate probabilities of transplant failure

Parameter, mean (SE)	Living donor transplant failure		Deceased donor transplant failure	
	Without cancer	With cancer	Without cancer	With cancer
Distribution	Spline	Generalised gamma (Prentice 1975)	Spline	Generalised gamma (Prentice 1975)
Mu (μ)	-	9.58 (0.13)	-	8.28 (0.27)
Sigma (σ)	-	0.56 (0.04)	-	0.49 (0.07)
Q	-	2.27 (0.20)	-	2.54 (0.48)
Gamma 0 (γ0)	-4.26 (0.14)	-	-5.04 (0.18)	-
Gamma 1 (γ1)	0.41 (0.02)	-	0.44 (0.03)	-
Gamma 2 (γ2)	0.09 (0.01)	-	0.04 (0.004)	-
Gamma 3 (γ3)	-0.30 (0.09)	-	-0.09 (0.05)	-
Gamma 4 (γ4)	0.47 (0.31)	-	0.14 (0.18)	-
Gamma 5 (γ5)	-1.04 (0.45)	-	-0.50 (0.34)	-
Gamma 6 (γ6)	0.94 (0.26)	-	0.51 (0.25)	-
Knot 1	5.88	-	4.44	-
Knot 2	7.47	-	6.66	-
Knot 3	8.02	-	7.41	-
Knot 4	8.41	-	7.91	-
Knot 5	8.78	-	8.32	-
Knot 6	9.79	-	9.22	-
Number of previous transplants	0.22 (0.05)	0.07 (0.06)	0.37 (0.04)	0.06 (0.08)
Blood group A	-0.04 (0.04)	0.04 (0.05)	0.05 (0.05)	0.04 (0.07)
Blood group B	-0.11 (0.07)	0.004 (0.09)	0.09 (0.08)	-0.17 (0.10)
Blood group AB	0.11 (0.11)	-0.17 (0.15)	0.14 (0.11)	-0.58 (0.14)
Female	-0.08 (0.04)	0.05 (0.05)	0.06 (0.05)	0.06 (0.08)
Number of comorbidities	0.04 (0.04)	-0.15 (0.05)	0.20 (0.03)	-0.05 (0.04)
Age at transplant	-0.03 (0.001)	0.02 (0.004)	-0.03 (0.002)	0.07 (0.01)
DBD standard criteria donor	-	-	0.003 (0.08)	0.59 (0.18)
DBD expanded criteria donor	-	-	0.10 (0.09)	0.44 (0.21)
Donor female	0.61 (0.04)	-0.14 (0.05)	0.02 (0.05)	-0.03 (0.07)
Donor age	-0.0007 (0.002)	-0.01 (0.002)	0.002 (0.003)	-0.005 (0.01)
KDPI	-	-	0.01 (0.002)	0.002 (0.002)
Age at cancer diagnosis	-	-0.03 (0.004)	-	-0.08 (0.01)

SE, standard error; DCD, donation after circulatory death; DBD, donation after brain death; KDPI, kidney donor profile index

Supplementary Table 6.S10: Utility values for cancer by site and stage at diagnosis

Cancer site	Incidence (2011)	Proportion	Utility	Lower	Upper
Stage I					
Breast	6,110	0.10	0.73	0.56	0.90
Colorectal	3,098	0.05	0.71	0.64	0.77
Lung	1,183	0.02	0.73	0.59	0.86
Melanoma	8,730	0.14	0.69	0.58	0.80
Prostate	7,186	0.11	0.87	-	-
Total	26,307	0.42	0.75	0.58	0.83
Stage II					
Breast	4,936	0.08	0.64	0.48	0.79
Colorectal	3,399	0.05	0.64	0.56	0.72
Lung	662	0.01	0.69	0.56	0.81
Melanoma	1,577	0.02	0.69	0.58	0.80
Prostate	9,245	0.15	0.87	-	-
Total	19,819	0.31	0.75	0.53	0.77
Stage III					
Breast	1,721	0.03	0.61	0.45	0.77
Colorectal	3,299	0.05	0.64	0.56	0.72
Lung	1,131	0.02	0.58	0.27	0.89
Melanoma	331	0.01	0.62	0.54	0.70
Prostate	2,246	0.04	0.55	-	-
Total	8,728	0.14	0.60	0.48	0.76
Stage IV					
Breast	660	0.01	0.61	0.35	0.86
Colorectal	2,474	0.04	0.42	0.30	0.53
Lung	4,273	0.07	0.75	0.66	0.84
Melanoma	233	0.00	0.66	0.58	0.80
Prostate	836	0.01	0.55	-	-
Total	8,476	0.13	0.62	0.51	0.74
All stages					
Breast	13,427	0.21	0.67	0.51	0.84
Colorectal	12,270	0.19	0.61	0.53	0.69
Lung	7,249	0.11	0.71	0.58	0.85
Melanoma	10,871	0.17	0.69	0.58	0.80
Prostate	19,513	0.31	0.82	-	-
Total	63,330	1.00	0.71	0.54	0.79

Based on cancer data from the Australian Institute of Health and Welfare (AIHW) [3] and a systematic review by Pourrahmat et al., 2021 [6]

6.12.3 Appendix 1 – Health state transitions

Patients entered the model on the deceased donor transplant waitlist, receiving dialysis. If they developed cancer whilst waiting, they were moved off waitlist and continued dialysis but were ineligible for a transplant, consistent with national guidelines [1]. Some patients found a suitable living donor (either a relative/friend or through paired kidney exchange) whilst on the deceased donor waitlist [2], while others received a deceased donor kidney from the waitlist, or died.

We assumed that living donor transplants did not carry a risk of PBM transmission, so these recipients remained in the transplanted health state until transplant failure, *de-novo* cancer, or death. If PBM was transmitted from a deceased donor to a recipient, they had the same probability of transplant failure or death as a recipient diagnosed with *de-novo* cancer. We assumed that the transmission would be diagnosed after nine months (i.e., three model cycles), which was the average time from transplant to diagnosis among nine kidney transplant recipients with transmission from a donor with brain cancer identified in published case reports [7-12]. After nine months, the transplanted kidney was removed, and the patient remained in transplant failure with donor-transmitted cancer health state until death. Recipients without a transmission remained in the transplanted health state until they developed a *de-novo* cancer, transplant failure, or death.

After transplant failure, patients returned to dialysis but did not return to the waitlist. Instead, they remained on dialysis until death. We did not account for subsequent transplants in our model as 89% of kidney transplants are in first-time recipients [2]. We also assumed cancer was irreversible, so once a patient was diagnosed with cancer (*de-novo* or donor-transmitted) the

cancer remained until death. We acknowledge that in contemporary clinical practice cancer can be effectively treated, however we did not account for this to reduce model complexity and because patients with cancer may still have worse outcomes and higher healthcare utilization than those without cancer, even after their cancer is in remission.

Evidence of the risk of transmission from donors with PBM is limited, and some population-level studies have failed to identify any cases of transmission [13,14]. We therefore relied on upper-limit estimates of transmission risk used in national donation guidelines [1]. We assumed that all potential donors with PBM who would currently be accepted for transplantation were classified as low-risk, which means a transmission risk of 2%. For new donors that would be accepted under our proposed interventions, those classified as not contraindicated/minimal-risk had a transmission risk of 0.1%, low-risk was 2%, and intermediate-risk was 6.4%. Since our transmission risk estimates were based on upper limits, we assumed they already accounted for the additional risk associated with radiation, chemotherapy, craniotomy, or ventriculoperitoneal shunt in the donor (<1% increase in transmission risk according to national guidelines [1]). We estimated the weighted average transmission risk among all newly accepted donors under each intervention.

We assumed that patients with a donor-transmitted cancer would experience the same rates of transplant failure and mortality as those who develop *de-novo* cancer. Evidence surrounding transplant recipient outcomes after donor brain cancer transmission is scarce, largely based on reviews of limited case reports [15,16]. A US registry-based study included 14 transplant recipients with confirmed transmission from a donor with a malignant central nervous system (CNS) tumor [17]. Of these, 11 (79%) died within 26 months follow-up, however

this was only reported in aggregate across all transplanted organs. Published reviews [15,16] identified nine unique case reports of transmissions from five donors with glioblastoma multiforme [8-10,15,18,19], one with malignant meningioma [7], one with malignant glioma [20], one with CNS non-Hodgkin's lymphoma [12] (which would be contraindicated in current national guidelines [1]), and one with medulloblastoma [11]. They donated organs to 23 recipients (14 kidney, four liver, three heart, one lung, and one kidney-pancreas), with 15 transmissions (eight kidney, four liver, one heart, one lung, and one kidney-pancreas). The lung recipient[15] and three liver recipients [18-20] died within 10 months post-transplant, while the fourth liver recipient's outcome was not reported[15]. Outcomes for kidney recipients were more favorable; six had their transplanted kidney removed and were still alive on dialysis after follow-up[7-11], one had their transplanted kidney removed and after 10 months in remission was retransplanted with no evidence of recurrence[12], one had their transplanted kidney removed and underwent chemotherapy but died eight weeks later due to cytomegalovirus pneumonia and pericarditis with autopsy showing no signs of tumor recurrence[12], and one kidney-pancreas recipient had their transplanted pancreas removed after three days due to arterial thrombosis, and their transplanted kidney removed after four months but died one month later [11]. Transmission was identified on average nine months after transplant (range 4 – 18 months).

We assumed that all patients with a transmitted cancer would have their transplanted kidney removed (i.e., nephrectomy) after nine months. Although it may be possible to treat a transmitted cancer without removing the transplanted kidney, our assumption that all patients would undergo nephrectomy was conservative (i.e., favored current practice), and was consistent with available case-reports.

A case-control study of 12,805 kidney recipients in the Netherlands reported median survival after *de-novo* cancer diagnosis of 2.1 years [21]. Considering that only two of nine (22%) transmissions from case reports of kidney recipients resulted in death during follow- up, our assumption that outcomes for patients with a donor-transmitted cancer would be similar to those with *de-novo* cancer seems appropriate.

6.12.4 Appendix 2 – Model inputs

6.12.4.1 Transition probabilities

6.12.4.1.1 Mortality

Mortality was based on Australian life tables for 2017-2019, stratified by age and sex [4]. We adjusted mortality by 10-year age group and sex specific standardized mortality ratios (SMRs) for dialysis and transplant derived from figures published in the ANZDATA annual report [22,23] (Table 6.S4). For patients with cancer, we further adjusted mortality (multiplicatively) based on relative survival reported by the Australian Institute for Health and Welfare (AIHW) for 2013-2017, stratified by 5-year age group, sex, and years since diagnosis [3] (Table 6.S5). Average relative survival across all cancer sites was weighted by annual incidence of each cancer. We applied SMRs for the nearest age-group to each simulated patient. Mortality rates applied to all simulated patients by age, sex, treatment, and years since cancer diagnosis are summarized in Table 6.S6.

6.12.4.1.2 Cancer

The probability of developing any cancer whilst on dialysis (i.e., on the waiting list or after transplant failure) was based on cancer incidence reported by AIHW, stratified by 5-year age group and sex, and summed over all cancer sites [3]. We multiplied this by an estimated

incidence rate ratio (IRR) of 1.60, based on the overall incidence of cancer among dialysis patients (22.2/1,000) [5] divided by the overall incidence of cancer in the Australian population (1390.4/100,000) [3]. Annual incidence rates of cancer among dialysis patients by 5-year age group and sex are presented in Table 6.S7.

For patients with a deceased donor kidney transplant, we determined the probability of developing *de-novo* cancer using data provided by ANZDATA. We compared all 11 default time-to-event models as well as a spline model from the flexsurv R package [24] to estimate the time to cancer after transplantation, adjusted for patient and donor characteristics. We selected the most appropriate model based on the Akaike Information Criterion (AIC) as well as by assessing visual fit. In the economic model, the probability of developing cancer was dependent on individuals' patient and donor characteristics. We used the modelled distribution of time to cancer to determine the probability of developing cancer during each 3-month cycle.

If a deceased donor had brain cancer, there was a risk of cancer transmission in addition to the underlying risk of the recipient developing *de-novo* cancer. We assumed that under current practice, donors with brain cancer would only be accepted for transplantation if they were considered minimal or low risk according to national donation guidelines [1]. We therefore applied the upper-limit estimate for transmission risk from low-risk brain cancers of 2% to all transplants regardless of patient or donor characteristics.

6.12.4.1.3 Transplant and transplant failure

We created separate time-to-event models to estimate time to living donor transplant and time to deceased donor transplant, adjusted for patient characteristics. The most appropriate

model was selected based on AIC and visual fit, and the modelled distribution determined the probability of transplant during each cycle. For simplicity, we assumed that being removed from the waiting list due to cancer, death on the waiting list, living donor transplant, and deceased donor transplant were independent and mutually exclusive events.

Time-to-event models for time to transplant failure from transplantation and from cancer diagnosis were adjusted for patient and donor characteristics, and we selected the most appropriate model based on AIC and visual fit. We assumed that death, cancer diagnosis, and transplant failure were independent and mutually exclusive events.

The distributions and parameters for models for the probabilities of transplant, cancer, and transplant failure are presented in Table 6.S8 and Table 6.S9.

6.12.4.2 Comparators

Reasons for underutilization of kidneys from deceased donors with PBM include inaccurate perception of PBM risk in potential donors with insufficient medical history available at the time of donation decisions, inconsistent decisions among different clinicians with tendencies to focus on increased relative risk rather than absolute risk, and reluctance to accept potential donors labeled as intermediate risk (6.4% transmission risk) according to donation guidelines.

We therefore considered three interventions that have previously been proposed to address these issues [25], and compared them with current practice (i.e., individual clinicians deciding which potential donors with PBM to accept or decline). Exactly how these interventions might be implemented is beyond the scope of this study, but briefly they were: 1) decision support

for clinicians in accurately estimating absolute donor risk for cancer transmission; 2) improved data accuracy with real-time data-linkage to hospital records and cancer registries to improve classification of potential donor cancer type and hence transmission risk; and 3) increased risk-tolerance to allow use of donors with intermediate-risk PBM (estimated transmission risk 6.4%) [1,25].

Both real-time data-linkage and increase risk tolerance were assumed to be in combination with decision support to ensure that donation decisions would adhere to guidelines [1]. In our previous study we did not identify any potential donors who would have been accepted if all three interventions (decision support, real-time data linkage, and increased risk tolerance) had been applied together. Nor did we identify any actual donors who would have been declined under all three interventions in combination with each other. In the absence of any evidence that combining these interventions would impact the number of donors with PBM or their average transmission risk [25], we therefore did not consider the combined effect of these three interventions.

Compared with current practice, each intervention would alter the model in two ways: 1) increasing the probability of receiving a deceased donor transplant (by increasing the number of deceased donor kidneys available), and 2) changing the cancer transmission risk associated with deceased donor transplant (e.g., by introducing more donors with PBM).

We estimated potential impacts using data from a published study of 472 potential donors from NSW 2010-2013, of whom 340 (72%) became actual donors (including 8 with PBM), and 172 (28%) were declined due to cancer [25]. We assumed two kidneys were available for transplant from all 340 donors, which is consistent with national average of 1.91 (888

kidneys from 463 donors) in 2020 [26]. We also assumed two kidneys per donor would be available from any additional donors with PBM, hence the proportional increase in donation would be the same regardless of whether it was expressed in terms of donors or kidneys.

6.12.4.3 Utility values

For patients on dialysis or with a transplant, we calculated the simple average of utilities reported in two studies on quality of life in chronic kidney disease (CKD): an Australian meta-analysis [27] and a multi-national cohort study [28]. The utility values for patients on dialysis from these quality-of-life studies were 0.70 and 0.76, hence the average utility applied to the model was 0.73. For patients with a kidney transplant, the utility values were
0.82 and 0.84, hence the average 0.83 was used.

For patients with cancer, we used utility values for the five most common cancer sites (breast, colorectal, lung, melanoma, and prostate) from a recent systematic review [6]. We calculated an average utility for each cancer stage (I, II, III, and IV) as well as overall, weighted by annual incidence by site and stage in Australia in 2011 reported by the AIHW [3]. We applied the average utility across all cancer stages (0.71) to patients with *de-novo* cancer. When a transmission occurs, the cancer in the recipient is likely to be a more advanced stage compared with a *de-novo* cancer since it has necessarily already metastasized in the donor. Therefore, we applied the weighted average utility for stage IV cancers (0.62) to patients with a donor-transmitted cancer. The utility values by cancer site and stage are summarized in Table 6.S10.

We assumed that the decrement in quality of life associated with kidney failure was independent of the decrement associated with cancer. Therefore, for patients with both kidney failure and cancer we multiplied the utility values for kidney failure and cancer together. For patients on dialysis with cancer, their utility value was 0.52 (0.73 x 0.71) for *de-novo* cancer and 0.45 (0.73 x 0.62) if the cancer was transmitted. For those with a kidney transplant and cancer, their utility value was 0.59 (0.83 x 0.71) for *de-novo* cancer and 0.51 (0.83 x 0.62) if the cancer was transmitted.

We did not account for a potential quality of life decrement for recipients of a kidney from a donor with PBM, associated with fear of transmission occurring. Such a decrement would likely be small in comparison to the improvement in quality of life after receiving a kidney transplant, and for patients who agree to accept a kidney with a risk of cancer transmission, this fear may be less likely to influence their quality of life.

6.12.4.4 Costs

All costs were converted to 2021 Australian dollars (AUD) using the consumer price index (CPI) for health, averaged across each calendar year [29]. We included costs associated with dialysis, kidney transplantation, and cancer treatment. All costs were separated into the first 3 months, months 4 to 12, year 2, year 3, year 4, and all subsequent years. Calculations of all costs are available here: https://github.com/james-hedley/PBM_economic_evaluation.

6.12.4.4.1 Dialysis

The cost of dialysis treatment was calculated as an average across home hemodialysis, hospital hemodialysis, and home peritoneal dialysis, weighted by the proportion of patients

using each modality reported in the ANZDATA annual report 2020 [2]. The annual cost of home hemodialysis and home peritoneal dialysis were derived from an Independent Hospital Pricing Authority (IHPA) costing study of home delivered dialysis [30], while the cost of hospital hemodialysis was based on Australian-refined Diagnosis Related Group (AR-DRG) L61Z (Hemodialysis) from the National Hospital Cost Data Collection (NHCDC) 2018-2019 [31].

6.12.4.4.2 Transplant

The costs associated with transplant that we included in our model were: organ retrieval, transplant procedure, drug utilization, and nephrologist consultations. These were based on the costs used in the Kidney Health Australia report of the economic impact of end-stage kidney disease in Australia: projections to 2020 [32].

The cost of retrieving a living donor kidney was based on the average of AR-DRGs for Kidney, Ureter and Major Bladder Interventions for Non-Neoplasm with major, intermediate, and minor complications (L04A, L04B, and L04C), weighted by the number of separations from the NHCDC 2018-2019 [31]. For deceased donors, the cost of kidney retrieval was based on an estimate from the Kidney Health Australia report [32].

The cost of transplanting a kidney into a recipient (from a living or deceased donor) was based on the average of AR-DRGs L10A (Kidney Transplant, Age <=16 Years or Major Complexity) and L10B (Kidney Transplant, Age >=17 Years and Minor Complexity), weighted by the number of separations from the NHCDC 2018-2019 [31].

We included costs for the most commonly prescribed induction, immunosuppression, and prophylaxis drugs for transplant recipients based on the ANZDATA annual report 2020 [2]. Induction drugs were basiliximab and thymoglobulin, immunosuppression drugs were tacrolimus, mycophenolate, and prednisolone, and prophylaxis drugs were valganciclovir, trimethoprim + sulfamethoxazole, and nystatin. The proportion of patients prescribed each drug was based on the ANZDATA annual report 2020 [2], while dosages were based on product information available from the Therapeutic Goods Administration (TGA) [33]. Where information was unavailable, we relied on expert opinion from two specialist nephrologist co-authors (MW and AW). The total costs for induction drugs were derived from a review of the Australian organ donation, retrieval, and transplantation system, while unit costs for immunosuppression and prophylaxis drugs were extracted from the Pharmaceutical Benefits Scheme Schedule [34].

We did not include additional costs for cancer screening or monitoring in recipients of a kidney from a donor with known PBM. It is unpredictable where the transmitted cancer might first appear in the recipient, and in the absence of a global test for cancer we assumed that monitoring would be included in routine post-transplant follow-up.

6.12.4.4.3 Nephrologist visits

The frequency of nephrologist consultations for patients on dialysis or with a kidney transplant was based on national guidelines [35] and the expert opinion of two specialist nephrologist co-authors (MW and AW). The cost associated with each nephrologist visit was based on Medicare Benefits Schedule items 104 (initial visit) and 116 (subsequent visit) [36].

6.12.4.4.4 Cancer

The costs associated with cancer diagnosis and treatment were based on a longitudinal study of health care in 266,000 people from NSW aged 45 and over, and included costs associated with hospital admissions, emergency department presentations, government subsidized prescription medications (PBS), and government subsidized medical services (MBS) [37]. Costs were provided for each of the first 5 years after diagnosis, and we assumed that all subsequent years would incur the same cost as year 5. For *de-novo* cancers we used the overall cost across all cancers. There were no costs reported specifically for brain cancer. We assumed that transmitted cancers would incur a higher cost due to their advanced stage at diagnosis, hence for transmitted cancers we used the cost associated with kidney cancer because this was higher than the average across all cancers and because transmitted cancers were likely to be diagnosed in the transplanted kidney.

6.12.4.4.5 Nephrectomy

Patients with a donor-transmitted cancer have their transplanted kidney removed after at most nine months. The cost of kidney removal is based on the average of AR-DRGs for Kidney, Ureter and Major Bladder Interventions for Non-Neoplasm with major, intermediate, and minor complications (L04A, L04B, and L04C), weighted by the number of separations from the NHCDC 2018-2019 [31].

6.12.4.5 Uncertainty analyses

For the probabilistic sensitivity analysis, we assumed a uniform distribution for discount rates (0-10%) and the increase in donation and average transmission risk (0-200% of base- case value). Statistical model parameters followed normal distributions based on means and

standard errors (SE). Utilities followed beta distributions based on mean (base-case) and reported SE [27] (for cancer utilities we assumed minimum and maximum reported utilities corresponded to the 0.05th and 99.95th percentiles [6]). We considered two alternative methods for combining simultaneous utilities: the minimum (upper estimate), and the sum minus one (lower estimate) [38]. Costs followed uniform distributions (±15%) [39].

We assessed which model inputs had the most influence on results by determining the marginal impact of a percentage change in each input, using linear regression of costs and QALYs adjusted for the randomly selected values of all inputs across 10,000 probabilistic sensitivity analysis simulations. We also performed an extreme worst-case scenario analysis where cancer transmission would result in immediate death for the recipient, as well as threshold analysis where the average transmission risk of new donors under decision support with increased risk tolerance was varied in increments of 5% from 10% to 50%, to determine how high the transmission risk would need to be before the intervention would no longer be cost-effective.

6.12.4.6 Willingness-to-pay threshold

Our willingness-to-pay (WTP) threshold was $28,000 per QALY as this was used in a recent Australian economic evaluation of kidney donation policy [39] and has been demonstrated to be appropriate in an Australian setting [40]. This is lower than the commonly used $50,000 threshold [41], hence the probability of interventions being cost-effective may be conservative.

6.12.5 References

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Chapter 7: Comparison of alternative model structures

7.1 Preface

This chapter presents an exploratory analysis that aimed to explore the impact of changes to model structure on the results and conclusions of the economic evaluation presented in Chapter 6 of this thesis.

This is an original chapter and has not been published previously.

7.1.1 Impact of including cancer after living donor transplant

This chapter compared an individual-level simulation with using average characteristics, a cohort-level model, and a discrete event simulation (DES). However, an earlier version of the economic evaluation presented in Chapter 6 included different health states than the final version. Specifically, this earlier version did not include health states for cancer diagnosis after living donor transplant, since this was not originally considered important to include in the model. This earlier model structure is presented in Figure 7.1.

As a result of this change, I was also able to compare results with and without inclusion of these post-living donor transplant health states. The results in terms of both incremental costs and incremental QALYs were very similar, and the largest difference (incremental costs under decision support with increased risk tolerance) was only 12%. The 95% confidence intervals for all original results included the point estimates from the final results, and vice versa, suggesting there was no significant difference between the two model structures. Importantly, the conclusions remained the same regardless of whether or not these additional health states were included. The results of the economic evaluation from the original and final versions of the model structure are presented in Table 7.1.

Figure 7.1: Previous version of the Markov model used to simulate individual patients in the economic evaluation presented in Chapter 6

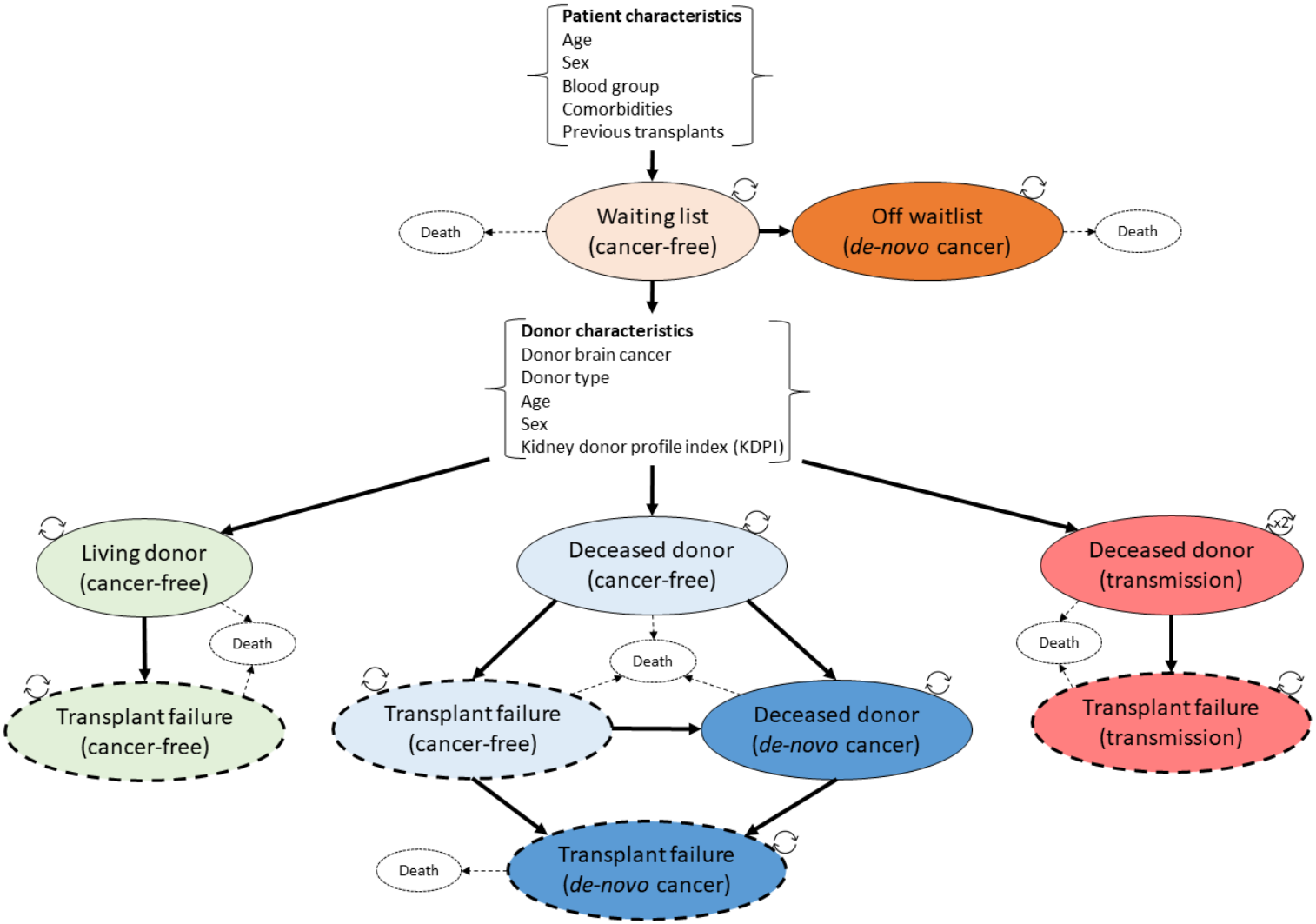


Table 7.1: Comparison of results from the economic evaluation presented in Chapter 6 based on the original vs. final model structure

	Original	Final
Decision support		
Incremental QALYs	3.1	3.3
Incremental QALYs 95% CI	(-4.0, 16.4)	(-7, 17.3)
Incremental costs	-$361,144	-$349,563
Incremental costs 95% CI	(-$1,583,112, $212,890)	(-$1,387,484, $521,979)
Proportion dominant	71%	78%
Proportion cost-effective	75%	82%
Decision support + real-time data linkage		
Incremental QALYs	6.3	6.8
Incremental QALYs 95% CI	(-4.7, 23.4)	(-6.8, 25.4)
Incremental costs	-$729,334	-$712,912
Incremental costs 95% CI	(-$2,372,786, $233,308)	(-$2,093,160, $414,348)
Proportion dominant	76%	80%
Proportion cost-effective	79%	84%
Decision support + increased risk tolerance		
Incremental QALYs	20.7	18.8
Incremental QALYs 95% CI	(-4.0, 50.7)	(-9.5, 51.1)
Incremental costs	-$2,463,977	-$2,159,736
Incremental costs 95% CI	(-$5,201,290, -$234,778)	(-$4,607,211, $120,887)
Proportion dominant	93%	87%
Proportion cost-effective	94%	88%

7.2 Introduction

Markov models are frequently used in economic evaluations of health technologies and public health interventions [1-4], and the advantages over alternatives such as decision trees and dynamic agent-based models are well understood [4]. Guidelines have been developed to assist in selecting an appropriate model structure [4,5], and although more complex models are sometimes superior [6], in general there is a preference towards more parsimonious Markov models where possible [7]. However, there is a dearth of research into the impacts on results of alternative models.

Empirical case studies of economic evaluations have compared results obtained from unilateral variations in model structure. In an evaluation of therapies used to treat metastatic melanoma, treatment was cost-effective when based on a patient-level simulation (10,000 patients and 100 repetitions), but not cost-effective when based on a cohort-level Markov model [8]. Another evaluation of interventions in hypertension found virtually no difference between five Markov models with varying levels of complexity (number of health states) [9]. Similarly, an evaluation of transplanting lower quality kidneys reported similar results from Markov models with 6-month or 12-month cycles as well as for discrete event simulations (DES), compared over time horizons of 5 and 20 years [10].

We sought to explore how variations to model structure could impact results and conclusions from a single economic evaluation. Specifically, we considered as a case study an economic evaluation of increasing utilization of kidneys for transplantation from deceased donors with primary brain malignancy (PBM), which was based on an individual patient-level simulation Markov model [11].

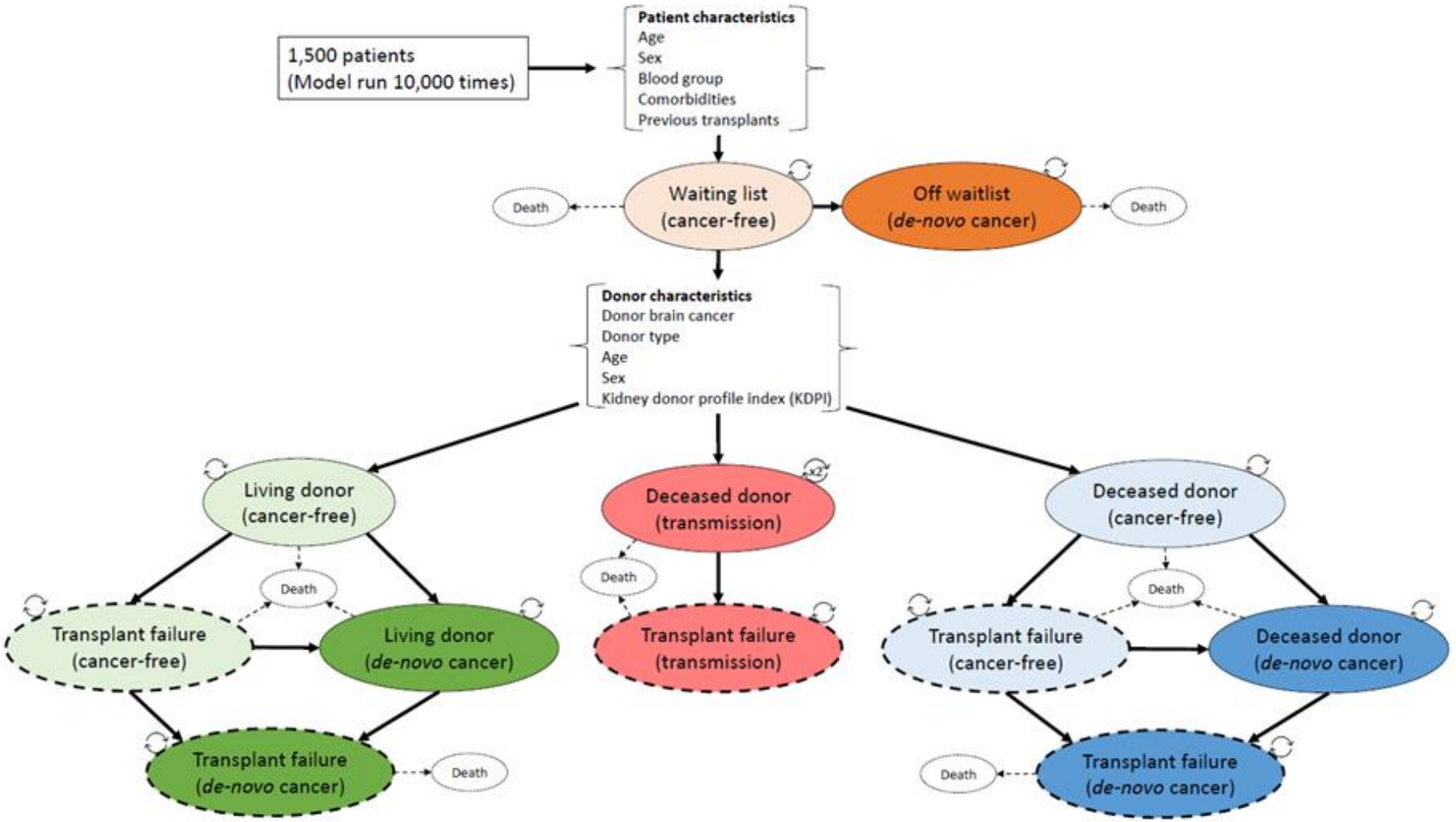
7.3 Methods

7.3.1 Case study economic evaluation

The motivating example and case study economic evaluation used to compare changes to model structure was a cost-effectiveness analysis of increasing utilization of kidneys for transplantation from deceased donors with primary brain malignancy (PBM economic evaluation) [11]. Accepting donors with brain cancer increases the number of kidneys available for transplant (i.e., increased probability of receiving a transplant), but carries an additional risk of cancer transmitting from donor to recipient (i.e., increased probability of developing

cancer after transplant). Details of this model have been described previously [11]. Briefly, 1,500 patients with kidney failure transitioned between health states for waiting list, cancer, transplant, transplant, transplant failure, and death. The model was run with 3-monthly cycles over a 25-year time horizon, with 10,000 simulations, and the model structure is shown in Figure 7.2 (reproduced from Figure 1 in Hedley et al., 2023 [11]). For this study, we only considered the most cost-effective intervention, which was increased risk tolerance (in conjunction with decision support).

Figure 7.2: Structure of the Markov model used to simulate individual patients



7.3.2 Alternative model structures

We considered four alternative model structures: 1) individual-level, 2) average characteristics, 3) cohort-level, and 4) discrete event simulation (DES). The individual-level model was the base case model structure used in the PBM economic evaluation [11].

In the average characteristics model, we applied the same average characteristics to all individuals rather than simulating individual characteristics. These characteristics were used to determine transition probabilities, which were estimated using time-to-event analysis of data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) and Australia and New Zealand Organ Donor Registry (ANZOD), supplemented with life tables from the Australian Bureau of Statistics (ABS) and cancer relative survival rates from the Australian Institute of Health and Welfare (AIHW). Estimated probabilities were based on characteristics of individual patients (age, sex, blood group, number of previous transplants, and number of comorbidities) and of their donors (age, sex, donor type, presence of brain cancer, and kidney donor profile index).

For the cohort-level model we used average probabilities over time for all health state transitions. The final alternative structure we considered was a discrete event simulation (DES), which was essentially the same as the individual-level simulation but with time considered as continuous rather than in discrete 3-monthly cycles.

For all models we reported results in terms of incremental costs (2021 Australian dollars, AUD), incremental quality-adjusted life-years (QALYs), and whether the intervention was cost-effective under a willingness-to-pay (WTP) threshold of $28,000 [12].

7.3.3 Health state costs

In the case study economic evaluation, costs associated with each health state changed over time (for example the cost of cancer treatment was higher in the first year and reduced gradually over subsequent years). However, a cohort-level model does not record the amount of time an individual has spent in each health state, so applying time-dependent costs was not possible. Therefore, to ensure consistency between all models, we used fixed (i.e., non-time-dependent) cycle costs for each health state, estimated using the average cycle cost over the first five years spent in each health state. Costs were discounted by an annual rate of 5%, calculated each cycle or continuously for the DES.

7.4 Results

7.4.1 Model inputs

Most of the costs, utility values, and transition probabilities used in this study are identical to those used in the original economic evaluation, and have been thoroughly described [11]. The fixed cost for each 3-month cycle (average of the time-varying cycle costs over the first 5 years) was $19,710 for dialysis, $1,858 for kidney transplant, $3,778 for *de-novo* cancer, and $4,837 for transmitted cancer. A comparison of the time-varying cycle costs used in the original economic evaluation, and the fixed cycle costs used in this study is presented in Table 7.2.

Table 7.2: Comparison of the time-varying cycle costs used in the case study economic evaluation and the fixed cycle costs used in the comparison of model structures

	Cost per 3 months			
Timepoint	Dialysis	Transplant	De-novo cancer	Transmitted cancer
Initial (first 3 months)	$19,717.31	$12,443.99	$11,356.15	$12,004.52
Months 4-12	$19,709.36	$2,970.76	$11,356.15	$12,004.52
Months 13-24	$19,709.36	$987.23	$2,942.75	$3,017.69
Months 25-36	$19,709.36	$987.23	$1,881.54	$3,292.36
Months 37-48	$19,709.36	$987.23	$1,490.11	$2,660.72
Months 49+	$19,709.36	$987.23	$1,218.79	$3,211.06
Average over 5 years (used in comparison of model structures)	$19,709.76	$1,857.60	$3,777.87	$4,837.27

In the average characteristics model, each simulated patient was 49 years old, 37% female, 45% blood group O, had 0.8 comorbidities, and 0.02 previous transplants. Their transition probabilities were simulated based on these characteristics and remained time dependent. For the cohort-level model, patient and donor characteristics which were dependent on age at event (transplant or *de-novo* cancer diagnosis) were based on age at waitlisting and the median time to transplant or cancer diagnosis. Cycle transition probabilities were based on the probability of each transition occurring over a period of 5 years, adjusted to a constant 3-monthly probability using the traditional approach described by Chhatwal et al. [13]. Since transition probabilities in our economic evaluation were time-varying, adjustment to 3-monthly cycle probabilities using eigendecomposition would be inappropriate [13]. All patient and donor characteristics for the average characteristics and cohort-level models are summarized in Table 7.3.

Table 7.3: Patient and donor characteristics used in the average characteristics and cohort-level models

Characteristic	Average characteristics model	Cohort-level model
Patient		
Age	49.6	49.6
Sex		
Female	0.37	0.37
Male	0.63	0.63
Blood group		
O	0.45	0.45
A	0.37	0.37
B	0.13	0.13
AB	0.04	0.04
Comorbidities	0.8	0.8
Previous transplants	0.02	0.02
Donor		
Age	-	45.1
Sex		
Female	-	0.43
Male	-	0.57
Primary brain malignancy	-	0.008
Type		
Living	-	0.19
Deceased DBD	-	0.52
Deceased DBD (expanded criteria)	-	0.15
Deceased DCD	-	0.14
Kidney donor profile index (KDPI)	-	55.7

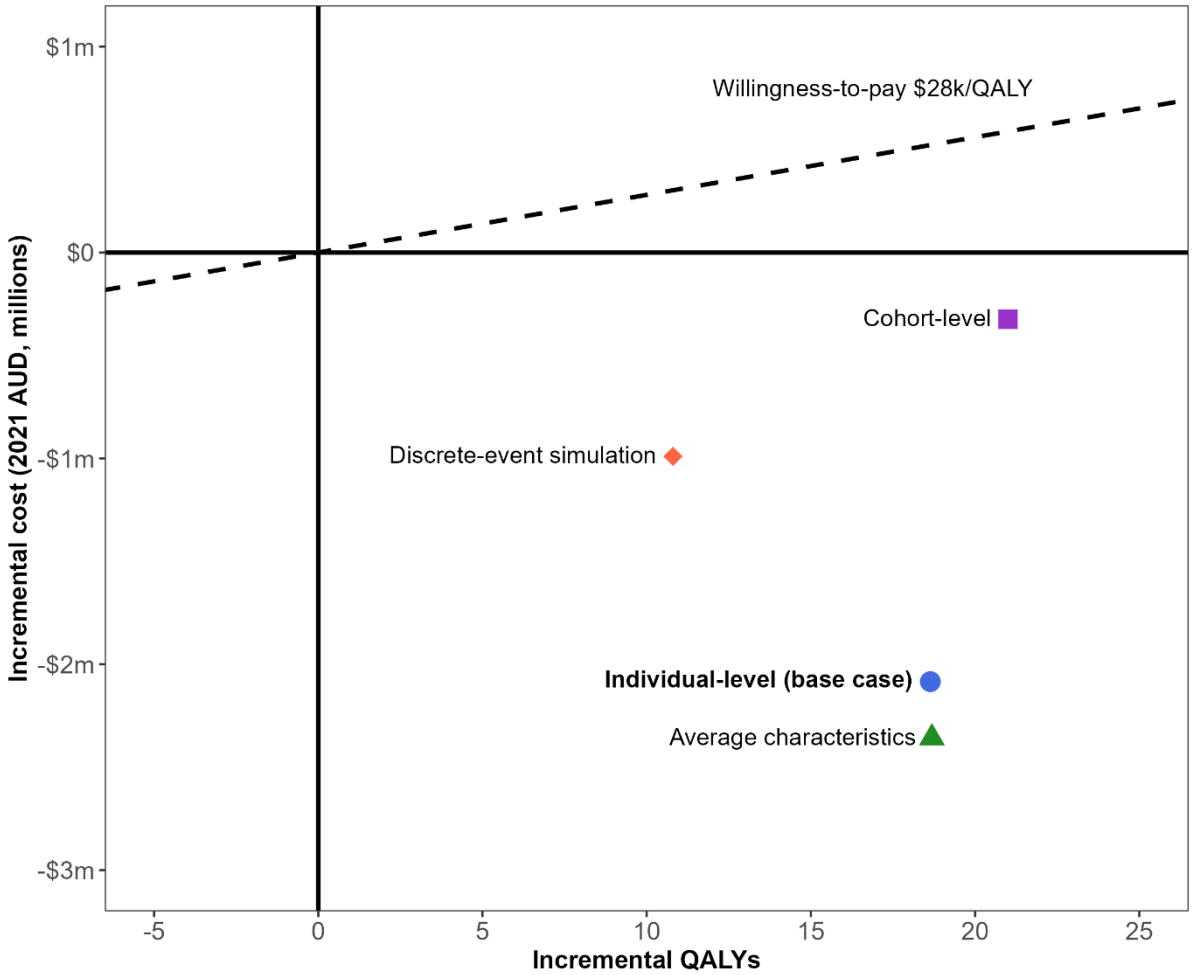
DBD, donation after brain death; DCD, donation after circulatory death

7.4.2 Alternative model structure results

In the base case individual-level model, increased risk tolerance resulted in 18.6 incremental QALYs gained and cost-savings of $2.2 million. Incremental QALYs were similar between the individual-level model, the average characteristics model, and the cohort-level model. Incremental costs were similar between the individual-level and average characteristics models, but the cohort-level model resulted in less cost-savings ($324k).

The discrete event simulation produced broadly similar results to the individual-level model with a with an additional 10.8 QALYs and $990k cost-savings compared to current practice. Results from all alternative model structures are presented in Figure 7.3. Regardless of the model structure or cycle length selected, the conclusion was always the same – that increased risk tolerance was dominant with improved health outcomes and reduced overall healthcare expenditure.

Figure 7.3: Incremental costs and quality-adjusted life-years (QALYs) gained compared with current practice calculated using alternative model structures



7.5 Discussion

We used four alternative model structures for the same economic evaluation and found that while there were some differences in results in terms of incremental costs and QALYs, conclusions remained unchanged regardless of the model structure chosen. These findings concur with a comparison of model structures in a similar economic evaluation which showed there was very little difference between a Markov model and a discrete event simulation [10].

Incremental QALYs were similar between the individual-level (18.6), average characteristics (18.7), and cohort-level (21.0) models, but were much lower in the discrete event simulation (10.8). Since the discrete event simulation effectively uses a cycle length of 1 day, this may suggest that a shorter cycle length could reduce the benefit observed. Incremental costs were similar between the individual-level (-$2.08m) and average characteristics (-$2.36m) models and were higher in the discrete event simulation (-$990k) and cohort-level (-$324k) models. Costs in the cohort-level model were averaged across a five-year period and are likely to be less accurate than the other models. However, the reduced cost savings in the discrete event simulation again may suggest that a shorter cycle length would reduce the benefits observed.

Our findings are especially useful in the context of the PBM economic evaluation, which was an individual patient-level simulation and was therefore computationally intensive. The base case analysis alone took approximately 80 hours to run (on a Dell Latitude 7290 with an Intel® Core™ i5-7300U processor and 8GB RAM), with sensitivity analyses taking even longer. We demonstrated that a much simpler model structure, which could be run in a few

seconds, produced comparable results to the individual-level model and may therefore be appropriate in some circumstances. There are however other considerations besides incremental costs and QALYs that should also be accounted for when selecting a model structure. For example, compared to a cohort-level model, an individual-level model allows for identification of subgroups of patients who would be unfairly advantaged or disadvantaged by the proposed intervention, and provides a better understanding of how health outcomes might be distributed across individuals.

A major strength of our study was the granularity of model structures that we considered. Whereas previous studies have generally only considered two major variations to a model structure, for example individual-level vs. cohort-level models [8,10], we included an intermediate structure (average characteristics) which allows us to better understand what model features are potentially driving the different results.

A limitation of our study was our reliance on a single case study economic evaluation. It is unclear whether our findings are generalizable to economic evaluations in other clinical contexts. Furthermore, we only considered changes to a single aspect of model structure, i.e., granularity of patient characteristics. Future work could involve a simulation study to verify our conclusions in a variety of different economic evaluations, and with changes to other aspects of model structure (e.g., number of health states or cycle length).

We showed that for a specific case study economic evaluation, conclusions of cost-effectiveness were unchanged regardless of the model structure used. Depending on the aims of the economic evaluation, for complex or computationally intensive models it may be

appropriate to use a simplified model structure to obtain the same cost-effectiveness conclusion with a more parsimonious model that is easier to develop, easier to understand, and faster to compute.

7.6 Conclusions

We used a specific case study economic evaluation to demonstrate that a simple cohort-level model produces similar results and identical cost-effectiveness conclusions as more complex model structures including individual-level, individual-level with average characteristics, and DES. In economic evaluations where the distribution of benefits across individuals or subgroups is not of importance, a simplified cohort-level model structure may be appropriate without affecting cost-effectiveness conclusions.

7.7 References

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Chapter 8: Methods for probabilistic sensitivity analysis in simulation models

8.1 Preface

This chapter presents two alternative methods that I developed for one-way sensitivity analysis (OSA) in a simulation-based economic evaluation. The aim was to develop a method for sensitivity analysis that was computationally efficient, could be displayed on a traditional tornado plot, and would also allow ranking parameters in terms of their influence on model results. This study was conceived after discussions with the University of Sydney Health Economics Discussion group (SHED), where I presented the sensitivity analysis from the economic evaluation in chapter 6 of this thesis, with a focus on some of the problems I had encountered along the way. The distribution method proposed in this study was inspired by the modified tornado plot from Awotwe et al., 2016 [1].

This is an original chapter and has not been published previously.

8.2 Introduction

Sensitivity or scenario analyses address uncertainty in economic evaluations and are required by health technology assessment agencies worldwide [2-4]. The two main types of sensitivity analysis to address parameter uncertainty are deterministic (including one-way or multi-way), and probabilistic [5]. Deterministic one-way sensitivity analysis (OSA) addresses uncertainty around individual parameters, whereas probabilistic sensitivity analysis (PSA) addresses uncertainty around all parameters simultaneously. While deterministic sensitivity has many advantages (typically simpler to model, allows ranking of parameters in order of sensitivity, and enables production of a tornado plot), results may be misinterpreted or biased, especially when parameters are correlated [3,6,7].

Furthermore, deterministic OSA may not be feasible for an individual patient-level simulation Markov model, due to computational complexity and long running time. One-way PSA has been proposed as a potential solution [1], and has been used in recent economic evaluations [6,8]. However, this method does not completely address the problem of computational burden. An alternative method for threshold analysis involving regression analysis of results from a standard PSA has been shown to be accurate and computationally efficient [9], but only provides a threshold value rather than an indication of how sensitive the model is to each parameter.

I propose two alternative methods for OSA that allow ranking of parameters in terms of their influence on model results, which can be displayed on a tornado plot as recommended by health technology assessment guidelines [2,4]. These methods are computationally efficient, have shorter running times, and may be suitable for complex individual-level simulation Markov models.

8.3 Methods

The motivating example for this work was a cost-effectiveness analysis of increasing utilization of kidneys for transplantation from deceased donors with primary brain malignancy (PBM economic evaluation) [10]. Details of the model structure have been described previously [10], but briefly, a cohort of 1500 people on the waiting list for a deceased donor kidney transplant were simulated through a Markov model with health states for dialysis, kidney transplant, transplant failure, cancer, and death. The original economic evaluation considered three alternative interventions, however for this work I only considered the most cost-effective intervention, decision support with increased risk tolerance.

I developed two alternative approaches to one-way PSA that were much less computationally intensive whilst also serving the same purpose as a deterministic OSA in identifying parameters to which the model results were most sensitive (i.e., influential parameters). For this work, results were reported in terms of incremental costs, and incremental quality-adjusted life-years (QALYs). The two proposed methods were 1) using the distribution of results from the PSA, and 2) determining the marginal effect of changes in each parameter using linear regression.

8.3.1 Distribution of results from probabilistic sensitivity analysis

8.3.1.1 Methodology

The first method (distribution method) used the output from a standard PSA to determine the distribution of costs and QALYs with respect to the distribution of values for each parameter. This was performed in four steps. The first step was to organize the results of the PSA into a single table with a row for each iteration or 'run' of the PSA, a column with the incremental costs, a column with the incremental QALYs, and columns with the value of each parameter. For example, in the PBM economic evaluation the PSA was re-run 10,000 times and there were 193 different parameters plus two outcomes (incremental costs and incremental QALYs), hence the results were organized into a table with 10,000 rows and 195 columns. All subsequent steps were performed separately for each parameter. The second step was to sort the table by the parameter of interest, in ascending order. This ensured that the results were arranged in order from those generated using the lowest values of the parameter, to those generated using the highest values. The third step was to collapse the table by rows into evenly sized groups by taking the mean for each column. For example, collapsing into 100 different groups would mean each group represents a percentile of the parameter. The fourth and final step was to calculate the density of the group means of

incremental costs and QALYs (e.g., using the density() function in base R [11]). A flowchart for this method is presented in Figure 8.1.

Figure 8.1: Method for calculating the probability distribution of results from probabilistic sensitivity analysis

Step 1: Organize probabilistic sensitivity analysis data

	Outcomes		Paramater values		
Iteration	Costs	QALYs	A	B	...
1					
2					
...					

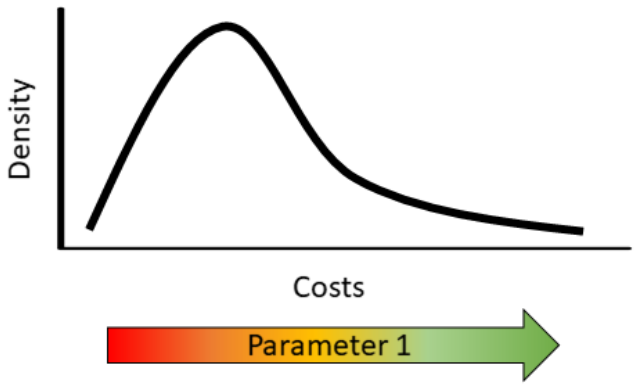
Step 2: Sort by parameter of interest in ascending order

Outcomes		Paramater values
Costs	QALYs	1 ⇩

Step 3: Collapse outcomes into groups and summarize means

	Outcomes	
Rows	Costs	QALYs
1-100	*mean[rows 1-100]*	*mean[rows 1-100]*
101-200	*mean[rows 101-200]*	*mean[rows 101-200]*
...		

Step 4: Calculate density of outcomes



8.3.1.2 Plotting results

Since each group of rows is the same size (e.g., a percentile), each group mean of incremental costs and QALYs are equally likely to occur. Therefore, the distribution of outcomes associated with each parameter can be plotted together to produce a plot that is visually similar to a tornado plot, but also shows the probability of each outcome. I developed two examples of how these results could be plotted, both of which were visually similar to a traditional tornado plot with incremental costs or QALYs on the horizontal axis, with parameters arranged in descending order of influence on model results on the vertical axis. The first plot displayed the probability distribution of outcomes associated with values of each parameter as a line with height corresponding to probability density.

The second plot displayed this same probability distribution as a bar, with the ends of the bar extending to the lowest and highest values for each outcome, and with darker or lighter shading to represent areas of higher or lower probability density, respectively.

Due to the large number of parameters considered in the PBM economic evaluation, both plots from the distribution method include only the most influential parameters to ensure information can be clearly seen.

8.3.2 Marginal effect of parameter changes using linear regression

8.3.2.1 Methodology

The second method (marginal effect method) also used the output from a standard PSA, organized into a table with rows for each iteration or 'run' of the PSA, and columns for incremental costs, incremental QALYs, and for each parameter.

A linear regression was then performed for each outcome (incremental costs and QALYs), using all parameters as explanatory variables, to determine the marginal effect on incremental costs and QALYs associated with a change in the value of each parameter. The equations for these regression models (for a PSA with k parameters) are shown in equations 8.1 and 8.2.

$$Incremental\ costs = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k \qquad \text{(Equation 8.1)}$$

$$Incremental\ QALYs = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k \qquad \text{(Equation 8.2)}$$

8.3.2.2 Plotting results

Although this marginal effect does not account for the probability distribution of changes in parameter values, it does allow ranking of parameters in terms of their impact on incremental costs and QALYs. I developed two examples of how these results could be plotted. The first was a forest plot, with the change in outcome (incremental costs or QALYs) on the horizontal axis, and parameters arranged in descending order of their influence on model results on the vertical axis. Each parameter was plotted as a point representing the change in outcome associated with a 1% increase in the parameter value (i.e., marginal effect), and a line representing the 95% confidence interval for the marginal effect. Dashed vertical lines were used to mark a 1% change in the outcome, as it may be reasonable to conclude that the model is sensitive to any parameter where a 1% increase in its value would change the outcome by more than 1%. This is the plot that was included in the original economic evaluation [10].

The second plot essentially combined the forest plots for incremental costs and incremental QALYs into a single plot. The horizontal axis was the change in incremental QALYs, and the

vertical axis was the change in incremental costs. Each parameter was plotted as a point, with both vertical and horizontal lines representing 95% confidence intervals. A diamond was drawn around the origin to indicate the area of the plot where the sum of the absolute change in incremental costs and QALYs was more than 1%. Points within this are may be considered influential, as a 1% increase in the value of the parameter is associated with a greater than 1% absolute change in incremental costs and QALYs. Since both the horizontal and vertical axes were used to show changes in outcomes, it was not possible to order the parameters by their influence on model results.

8.4 Results

The two alternative plots from the distribution method are presented in Figure 8.2 and Figure 8.3, while the two alternative plots from the marginal effect method are presented in Figure 8.4 (reproduced from Supplementary Figure 3 in Hedley et al., 2023 [10]) and Figure 8.5. Advantages and disadvantages of each method are summarized in Table 8.1.

Table 8.1: Advantages and disadvantages of the distribution method and the marginal effect method

Method	Advantages	Disadvantages
Distribution	- Computationally efficient - Accounts for underlying probability distribution	- Requires assumption that selected group size is appropriate
Marginal effect	- Computationally efficient - Previously demonstrated to be accurate	- Does not explore a range of values and therefore cannot be used for a tornado plot

Figure 8.2: Tornado plot of most influential parameters on incremental costs and QALYs determined using the distribution method, plotted as a line with height representing probability distribution

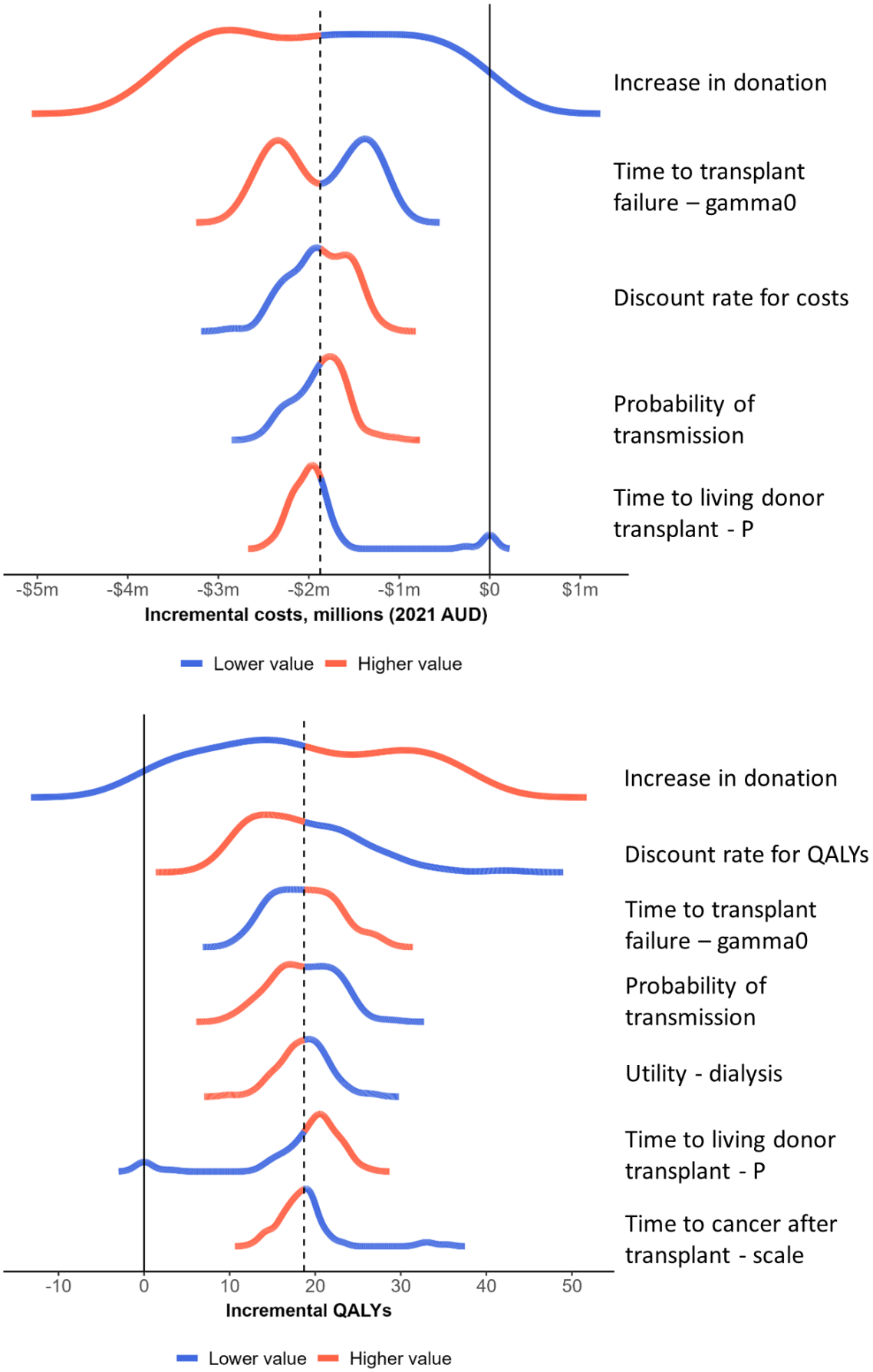
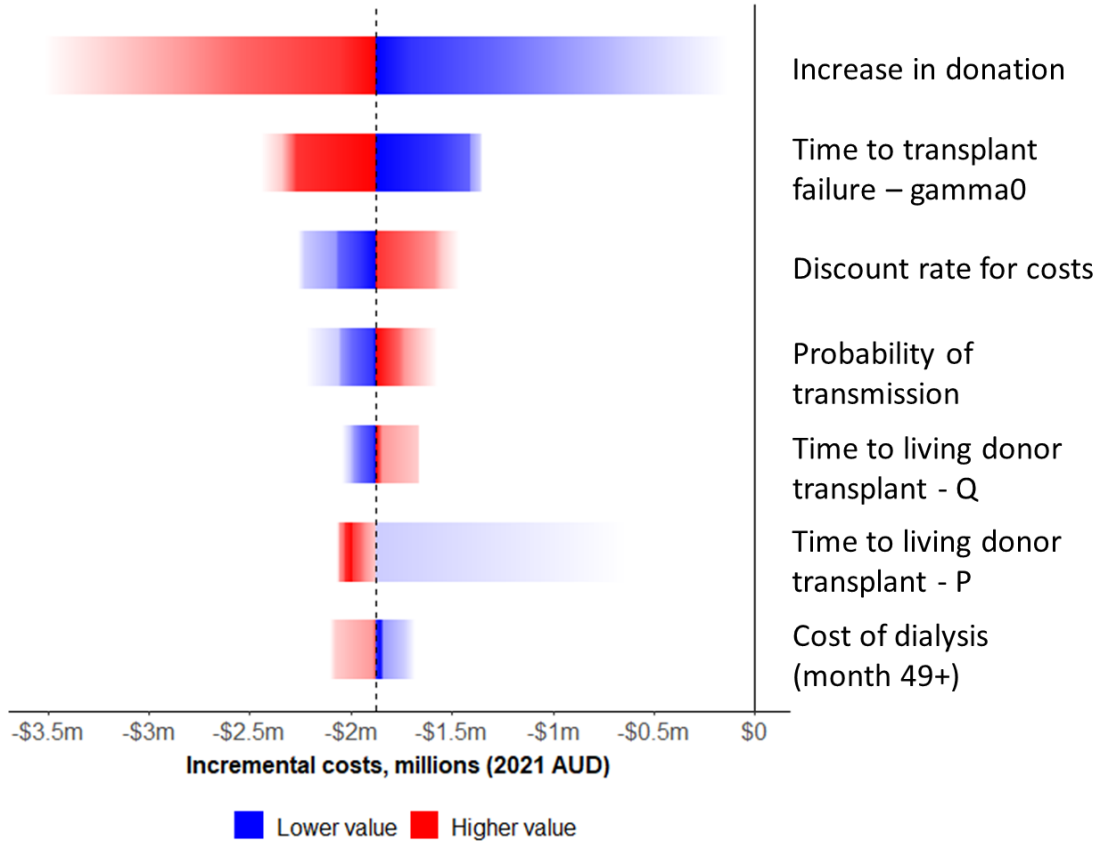


Figure 8.3: Tornado plot of most influential parameters on incremental costs and QALYs determined using the distribution method, plotted as a bar with color shading representing probability distribution



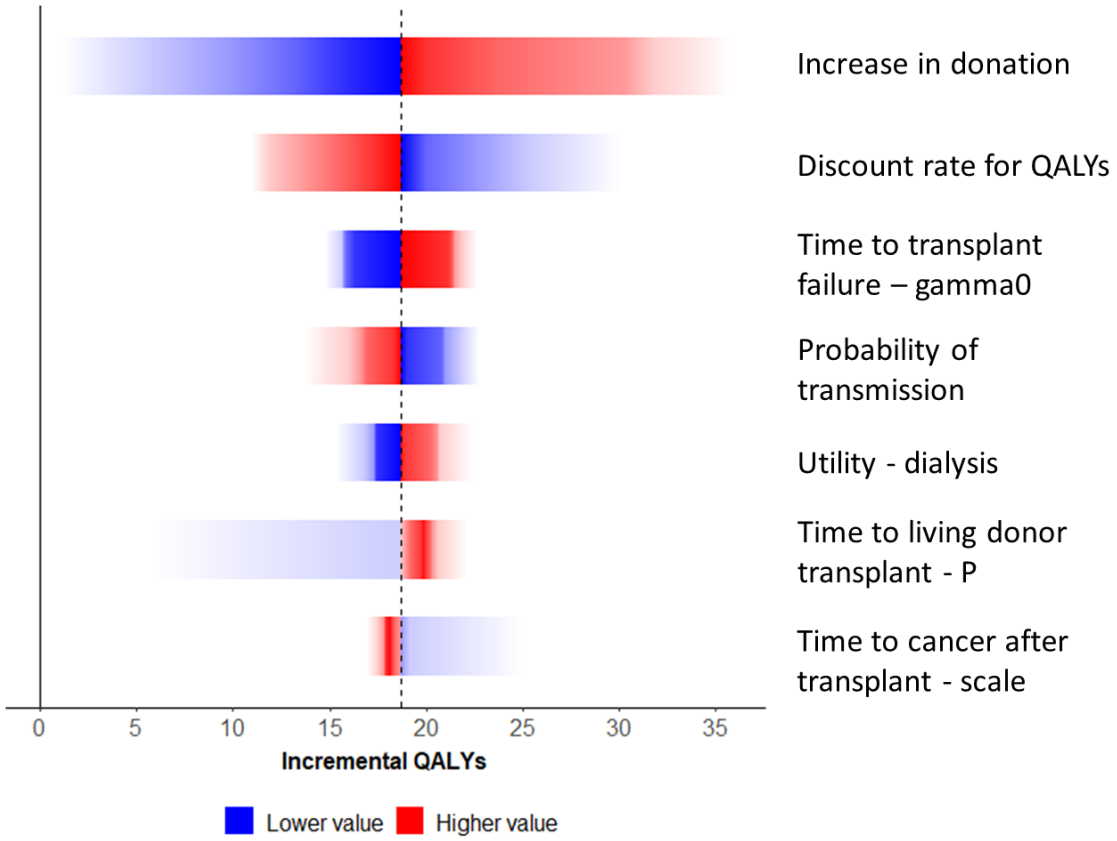
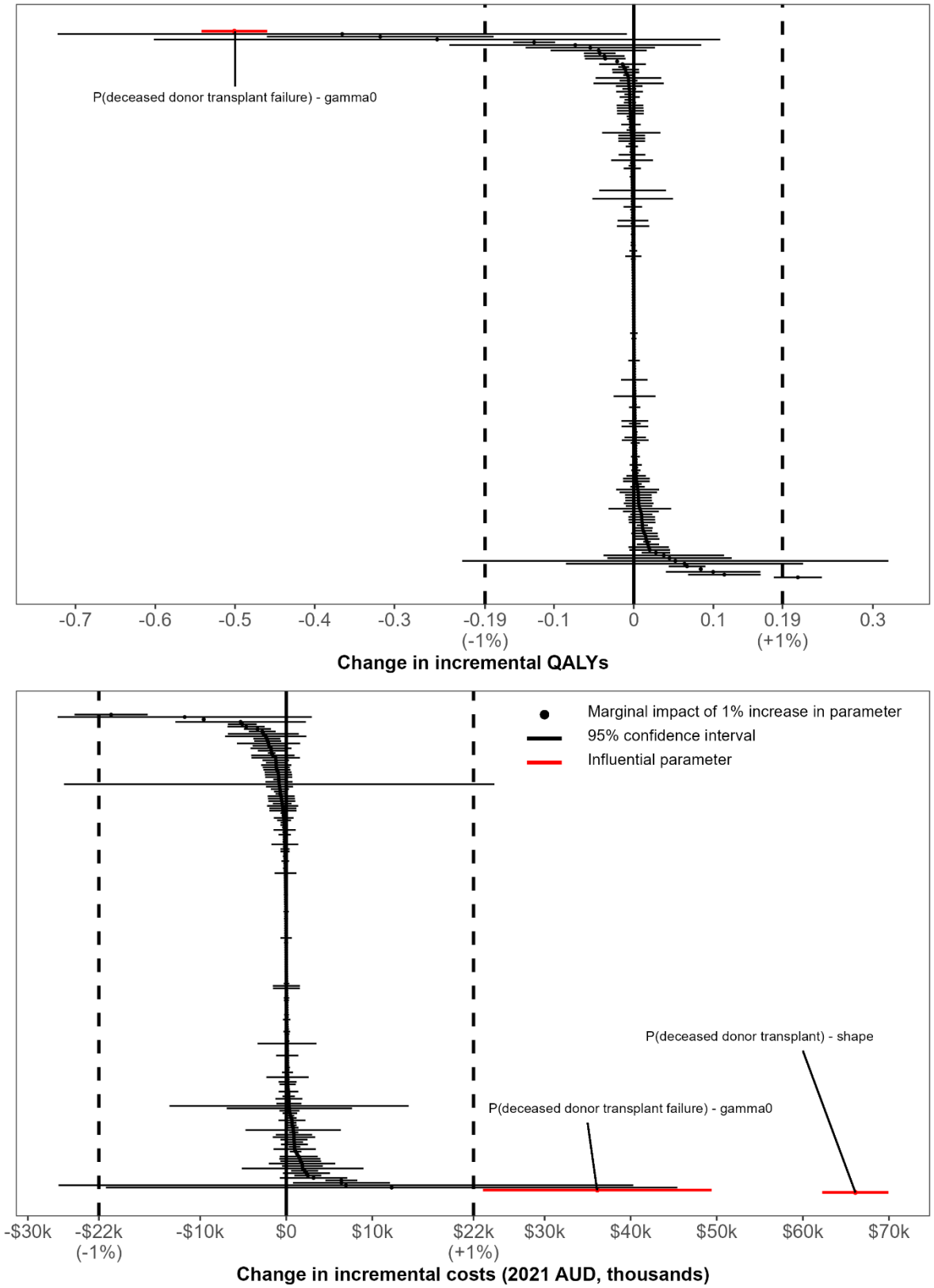
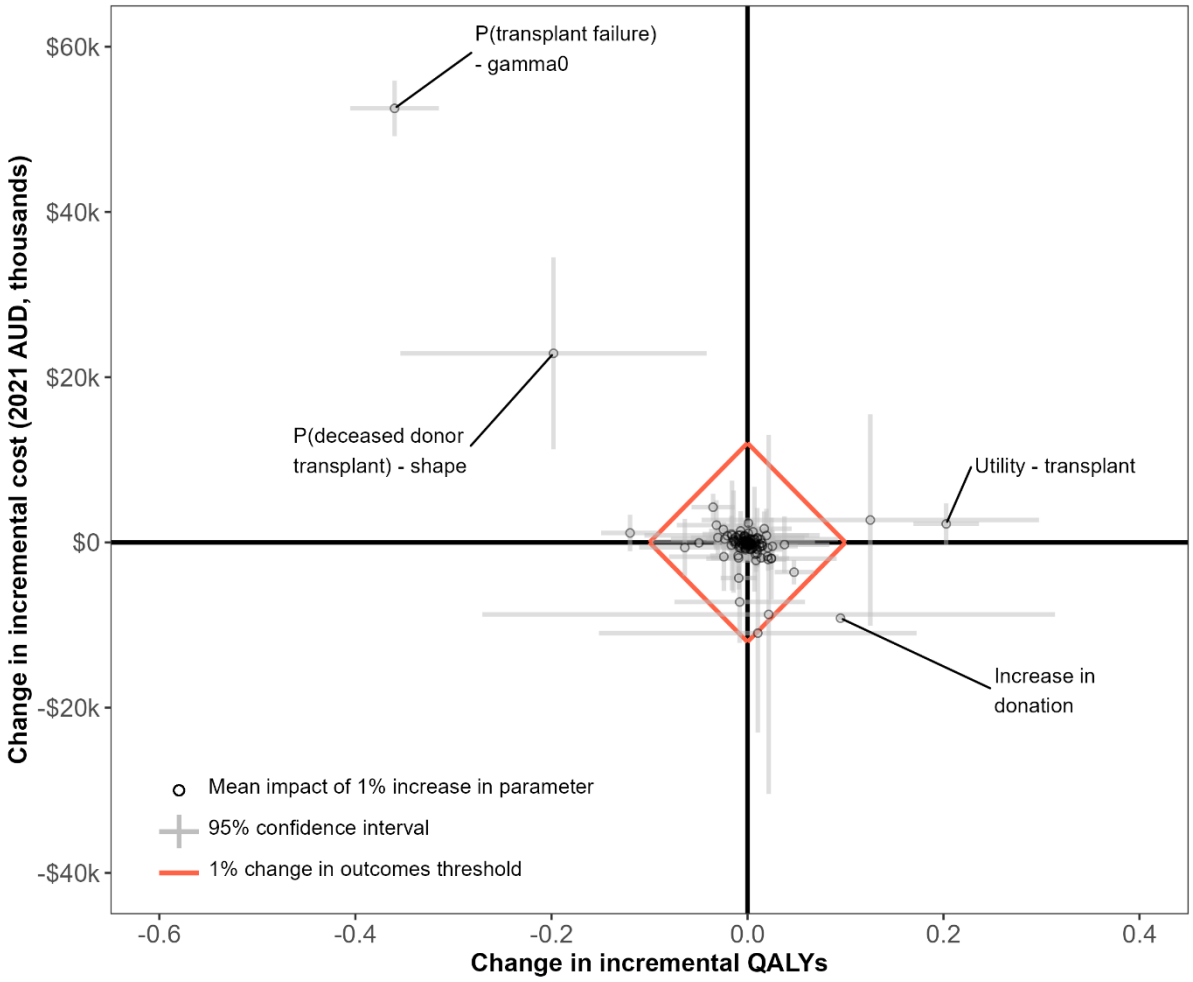


Figure 8.4: Marginal effect on incremental costs and QALYs from a 1% increase in each parameter, plotted as separate forest plots



Based on a linear regression of the results from 10,000 probabilistic sensitivity analysis simulations.
Each point represents a model paramater. Dashed lines represent a 1% change in incremental costs or QALYs (in the decison support + increased risk tolerance scenario). Parameters with a 95% CI that lies outside the dashed lines may be considered influential, i.e. the model is sensitive to changes in these parameters (highlighted in red and labeled).

Figure 8.5: Marginal effect on incremental costs and QALYs from a 1% increase in each parameter, plotted as points on a single plot



8.5 Discussion

I have developed two methods for sensitivity analysis for economic evaluations based on large or individual-level simulation models that allow model parameters to be compared in terms of their influence on results. Both methods are much more computationally efficient compared to previously proposed approaches [1] as they utilize existing data from PSA, and both overcome known disadvantages of traditional deterministic sensitivity analyses.

The primary advantage of the distribution method is that it allows production of a plot that looks similar to a traditional tornado plot, which is already commonly used and well understood by health economists. In addition to comparing parameters in terms of their influence on results, this method also accounts for the underlying probability distribution of parameter values. This allows deeper interpretation of the tornado plot, for example by determining the probability that a parameter would take a value so extreme as to change conclusions (i.e., the probability that a parameter would exceed a threshold value).

A limitation of the distribution method is that the choice of group size (i.e., the number of iterations to be included in each mean calculation) could impact the interpretability of the resulting plots. Groups must be sufficiently large that the means are not largely affected by random variation in other parameters within each group, but the larger the groups are the fewer groups there will be. However, with too few groups the resulting distribution plots will not be smooth and may therefore lack generalizability. A group size equal to the square root of the total number of iterations in the PSA may be optimal (such that the group size is equivalent to the number of groups), but this has not yet been proven.

The marginal effect method has several advantages over the distribution method. Firstly, performing regression analysis of PSA results has previously been shown to be an accurate method for estimating threshold values [9]. Furthermore, performing regression analysis is much simpler in modern statistical software with pre-existing functions, whereas the distribution method is a much more bespoke approach. In addition to comparing parameters to each other, the marginal effect method also provides a natural threshold for determining whether an individual parameter is influential or not (i.e., if a 1% increase in the parameter changes results by more than 1%).

The major limitation of the marginal effect method is that it does not account for the underlying probability distribution of each parameter. Therefore, although parameters can be compared in terms of their effect on results from a 1% increase in value, it is unclear how likely such an increase is to occur. Furthermore, since only a single effect is provided for each parameter, results cannot be plotted on a traditional tornado plot, which is commonly used, easily understood, and may be expected in some instances.

Both the distribution method and the marginal effect method allow use of existing data from a PSA to compare parameters in terms of their influence on results, even for complex simulation models where traditional OSA would be infeasible due to computational burden. I have discussed the advantages and disadvantages of each method and provided examples of how these results could be plotted. Future work could involve a simulation study to explore whether these methods produce similar results to a traditional OSA, as well as expanding these methods to multi-way sensitivity analysis.

8.6 Conclusions

Both the distribution method and the marginal effect method can be used to compare parameters in terms of their influence on an individual-level patient simulation model. While the distribution method produces plots similar to the more familiar tornado plot, the marginal effect method is simpler and has been previously demonstrated to be accurate. Both methods are more computationally efficient for simulation models and avoid the known disadvantages of deterministic sensitivity analysis.

8.7 References

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Chapter 9: Discussion

9.1 Main findings and contributions

Many Australians with kidney failure would benefit from a kidney transplant, but there remains a shortage of suitable donors. This thesis aimed to identify potential missed opportunities for organ donation from deceased donors with primary brain malignancy, to determine outcomes of patients who receive an organ transplant from a donor with cancer, and to determine the cost-effectiveness of interventions that could improve utilisation of these potential donors. A generalisable contribution of this thesis is the development of an economic evaluation to assess the cost-effectiveness of proposed interventions that could increase the number of donor kidneys available for transplantation.

9.1.1 Missed opportunities for organ donation

Chapter 2 of this thesis included an analysis of SAFEBOD data to compare perceived and verified cancer information in a cohort of potential deceased donors in NSW. This study found that cancer information available at the time of donor referral is often lacking. Despite the poor availability of information, most donation decisions were appropriate. However, there were still many potential donors declined for donation on the basis of a perceived cancer transmission risk that was either verified to be much lower than first thought or should not have precluded donation according to national clinical guidelines. Among all potential donors declined due to a perceived cancer transmission risk, 29% were verified suitable for donation and were therefore missed opportunities.

Three interventions were proposed that could potentially avoid some of these missed opportunities and increase the number of donors available for transplantation. These were:

1) Decision support

This would involve assisting clinicians in following donation guidelines consistently and would ensure that whatever risk threshold is deemed acceptable, all those with a lower risk would be accepted for donation and all those with a higher risk would be declined.

2) Real-time data-linkage

This would allow clinicians to search potential donor's existing cancer registry and hospital admission records to confirm details of suspected cancers, or to identify previously unknown cancers.

3) Increased risk tolerance

This would involve increasing the risk tolerance threshold implied in donation guidelines, explicitly recommending that potential donors with an intermediate risk of cancer transmission (6.4%) be accepted.

This study demonstrated that each of these interventions could increase the number of donors available for transplantation, with the largest increase of 2.1% coming from increased risk tolerance.

9.1.2 Patient outcomes after transplantation from a donor with cancer

Chapter 3 of this thesis was a study that summarised patient outcomes after receiving an organ transplant from a donor with any cancer history. There were 38 donors with cancer identified, who donated organs to 68 recipients. Only 4 (6%) cases of cancer transmission were identified, all of which were kidney recipients from donors with known kidney cancer

at the time of donation. Importantly, this study highlighted how rare cancer transmissions are and how transplanting organs from donors with cancer is relatively safe. Overall, 94% of transplants from donors with a verified cancer history did not result in transmission, and the recipients experienced much better outcomes than they would have if they had remained on a waiting list.

The second most common cancer among donors in this study was brain cancer, which is the focus of this thesis. There were 7 donors with brain cancer (4 grade IV, 2 grade II, and 1 unknown grade) who donated organs to 25 recipients (including 10 kidneys), none of which were transmitted. Many of these recipients remained alive with a functioning transplant at the end of follow-up.

In addition to the detailed analysis presented in chapter 3, the literature review described in chapter 1 also provides a summary of published case reports of brain cancer transmissions. Among 10 kidney recipients who were diagnosed with a donor-transmitted cancer following transplantation from a donor with brain cancer, 8 (80%) had their transplanted kidney removed and remained cancer free until the end of follow-up, including 1 patient who was eventually retransplanted. This provides further support for the conclusions of chapter 3 that transplantation of kidneys from donors with brain cancer is very likely to be safe, with fatal outcomes in only a small proportion of recipients. Some patients may consider this small chance of a severely negative outcome worthwhile, especially when compared to the guaranteed harm of remaining on dialysis.

9.1.3 Cost-effectiveness of increasing use of kidneys from deceased donors with PBM

Chapters 4, 5, and 6 of this thesis describe an economic evaluation that assesses the cost-effectiveness of implementing the interventions proposed in chapter 2 to improve utilisation of kidneys from deceased donors with PBM, i.e., decision support, real-time data-linkage, and increased risk tolerance. This economic evaluation demonstrated that any increase in use of kidneys from deceased donors with PBM would improve patients' health outcomes and save money (since in the long-term transplantation is much less expensive than dialysis). The largest benefit would come from increasing risk tolerance to accept donors with even the highest-grade brain cancers (grade IV, intermediate risk, 6.4%). On average this would result in an additional 18.6 QALYs and cost-savings of $2.2m, with an 88% chance of being cost-effective.

The scenario analyses presented in chapter 6 and alternative model structures presented in chapter 7 showed the robustness of these conclusions. Results were similar when model input parameters were randomly varied, and under different model structures. Even in a worst-case scenario where all cases of cancer transmission were assumed to result in instant death, increasing risk tolerance was dominant (i.e., improved health outcomes and saved money). The same was true even if the risk of transmission were as high as 20% (much higher than the current upper limit estimate of 6.4%).

9.1.4 Alternative methods for probabilistic sensitivity analysis

Chapter 8 of this thesis describes two new methods for performing probabilistic sensitivity analysis for a simulation-based economic evaluation. The distribution method was adapted from an alternative tornado plot presented in a poster by Awotwe et al., 2016 [1], while the

marginal effect method was adapted from the regression-based method described in Peters et al., 2020 [2]. These methods are more computationally efficient than those that have been used previously and overcome several known disadvantages of traditional deterministic sensitivity analyses. Furthermore, the distribution method allows production of a plot that looks similar to a traditional tornado plot but improves on this by also accounting for the underlying probability distribution of parameter values.

9.2 Implications for organ donation policy and clinical practice

The work presented in this thesis has several important implications for organ donation policy as well as for donation specialists and transplant clinicians. Firstly, I have shown that despite existing efforts to maximise donation, there remain some missed opportunities for donation which present an avenue for further increasing the number of donors available. This finding has implications for the donation service in NSW as well as in other states and territories, as it highlights an area where efforts could be focussed to further increase the number of donors available.

Secondly, I have added to the body of evidence showing that cancer transmissions are rare and have also shown that the consequences of cancer transmission are not as severe as might be expected. My research into outcomes following transplantation from donors with cancer was being conducted at the same time as a major revision to the TSANZ donation guidelines was being drafted, and some of my early findings were considered in discussions around which donor cancers should be recommended as suitable for donation. My findings have also helped some individual clinicians considering whether to accept or decline a specific potential donor with a known cancer history.

Finally, the results and conclusions from my economic evaluation have important implications for policy makers deciding on future strategies to increase donation. I have shown that decision support to assist clinicians in following guidelines when making donation decisions could increase the number of donors available overall and would very likely be a cost-effective intervention.

9.3 Strengths and limitations

The major strengths and limitations of this thesis overall are described below.

9.3.1 Strengths

The major strength of this thesis is its use of SAFEBOD data, which is a novel and incredibly detailed linked dataset. The inclusion of potential donor referral logs from OTDS made it possible to identify missed opportunities for donation that may not have been recorded in many other jurisdictions. Furthermore, the inclusion of linked administrative health data such as hospital admissions (APDC) and the cancer registry (CCR) provided a high degree of confidence that all donor and recipient cancers have been identified. This is exemplified by the fact that there were several donors with cancers that were not notified to the CCR which would have been missed entirely had we not supplemented CCR data with other data sources such as APDC. The SAFEBOD dataset also had complete coverage of its target population, including all potential donors, actual donors, and recipients who were resident in NSW at the time of donation/transplantation. The study presented in chapter 2 is the first to identify cancer transmissions and non-transmissions using both transplant registry and population-level cancer registry data.

Another strength of this thesis overall is the comprehensiveness of the modelling that underpins the economic evaluation presented in chapter 6. Health state transition probabilities were estimated based on transplant registry data requested as part of the MODUS study (rather than relying on published summary-level data). This allowed transition probabilities to be dependent on a range of patient and donor characteristics, as well as varying over time, ensuring accuracy and relevance to the Australian kidney waitlist. The economic model also accounted for beneficial side-effects of the proposed interventions to increase donation, including improvements in the quality of donors in terms of their younger age and fewer comorbidities (apart from PBM). We also demonstrated that the results of this modelling were robust to many different scenario analyses, including probabilistic sensitivity analysis, a worst-case scenario (where transmission is assumed to result in instant death), a threshold analysis (showing that even with a transmission risk of 20%, donors with PBM should be accepted), and major variations in model structure as described in chapter 7.

9.3.2 Limitations

One limitation of this thesis is that estimates of the number of missed opportunities for donation and the impact that proposed interventions could have on increasing the number of donors available for transplantation are based on a somewhat small and not wholly contemporary dataset. At the time of analysis, complete cancer registry data in SAFEBOD was only available until 2013, while data on potential donors was only available from 2010 onwards, hence missed opportunities could only be identified from a cohort of potential donors spanning 4 years, 2010-2013. There were only 132 potential donors declined due to their perceived cancer transmission risk, 38 of which were identified as missed

opportunities for donation. When considering missed opportunities among potential donors with PBM, only 1 would have been accepted with decision support, 2 would have been accepted with real-time data-linkage, and 7 would have been accepted with increased risk tolerance. Although the estimated impact of each proposed intervention is based on very small numbers and therefore highly variable, the economic evaluation demonstrated that any increase in donation due to accepting more donors with PBM would be beneficial. Probabilistic sensitivity analysis also showed that variation in the assumed increase in donation associated with each intervention did not have affect the direction of results, and hence did not affect the conclusion of cost-effectiveness.

Another limitation is our lack of consideration for how the interventions proposed in chapter 2 could be implemented. We assumed that a theoretical decision support tool could help keep donation decisions and risk tolerance thresholds consistent for all potential donors, however its unclear exactly how this support could be provided in practice. Depending on what such a decision support tool looks like, it may not be 100% effective at guaranteeing consistent decision making. We also did not include estimates of the cost of implementation for our proposed interventions. A decision support tool might involve significant up-front development costs (e.g., to build an app), and it might be costly or challenging from a data security perspective to provide donation service staff with real-time access to administrative health datasets. It may also be difficult to enforce the wide-spread behaviour change required to increase risk tolerance thresholds, or even to overcome possible clinician biases against certain types of cancer when developing a decision support tool (for example, some clinicians may instinctively decline a potential donor at the very mention of the word cancer without giving them full consideration). Despite this, it is likely

that any costs involved would primarily be one-off expenses and may prove worthwhile in the long run, especially if the benefits in terms of improved health outcomes and cost-savings are extended to other types of cancer (rather than just PBM) and other transplantable organs (rather than just kidneys).

9.4 Future research

This thesis has made a significant contribution towards understanding how potential organ donors could be better utilised and has paved the way for future research that could expand on this body of work.

Firstly, a new round of SAFEBOD linkage was completed in 2022, with data from the CCR up to 2018. This new data could be re-analysed to provide updated estimates of the number of missed opportunities for donation, as well as updated estimates of the impact of proposed interventions to improve utilisation of these potential donors.

A natural next step after this thesis would be to develop a decision support tool to assist clinicians with following guidelines and making donation decisions, especially for donors with a cancer transmission risk. Alongside this, there is also a need for more research into how to communicate transmission risks to potential recipients to ensure they can become more involved in donation decisions and are able to provide informed consent.

One limitation of the economic evaluation presented in chapter 6 is that it did not account for a dynamic waiting list. Future work could build on this economic model to incorporate patient transitions on and off the waiting list. An intervention that results in more kidneys

available for transplantation could mean that some patients are transplanted earlier, potentially before they would otherwise have been temporarily removed from the waiting list. This could have downstream effects on the characteristics of those who do receive a transplant, and it is unclear how considering a dynamic waiting list might influence the conclusions of the economic evaluation in terms of equity. For example, it may be that some groups of patients at high risk of being removed from the waitlist would be much better off with more availability of kidneys from donors with PBM, but these patients may also have poorer post-transplant outcomes which could potentially reduce overall health benefits within their subgroup. However, kidney transplantation has previously been demonstrated to be cost-effective even among the oldest and most comorbid patients [3], so benefits would likely be maintained in all patient subgroups.

Finally, the economic evaluation in chapter 6 demonstrated that at a population level, accepting more donors with PBM is beneficial in terms of patients' health outcomes. However, for individual patients, the decision to accept or decline a kidney with a cancer transmission risk will depend on their individual characteristics. For example, a younger patient who has already been on the waitlist for a few years might expect to receive a kidney offer within a short time frame and may have less incentive to accept a transmission risk than an older patient who has only recently been waitlisted. Future work could involve developing a calculator to help individual patients and their clinicians understand their expected remaining waiting time, and their expected outcomes if they were to accept a kidney transplant with a risk of cancer transmission vs. remaining on dialysis while waiting for a better offer.

9.5 Conclusion

This thesis leveraged linked data from the SAFEBOD study to identify missed opportunities for donation due to potential donors being declined for donation due to a perceived cancer transmission risk, despite being verified suitable for donation. Based on this, several interventions were proposed and their potential impact in terms of increasing donation was estimated. Cases of cancer transmission and non-transmission were summarised to better understand patient outcomes following transplantation from a donor with cancer. These analyses informed an economic evaluation, which determined that any increase in utilisation of kidneys for transplantation from donors with PBM would improve health outcomes and be cost-saving. In particular, increasing risk tolerance to accept donors with even the highest-grade brain cancer (grade IV, intermediate risk of transmission 6.4%) would be the most beneficial in terms of patients' health outcomes and reducing healthcare expenditure.

9.6 Personal development

During my candidature I have gained invaluable experience with many facets of academia. In addition to my research presented in this thesis, I have had the opportunity to work on many other research projects both within my research team at University of Sydney and externally. Collaborating with people from a range of educational backgrounds and at various career stages has helped me better understand my own strengths and weaknesses and the best way I can contribute to any team. I developed new skills in statistics and economics by undertaking formal coursework at the university (BSTA5017 Causal Statistical Inference and PUBH5317 Decision modelling for economic analysis), workshops organized by the Statistical Society of Australia (e.g., machine learning with python and advanced data

visualisation in R), and participating in numerous informal seminars, discussion groups, and journal clubs. I was also afforded the opportunity to attend many conferences throughout my candidature, and received several awards for presenting my research (3 x TSANZ early career researcher award and ESOT full bursary).

I have improved my confidence in teaching by working as a casual tutor for several courses within the Sydney School of Public Health (PUBH5018 Introductory Biostatistics, PUBH5215 Analysis of Linked Data, and BSTA5003 Health indicators and Health Surveys). For PUBH5215 and BSTA5003 I also greatly contributed to course development (preparing module notes, running lectures and webinars, and creating assignments and solutions). Furthermore, I have been able to give back to the research community by volunteering to mark final workplace projects for the Master of Biostatistics degree, as well as reviewing two journal articles submitted for publication.

Alongside my academic involvements at the University of Sydney, I have also worked as a consultant (statistical analysis for a cardiothoracic research project at St. Vincent's Hospital Melbourne lead by Dr. Francis Cheung, and REDCap database development for the Arrow trial at Deakin University with oversight from Prof. Peter Vuillermin), and as a data manager for the Barwon Infant Study at Murdoch Children's Research Institute (part of this role included providing one-on-one statistical support for other PhD students analysing data from the study).

The broad range of research-related activities I have undertaken during my PhD have helped me become a more well-rounded academic with the skills and confidence necessary to continue building my career.

9.7 References

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Appendices

Appendix A – Additional published work completed during my candidature

During the course of my PhD, I contributed to numerous publications which were not included in this thesis. These publications are listed below, separately for those where I lead the analysis and other publications that I contributed to.

A.1 Publications during my PhD for which I lead the analysis

1. Webster AC, **Hedley J**, Robertson P, Mulley WR, Pilmore HL, Pleass H, Kelly PJ, on behalf of Australia and New Zealand Pancreas Transplant Collaborators. Australia and New Zealand Islet and Pancreas Transplant Registry Annual Report 2019-Pancreas Waiting List, Recipients, and Donors. *Transplantation Direct*. 2020; 6(7);e564. https://doi.org/10.1097%2FTXD.0000000000001015

2. Webster AC, **Hedley JA**, Anderson PF, Hawthorne WJ, Radford T, Drogemuller C, Rogers N, Goodman D, Lee, MH, Loudovaris T, Kelly PJ, on behalf of the Australian Islet-cell Transplant consortium. Australia and New Zealand Islet and Pancreas Transplant Registry Annual Report 2019: Islet Donations, Islet Isolations, and Islet Transplants. *Transplantation Direct*, 2020; 6(7):e565. https://doi.org/10.1097%2FTXD.0000000000001014

3. Waller KMJ, **Hedley JA**, Rosales BM, De La Mata N, Thomson IK, Walker J, Kelly PJ, O'Leary M, Cavazzoni E, Wyburn KR, Webster AC. Effect of language and country of birth on the consent process and medical suitability of potential organ donors; a linked-data cohort study 2010-2015. *Journal of Critical Care*, 2020; 57:23-29. https://doi.org/10.1016/j.jcrc.2020.01.025

4. Loughman A, **Hedley J**, Olsson CA, Berk M, Moylan S, Saffery R, Sly PD, Tang MLK, Ponsonby A-L, Vuillermin P, the BIS Investigator Group. Increased maternal mental health burden in a representative longitudinal community cohort coinciding with COVID-19 lockdown. *Australian Journal of Psychology*, 2021; 73(4):578-585. https://doi.org/10.1080/00049530.2021.1956286

5. **Hedley JA,** Kelly PJ, Webster AC. Patient and kidney transplant survival in type 1 diabetics after kidney transplant alone compared to simultaneous pancreas-kidney transplant. *Australian and New Zealand Journal of Surgery*, 2022; 92(7-8):1856-1862. https://doi.org/10.1111/ans.17663

6. Thomson IK, **Hedley J**, Rosales BM, Wyburn K, O'Leary MJ, Webster AC. Potential organ donors with primary brain tumours: missed opportunities for donation and transplantation identified in Australian cohort study 2010–2015. *Australian and New Zealand Journal of Surgery*, 2022. https://doi.org/10.1111/ans.18037

A.2 Other publications that I contributed to during my PhD

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Appendix B – Other work during my PhD

In addition to the publications listed in Appendix A, I performed a lot of other work during my PhD which is not included in this thesis.

I contributed to numerous other manuscripts which at the time of writing had not yet been published. Many of these were part of ongoing research with the CODE team at the University of Sydney, but I also performed an analysis of cardiothoracic data lead by Dr. Francis Cheung at St. Vincent's hospital (Melbourne) and contributed to an updated cohort profile for the Barwon Infant Study lead by Prof. Peter Vuillermin at Deakin University. I also peer-reviewed a study for the Journal of International Medical Research.

During my candidature I undertook various forms of paid employment. I was a part-time data manager for the Barwon Infant Study, a role which I performed throughout the majority of my candidature. I was also employed casually for various roles for my supervisor Prof. Angela Webster at the University of Sydney, including preparing ANZIPTR reports and maintaining ORCHARD and SAFEBOD datasets. In addition to this, I also did some casual teaching work at the University of Sydney, tutoring for Introductory Biostatistics (PUBH5018), and doing some tutoring, lecturing, and course development for Analysis of Linked Data (PUBH5215) lead by my supervisor A/Prof. Patrick Kelly, as well as for Health Indicators and Health Surveys (BSTA5003) lead by Dr. Nicole De La Mata.