Redesigning deceased donor kidney transplant allocation in Australia

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Abstract

Kidney transplantation is a life changing event for a person living with end stage kidney disease and the allocation of deceased donor kidneys can have profound impacts on who has access to this treatment, the benefit that is derived from the gift of donation and the long term outcomes for the individual receiving the organ. The system that determines the allocation of deceased donor kidneys comprises a number of interconnected processes and must address a range of competing priorities. This thesis presents a series of related studies that provide evidence on the current state of deceased donor kidney allocation and demonstrate the feasibility and effectiveness of a novel framework for redesigning organ allocation protocols in Australia.

In order to better understand the context in which allocation occurs, Chapters 3 and 4 address key knowledge gaps in the Australian deceased donor kidney transplant system, reporting on the predictors of access to kidney transplant waitlisting in Australia, highlighting the disadvantage experienced by key populations, and exploring the causes of a recent increase in kidney non-utilisation.

Chapter 5, 6 and 7 analyse the impacts of previous changes to the allocation system, assessing their effectiveness, unintended consequences and highlighting key areas in which further policy intervention is required. The study reported in chapter 5 demonstrates that the reporting of the Kidney Donor Performance Index (KDPI) with organ offers in Australia was associated with changes in acceptance behaviour but not an increase in non-utilisation and provide insights into how donor risk indices might be incorporated into future allocating

algorithms. Analysis of the impact of the introduction of calculated panel reactive antibody (cPRA) to define sensitization for kidney transplant candidates, described in chapter 6, reveals the scale of disadvantage experienced by very highly sensitized patients and the ineffectiveness of the current allocation system in addressing this, adding urgency to the call for policy change to address this.

Further evidence to support change is reported in chapter 7, in an analysis of the effectiveness of paediatric bonuses in the Australian deceased donor kidney allocation system. This shows that whilst paediatric candidates are achieving rapid access to high quality organs, under current rules children are not receiving kidneys with optimal immunological matching. Chapter 8 explores the association between HLA epitope based matching and clinical outcomes in the paediatric population to investigate whether this may have potential as a novel approach to reducing immunological risk through optimised allocation.

Addressing the broader question of what the allocation system should be trying to achieve, results of a best worse scaling choice experiment presented in Chapter 9 show key differences in the principles prioritized by healthcare professionals when compared to the general community.

The final chapter of the thesis reports the development, validation and implementation of a platform to simulate deceased donor kidney allocation in Australia. In working closely with the national Renal Transplant Allocation Committee (RTAC), this study not only provided proof of concept for the value of simulation in organ allocation policy development in

Australia but produced direct and tangible improvements in the policy that will be implemented.

In taking a holistic approach to the process of redesigning deceased donor kidney allocation this work reports several novel findings that have had a direct impact on policy development and lays the foundations for an ongoing framework of evidence-based design for deceased donor kidney allocation in Australia.

Declaration

I hereby declare that:

i) this thesis comprises only my original work towards the Doctor of Philosophy except where indicated in the preface

ii) due acknowledgement has been made in the text to all other material used; and

iii) the thesis is fewer than the maximum work limit in length, exclusive of tables, maps, bibliographies and appendices

Dr Matthew P Sypek Date:

Preface

Publication status of data chapters and contributions of co-authors

Chapter 2: Published by the *American Journal of Kidney Diseases*, May 2018

Matthew Sypek was the primary author and participated in study design, literature review, manuscript drafting, drawing of figures, editing, revision and submission. He contributed 90% of the content for this publication. Joshua Kausman, Steve Holt and Peter Hughes participated in study design and review of manuscript.

Chapter 3: Published by *Nephrology,* July 2019

Matthew Sypek was the primary author and participated in study design and performed data management, statistical analysis, manuscript drafting, editing, revision, and submission. He contributed 85% of the content for this publication. Philip A Clayton assisted with statistical analysis and participated in study design, formulation of discussion and manuscript revision. Peter Hughes and Stephen McDonald participated in study design, formulation of discussion and manuscript revision. Jenni Wright and Jeremy Chapman facilitated access to data from the National Organ Match Service and participated in manuscript review. Wai Lim and John Kanellis participated in manuscript review.

Chapter 4: Published by *Transplantation,* April 2019

Matthew P Sypek was the primary author, participated in study design, and performed data management, statistical analysis, manuscript drafting, editing, revision, and submission. He contributed 80% of the content for this publication. Shahid Ullah assisted in statistical

analysis and data interpretation. Peter D Hughes, Philip Clayton and Stephen McDonald participated in study design, formulation of discussion and review of the manuscript.

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Matthew P Sypek was the primary author, participated in study design, and performed data management, statistical analysis, manuscript drafting, editing, revision, and submission. He contributed 85% of the content for this publication. Philip D Clayton assisted with statistical analysis and participated in study design, formulation of discussion and review of the manuscript. Peter Hughes and Stephen McDonald participated in study design, formulation of discussion and review of the manuscript. Rhonda Holdsworth and John Kanellis participated in review of the manuscript.

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Matthew P Sypek was the primary author, participated in the study design, had primary responsibility for administering and performing analysis on the healthcare professional study, participated in qualitative analysis, performed manuscript drafting, editing, revision

and submission. He contributed 55% of the content for this publication. Martin Howell participated in study design, had primary responsibility for survey design and administering and performing analysis on the community study, including the latent class analysis, and participated in manuscript drafting and revision. Emily Duncanson was involved in qualitative analysis and participated in review of the manuscript. Germaine Wong, Philip D Clayton, Kirsten Howard and Stephen McDonald participated in study design, expert review of allocation principles, formulation of discussion and review of the manuscript.

Chapter 10: Unpublished material not submitted for publication

Matthew P Sypek was the primary author, participated in study design, revised all input files for the Kidney Pancreas Simulated Allocation Model (KPSAM) software, developed methods for imputation of calculated panel reactive antibody data, performed all simulations, developed reporting tools, presented finding the Renal Transplant Advisory Committee (RTAC), interpreted simulation outcomes and performed iterative simulations, performed manuscript drafting, editing and revision. The KPSAM software was developed by the Scientific Registry of Transplant Recipients (SRTR) in the United States. Philip D Clayton performed the original adaptation of KPSAM to simulate Australian deceased donor kidney allocation including writing the original versions of Stata .do files to generate model inputs and build statistical models that were later revised, developed methods of imputing waiting list history and centre credit difference, developed original .do files for outcome reporting, supervised the updating of the simulations performed by Matthew Sypek, participated in study design, discussions with RTAC committee and review of manuscript. Aarti Guylani worked on an interim adaptation of software for simulating organ donation in Australia and

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Statement of ethics

The studies reported in chapters 3,4,5,6 and 7 of this thesis involved analysis of deidentified data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). This research was conducted in line with approval obtained from the Central Adelaide Local Health Network Human Research Ethics Committee (reference number HREC/17/RAH/408). The interpretation of these data is the responsibility of the authors and should in no way be seen as an official interpretation of the registry.

The study reported in chapter 8 of this thesis involved the analysis of deidentified data from ANZDATA and the Victorian Transplantation and Immunogenetics Service (VTIS). The datasets were combined using a study specific identification key provided by the ANZDATA registry. This study was approved by Monash Health Human Research Ethics Committee (reference number 14324L).

The study reported in chapter 9 of this thesis involved online surveying of members of the general community as well as targeted surveying of healthcare professionals and was approved by the University of Sydney Human Research Ethics Committee (reference number HREC:2017/869).

The study reported in chapter 10 of this thesis involved the use of deidentified data from the ANZDATA registry for simulations using software produced by the Scientific Registry of Transplant Recipients (SRTR). The study was approved by the Melbourne Health Human Research Ethics Committee (reference number LNR/16/MH/237). The Kidney Pancreas

Simulated Allocation Model (KSPAM) software was obtained from SRTR with written permission provided for use in this research.

Written consent was obtained directly from the patient whose case details are included in the prologue and epilogue. A pseudonym has been used. The patient has approved the completed text of the epilogue and prologue and has provided permission for this to be made publicly available as part of this thesis.

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This body of work brings together a number of collaborative studies in which I have relied on the expertise, teaching and contributions of a number of people to help build a richer understanding of the complexity of the field of organ allocation. I would like to express my thanks to the staff at the Victoria Transplantation and Immunogenetics Service, who took me under their wing and into their laboratory, to help me understand the ever more complex world of HLA typing and antibody detection; to the researches at the University of Sydney School of Public Health, particularly Martin Howell and Kirsten Howard, who took the time to help me understand a new set of tools to explore what we should be trying to achieve in redesigning organ allocation; to the members of the TSANZ paediatric transplant working group and its chair, Fiona Mackie, who are passionate about improving the outcomes for children with kidney disease; and to the members of RTAC who volunteer their time and expertise to work towards building a better allocation system, in particular, Kate Wyburn, who made it possible for this work to move from the theoretical into the practical, and thus to help to enact tangible and meaningful change.

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List of publications

Manuscripts resulting directly from work encompassed in this thesis:

Sypek MP, Hughes P, Kausman JY. Educational Review Article: HLA epitope matching in pediatric renal transplantation. *Pediatr Nephrol.* 2017;32(10):1861-1869

Sypek MP, Kausman I, Holt S, Hughes P. HLA Epitope matching in Kidney Transplantation: On Overview for the General Nephrologist. *Am J Kidney Dis.* 2018; 71(5):720-731

Sypek MP, Clayton P, Lim W, Hughes P, Kanellis J, Wright J, Chapman J, McDonald S. Access to waitlisting for deceased donor kidney transplantation in Australia. *Nephrology* 2019;24(7):758-766

Sypek MP, Ullah S, Hughes PD, Clayton PA, McDonald S. Examining the increased rates of deceased donor kidney non-utilisation in Australia: what has changed? *Transplantation.* 2019;103(12):2582-2590

Sypek MP, Hughes P, Holdsworth R, Kanellis J, McDonald S, Clayton P. Insights into the labelling effect of KDPI reporting: the Australian experience. *Am J Transplant.* 2020;20(3):870-878

Sypek MP, Hiho S, Cantwell L, Clayton P, Hughes P, Le Page A, Kausman J. Human leukocyte antigen eplet mismatches and long-term clinical outcomes in pediatric renal

transplantation: a pragmatic, registry based study. *Pediatric Transplantation.* 2020 Jun;24(4)e13705

Sypek MP, Kausman J, Watson N, Wyburn K, Holt S, Hughes P, Clayton P. The introduction of cPRA and its impact on access to deceased donor kidney transplantation for highly sensitized patients in Australia. *Transplantation.* 2020 In Press

Sypek MP, Davies C, Le Page AK, Clayton P, Hughes P, Larkins N, Wong G, Kausman JY, Mackie F. Paediatric deceased donor transplantation in Australia, a 30 year review: what have paediatric bonuses achieved and where to from here? *Pediatr Transplantation* (submitted August 2020)

Sypek MP, Howell M, Howard, K, Wong G, Duncanson E, Clayton PD, Hughes P, McDonald S. Healthcare professional and community preferences in deceased donor kidney allocation. *American J Transplantation* (submission in process)

Manuscripts related to work contained in this thesis published during the candidature:

Kausman JY, Walker AM, Cantwell LS, Quinlan C, **Sypek MP**, Ierino FL. Application of an epitope-based allocation system in pediatric kidney transplantation. *Pediatr Transplant.* 2016; 20(7):931-938

Sypek MP, Alexander SI, Cantwell L, Ierino FL, Ferrari P, Walker AM, Kausman JY. Optimizing outcomes in pediatric renal transplantation through the Australian paired kidney exchange program. *Am J Transplant.* 2017; 17(2):534-541

Clayton PA, Dansie K, **Sypek MP**, White S, Chadban S, Kaneliis J, Hughes P, Gulyani A, McDonald S. External validation of the US and UK kidney donor risk indices for deceased donor kidney transplant survival in Australia and New Zealand population. *Nephrol Dial Transplant*. 2019;34:2127-2131

List of conference presentations

The following conference abstracts have been presented by Matthew Sypek during his PhD candidature directly related to work encompassed in this thesis.

Sypek MP, Hiho S, Cantwell L, Clayton P, Hughes P, Le Page A, Kausman J. HLA eplet mismatches predict DSA formation, graft survival and retransplantation rate in paediatric renal transplantation – American Transplantation Congress (ATC), Chicago, US, 2017; (Oral abstract)

Sypek MP, Hiho S, Cantwell L, Clayton P, Hughes P, Le Page A, Kausman J. HLA eplet mismatches predict DSA formation, graft survival and retransplantation rate in paediatric renal transplantation – Transplantation Society of Australia and New Zealand (TSANZ) Annual Scientific Meeting, Brisbane, Australia, 2017; (Oral abstract – President's Prize Session)

Sypek MP, Clayton P, Lim W, Hughes P, Kanellis J, Wright J, Chapman J, McDonald S. Factors associated with time to deceased donor renal transplant waitlisting in Australia – Transplantation Society of Australia and New Zealand (TSANZ) Annual Scientific Meeting, Melbourne, Australia, 2018; (Oral abstract)

Sypek MP, Clayton P, Lim W, Hughes P, Kanellis J, Wright J, Chapman J, McDonald S. Factors associated with time to deceased donor renal transplant waitlisting in Australia – The

Transplantation Society (TTS) Annual Scientific Meeting, Madrid, Spain, 2018; (Poster presentation)

Sypek MP, Ullah S, Hughes PD, Clayton PA, McDonald S. The increased rate of non-utilisation of kidneys retrieved for transplantation in Australia is independent of donor characteristics – Transplantation Society of Australia and New Zealand (TSANZ) Annual Scientific Meeting, Melbourne, Australia, 2018; (Oral abstract)

Clayton P, **Sypek MP**, Guylani A, McDonald S. Allocation of low-risk kidneys: can we optimize utilisation? Transplantation Society of Australia and New Zealand (TSANZ) Annual Scientific Meeting, Melbourne, Australia, 2018; (Oral abstract)

Sypek MP, Hughes P, Holdsworth R, Kanellis J, McDonald S, Clayton P. Insights into the labelling effect of kidney donor performance index reporting: the Australian experience. Transplantation Society of Australia and New Zealand (TSANZ) Annual Scientific Meeting, Sydney, Australia, 2019; (Oral abstract)

Sypek MP, Howell M, Howard, K, Wong G, Duncanson E, Clayton PD, Hughes P, McDonald S. Healthcare professional and community preferences in deceased donor allocation: do the priorities align.- Transplantation Society of Australia and New Zealand (TSANZ) Annual Scientific Meeting, Sydney, Australia, 2019; (Poster Presentation)

Sypek MP, Kausman J, Watson N, Wyburn K, Holt S, Hughes P, Clayton P. The introduction of cPRA and its impact on access to deceased donor kidney transplantation for highly

sensitized patients in Australia. Transplantation Society of Australia and New Zealand (TSANZ) Annual Scientific Meeting, Adelaide, Australia, 2020, (Abstract accepted for oral presentation – meeting cancelled due to COVID-19)

Sypek MP, Davies C, Le Page AK, Clayton P, Hughes P, Larkins N, Wong G, Kausman JY, Mackie F. Paediatric deceased donor transplantation in Australia, a 30 year review: what have paediatric bonuses achieved and where to from here? Transplantation Society of Australia and New Zealand (TSANZ) Annual Scientific Meeting, Adelaide, Australia, 2020, (Abstract accepted for oral presentation – meeting cancelled due to COVID-19)

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Best poster abstract, Transplantation Society of Australia and New Zealand (TSANZ), 2019

Early Career Research Award (Clinical Science), Transplantation Society of Australia and New Zealand (TSANZ), 2019

List of Abbreviations

ABS	Australian Bureau of Statistics
ACT	Australian Capital Territory
aHR	adjusted hazard ratio
aIRR	adjusted incidence rate ratio
AMR	antibody mediated rejection
ANZDATA	Australia and New Zealand Dialysis and Transplant Registry
ANZOD	Australia and New Zealand Organ Donation Registry
ANZSN	Australian and New Zealand Society of Nephrology
aHR	adjusted hazard ratio
aIRR	adjusted incidence rate ratio
aOR	adjusted odds ratio
aSHR	adjusted subdistribution hazard ratio
BEAT CKD	Better Evidence and Translation in Chronic Kidney Disease
BMI	body mass index
BWS	best worst scaling
CAKUT	congenital abnormalities of the kidney and urinary tract
CDC	complement dependent cytotoxicity
CDR	complementarity determining regions
CI	confidence interval
cPRA	calculated panel reactive antibody
CREG	cross reactive group
DBD	donation after brain death

DCD	donation after circulatory death
DD	deceased donor
DDTx	deceased donor transplant
dnDSA	de novo donor specific antibody
DSA	donor specific antibody
DSA	donor specific antibody
EDR	electronic donor record
EpMM	eplet mismatch
EPTS	esitmated post transplant survival
ESKD	end stage kidney disease
GN	glomerulonephritis
HLA	human leukocyte antigen
HR	hazard ratio
IQR	interquartile range
IRR	incidence rate ratio
KDPI	kindey donor perforance index
KDRI	kidney donor risk index
LD	living donor
LDTx	living donor transplant
MFI	mean fluorescence intensity
MHC	major histocompatibility complex
MLR	mixed lymphocyte reaction
NGS	next generation sequencing

NHMRC	National Health and Medical Research Council
NOMS	National Organ Matching Service
NSW	New South Wales
NT	Northern Territory
OPTN	Organ Procurement and Transplantation Network
OR	odds ratio
OTA	Organ and Tissue Authority
PKD	polycystic kidney disease
PRA	panel reactive antibody
PS	preference score
QLD	Queensland
QoL	quality of life
RRT	renal replacement therapy
RSA	Renal Society of Australasia
SA	South Australia
SAB	single antigen bead
SBWMNL	sequential best worst multinomial logistic regression
SEIFA	socio-economic indexes for areas
SHR	subdistribution hazard ratio
SRTR	Scientific Registry of Transplant Recipients
SSO	sequence specific oligonucleotides
SSP	sequence specific primers
TNA	Transplant Nurses Association

TSANZ	Transplantation Society of Australia and New Zealand
UK	United Kingdom
UNOS	United Network for Organ Sharing
US	United States
VIC	Victoria
VTIS	Victorian Transplantation and Immunogenetics Service
VUR	vesicoureteric reflux
WA	Western Australia

Prologue

Charlotte was 15 years old when I first met her in the peritoneal dialysis clinic of the children's hospital, 2 weeks after completing my training in adult nephrology and commencing a fellowship in paediatric nephrology. Having become accustomed to the efficiency required to see the patient numbers passing through most adult dialysis clinics – review symptoms, check numbers, update prescriptions, next – I was little prepared for the challenge of wading through the sea of emotions that this young woman brought with her into her monthly review. Most teenagers find navigating the quagmire of educational demands, social networks, hormonal changes and identity formation challenging enough without the added burdens of nightly dialysis and the fog of uraemic malaise that accompanied Charlotte's failing treatment as her heroic peritoneal membrane struggled after years of glucose exposure.

She was accompanied to the clinic by both of her parents who had spent far too many Tuesday afternoons here over the last 15 years discussing medication changes, dietary restrictions and therapy plans. Both had come forward four years ago to volunteer their kidneys when her first graft was starting to fail and both were in perfect health - ideal donors. But despite their willingness to donate to Charlotte, here she was still, trapped on dialysis, her Tenckhoff catheter sucking the happiness from the room like the Dementor that stared mockingly at me from the cover of 'The Prisoner of Azkaban' jutting from her school bag in the corner of the room. (Where was her transplant patronus?)

Charlotte had been diagnosed with congenital nephrotic syndrome in infancy and after 2 years of albumin infusions and sequential nephrectomies to manage her protein losses, she underwent a living donor kidney transplant from her grandfather. Although this generous gift was transformative for young Charlotte, it came with foreign HLA antigens whose legacy sat before me, glaring down at this enthusiastic but poorly equipped physician who clearly had no idea what it was like to be a 15 year old girl, never mind a 15 year old girl sentenced to failing peritoneal dialysis.

Mismatched at HLA -A2, -B44, -DR4, -DR52 and -DQ7 this kidney had given her 10 years of relative normality. Ten years to grow, develop, attend school, go on family holidays and enjoy a relatively healthy life, provided she took her tablets and attended her regular follow ups, which she dutifully did. Transplanted kidneys do not last forever and as her creatinine began to rise and the uraemic symptoms began to creep up, the nephrology team had searched feverishly for a replacement.

Anti-HLA antibody screening showed that Charlotte's youthful immune system had awoken to the presence of this foreign tissue. The pathways essential for fighting off foreign pathogens and mopping up potentially cancerous mutant cells had not been entirely fooled by the immunosuppressive veils her transplant team had drawn across in an attempt to hide the friendly but alien tissue. And the response was robust. With a calculated panel reactive antibody of 100%, Charlotte had formed donor specific antibodies not only to her mother and father, but to all save her immunogenetic doppelgänger. Here she sat, night after night on the deceased donor waiting list, run after run in the national paired kidney exchange, phosphate ever rising, pill burden ever increasing, awaiting her twin.

And so it was, in my somewhat confronting introduction to paediatric nephrology that the seeds for this body of work were planted. Kidney transplantation has come a long way since 1954 when Richard Herrick received the first successful kidney transplant from his own twin, Ronald, and with each achievement new challenges are unmasked. The successes in preventing and treating cell mediated rejection have revealed antibodies as not only the major cause of late graft loss, but also a formidable barrier to re-transplantation. The clinical trials that produce the evidence on which we base our practice tend to have follow up of, at most, a few years. Charlotte's dilemma has inspired me to approach these unsolved challenges thinking on a scale of not years, but a lifetime.

Foreword

This body of work began with a relatively narrow focus of enquiry, summarized in the original working title, "The role of human leukocyte antigen (HLA) epitopes in redesigning the Australian kidney transplant system". Inspired by the increasing recognition within the transplant literature of antibody mediated damage as the major cause of long term graft attrition[1–3], the plight of very highly sensitized transplant candidates languishing on the waiting list, and by a novel program developed by one of my PhD supervisors (Dr Joshua Kausman) to optimise HLA epitope matching in paediatric deceased donor kidney transplantation within the limitations of the current allocation system[4]. I was optimistic that HLA epitopes may have a key role to play in the future of deceased donor kidney allocation. As I began my investigation into this question, a series of barriers and limitations, as well as new opportunities and new questions have shaped this thesis into a cohesive body of work that now focuses on broader questions that are summarized by the revised title "Re-designing deceased donor kidney transplantation in Australia".

My original hypothesis was that long term clinical outcomes in kidney transplantation, including a reduction in antibody mediated rejection and a reduction in the rate of sensitization, could be improved by enhancing HLA epitope matching between donors and recipients and that simulation of the Australian deceased donor organ allocation program can be used to demonstrate the feasibility and consequences of incorporating HLA epitopes into allocation algorithms.

This question led me to undertake a literature review into the role of HLA epitopes in kidney transplantation, the key findings of which have been published in two review articles[5,6] and undertake a program of laboratory observation at the Victoria Transplant Immunogenetics and Transplant Service, based at the Australian Red Cross Bloods Service (now LifeBlood). It was in performing my first study focusing on human leukocyte antigen eplet mismatches and long-term clinical outcomes in paediatric renal transplantation (which now forms Chapter 8 of this thesis) that some of the key limitations of my initial research plan, particularly related to data availability became apparent and thus inspired a reassessment of the aims of this thesis.

A key limitation of research into HLA epitopes in transplantation is the requirement for high resolution extended HLA molecular typing for donors and recipients. As further outlined in Chapter 2 of this thesis, several systems for defining HLA epitopes have been proposed, but all require high resolution molecular HLA typing. While this is rapidly becoming standard practice across tissue typing laboratories in Australia, the majority of historical typing data available for kidney transplants is serological typing or antigen level molecular typing. We were able to adopt a pragmatic approach to assigning HLA alleles based on haplotype associations and local population frequencies for the purpose of the paediatric study, however, it became apparent that the accuracy of these methods would not be sufficient for the further national, registry-based studies and simulations that were to form the core of the planned thesis. Due to the long duration of follow up required to observe the key outcomes of antibody mediated rejection, graft failure and sensitization at re-listing, studies of prospective cohorts with high resolution were not a feasible option.

Through my investigations into deceased donor kidney allocation simulation, it was also becoming increasingly apparent that due to the complex interactions of many factors involved in deceased donor kidney allocation, the aim of examining the role a single factor in isolation (in this case HLA epitope matching) in the redesign of the allocation system was fraught and of limited value. Any argument for introducing changes into deceased donor kidney allocation would have to consider a broad range of competing priorities and be cognisant of the risk of unintended consequences.

It was in this early crisis of direction that a fortuitous opportunity presented itself in the form of an advertisement for the position of Epidemiology Fellow at the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). ANZDATA is a binational registry of all patients receiving renal replacement therapy (RRT) (both dialysis and transplantation) for the treatment of end stage kidney disease (ESKD) in Australia and New Zealand. Having formed in 1975 from the amalgamation of two existing registries[7] and with complete capture of all kidney transplants performed in Australia, ANZDATA is a rich source of data for epidemiological research into kidney transplantation. I had already planned that ANZDATA would be a major source of data for my research and the registry's Deputy Executive Officer, A/Prof Philip Clayton, was a key collaborator on the simulation aspects of my thesis (and would later agree to support me as a co-supervisor).

I was successful in my application for the position and relocated to Adelaide, where the registry is based, to undertake the Epidemiology Fellowship whilst continuing my PhD studies part time. In immersing myself in the data on deceased donor kidney wait listing, organ donation, kidney allocation and post-transplant outcomes as part of this fellowship,

several unanswered questions relevant to my thesis arose. These, and a comprehensive understanding of the interdependencies of the organ allocation system, have led to a number of complimentary studies which form the basis of this thesis.

Through the early challenges of focusing narrowly on the role of HLA epitopes in redesigning deceased donor kidney allocation and the subsequent opportunities to learn through the ANZDATA Epidemiology Fellowship, the aims of this thesis evolved to a broader and more comprehensive set of objectives:

- To identify knowledge gaps in the deceased donor kidney transplant allocation system in Australia and use registry analysis to address these
- To analyse the impact of previous changes to the deceased donor allocation system in Australia
- To build on an evidence base that can guide and inform changes in deceased donor kidney allocation in Australia
- To develop and demonstrate the feasibility of a simulation model that can be used to assess the impacts of introducing changes to the deceased donor allocation algorithm in Australia

Ultimately this thesis aims to present a comprehensive case for using data to develop an evidence-based approach to the ongoing redesign of deceased donor kidney allocation systems in Australia in order to optimise the long-term outcomes for patients with the ESKD.

Chapter 1 Background

1.1 Introduction

Kidney transplantation is a life changing event for people experiencing end stage kidney disease (ESKD). For adults with ESKD who elect to receive renal replacement therapy (RRT) and are assessed as suitable for transplantation, the treatment offers superior survival and quality of life compared to dialysis [8–11]. Additional benefits in growth, neurocognitive development and education outcomes have also been demonstrated for children receiving kidney transplants compared to those on dialysis[12–15], providing an even stronger argument for preferencing this treatment in a younger population. Some patients are fortunate enough to have a suitable family member, friend or altruistic donor come forward, facilitating living donor kidney transplantation, however, many rely on deceased donation transplantation programs in order to access this transformative treatment.

Deceased donor transplantation is a profound accomplishment of modern human societies. Collectively we have managed to create systems that enable the gift of a functional organ to be transferred from one individual who has no hope of surviving to another person with whom the they typically have no personal connection, that will often restore near normal functional capacity. By their nature these systems are complex and present a range of interconnected logistical challenges and nuanced ethical considerations. Wherever functional deceased donor transplantation programs have been established, the demand for organs far exceeds the supply and a process for allocating organs must balance a number of competing priorities and principles.

A series of connected processes are necessary in order for a patient with ESKD to access an appropriate deceased donor kidney for transplantation. Firstly, a patient must be assessed as suitable for transplantation and be placed on a waiting list. A broad range of factors impact organ availability including donor referral, assessment and workup processes, consenting for donation and organ retrieval technical factors and logistics. Once an organ is retrieved it must be allocated to an individual on the waiting list and a decision made as to whether or not to accept the allocated organ. If accepted, the organ must be transported to the recipient, surgically implanted and immunosuppressive and other medical treatments provided to ensure optimal functioning of the organ. The complexity of the systems required to achieve a successful and optimised deceased donor transplantation system are only alluded to by this brief summary. Attempts to adjust an isolated aspect of the process are likely to have impacts on other components.

As a scarce and valuable resource, the system that determines how deceased donor kidneys are utilised should aim to optimise their usage to reflect the values of the community who provide this resource and achieve the best possible outcomes of the population most in need and most likely to benefit from kidney transplantation. Appreciating the complexity and interconnectivity of this system, this thesis takes a comprehensive, multidimensional approach to the goal of developing a framework for redesigning an optimised deceased donor kidney allocation system in Australia with the overarching aim of improving long term outcomes for patients receiving this treatment.

Four key questions have been used to frame this body of work:

1) What is the current state of the deceased donor allocation system in Australia?

2) What have been the impacts of previous changes to the system?
3) What additional evidence is needed to support future changes in the system?
4) What will be the likely impacts of future changes?

The thesis comprises eight distinct studies each addressing one of the above questions relating to a specific area of the deceased donor transplantation system in Australia where a key knowledge gap was identified. Chapters 3-10 are presented as completed manuscripts, each containing a review of the relevant literature within their background and discussion sections. In this introductory chapter I review the ethical considerations relating to deceased donor kidney transplantation, provide a detailed description of the current Australian deceased donor kidney allocation algorithms, highlight variations in international allocation systems and identify knowledge gaps in the Australian system. In doing so I hope to present a cohesive framework on which the subsequent chapters will build and provide rationale for why the specific studies were pursued. Detailed discussion of the chapter specific literature is contained within each chapter and not reproduced here. In addition, a comprehensive literature review of the role of HLA epitope-based matching in deceased donor kidney transplantation, published in the American Journal of Kidney Diseases (AJKD), is presented in Chapter 2.

1.2 Ethical considerations in diseased donor kidney transplantation

The demand for kidney transplantation in Australia far exceeds the available supply of suitable organs. During 2018, 911 deceased donor kidney transplants were performed in Australia[16], however, at the end of that year, 966 patients remained active on the waiting list in need of a kidney[17]. The pattern is similar throughout the world, in the United States (US) for example, just over 15,000 deceased donor kidney transplants were performed in 2018 with around 60,000 patients remaining active on the waiting list at the end of that year[18] and in the United Kingdom (UK) 4647 adult patients were active on the deceased donor kidney transplant waiting list in mid 2019 after 2339 adult kidney only transplants were performed in the preceding 12 months[19]. The imbalance between supply and demand in Australia is despite a more than doubling of the annual number of deceased organ donors[20] since the launch of a coordinated national reform program of organ and tissue donation for transplantation in 2008[21].

This situation of scarcity of a high value resource in the context of high demand is a common dilemma faced in the delivery of health care and has been sharply brought into focus by the global COVID-19 pandemic[22]. Persad et al (2009) offer a useful framework for considering the principles involved in the allocation of scare medical interventions[23]. They present eight ethical principles, classified in four categories according to their core ethical values: treating people equally, favouring the worst off, maximising total benefits and promoting and rewarding social usefulness. It is not argued that each of these principles hold equal weight, but rather that each situation of scarcity requires analysis of how these values should be

applied and which should have greater or lesser priority according to the specific circumstances and goals[22]. It is also clear that at times these values will be in competition, in that the result of prioritising one will be the compromising of another. In transplantation for example, maximising the total benefit of transplanted kidneys will likely be achieved by prioritising younger, fitter patients with the best long-term survival, however, this is likely to result in reduced access to organs for the worst off, who may gain the greatest individual benefit from a transplant but whose relative survival post-transplant is much poorer and would therefore reduce the overall utility of the system.

Access to transplantation and by extension, the development of organ allocation policy, must also be viewed with respect to human rights. Article 25 of the 1948 declaration of human rights outlines the universal right to a standard of living adequate for health and to access to medical care[24]. These rights are expanded on considerably in the 2015 Universal Declaration on Bioethics and Human Rights[25]. In reviewing the application of this declaration in organ allocation policy, Petrini (2016) highlights a number of relevant principles including: benefit and harm (Article 4), equality, justice and equity (Article 10), non-discrimination and non-stigmatization (Article 11), solidarity and cooperation (Article 13), social responsibility and health (Article 14) and sharing of benefits (Article 15). While much of the human rights discussion in transplantation has appropriately focussed on preventing donor coercion[26], deceased donor consent processes[27] and protecting living donor rights[28], it is clear that human rights issues must also be considered in allocation protocols.

Many national and international health bodies, including the National Health and Medical Research Council (NHMRC) in Australia, have produced ethical guidance on the allocation of

organ transplants[29–31]. These offer overviews of the principles and values that should underpin policy development. In the case of the NHMRC guidance[29] there is a particular focus on the principles of non-discrimination in allocation policy with section 2.2.2 stating:

"There must be no unlawful or unreasonable discrimination against potential recipients on the basis of:

- *race, cultural and religious beliefs, gender, relationship status, sexual preference, social or other status, disability or age*
- *need for a transplant arising from the medical consequences of past lifestyle*
- *capacity to pay for treatment*
- *location of residence (e.g. remote, rural, regional or metropolitan)*
- *previous refusal of an offer of an organ for transplantation*
- *refusal to participate in research."*

A white paper produced by the US Organ Procurement and Transplantation Network (OPTN)[30] offers a suggested framework for resolving conflict among competing ethical principles:

"When principles appear to conflict, policies should strive to ensure that: the policy is likely to be effective in achieving its aim; the infringement of a principle is minimized as far as possible; the good to be achieved is proportionate to the infringement of conflicting principles; and such policies are developed in a transparent manner allowing input from various stakeholder groups".

Deceased donor transplantation presents a unique challenge in considering the input of a key group of stakeholders, as due to the nature of events leading to donation, actual donors providing organs for transplantation are unable to express their wishes or desires for how their organs should be utilised. As such, the opinions of the community as a whole, who constitute the pool of potential donors, can be taken as a proxy for those of donors themselves. Previous studies on community preferences for the allocation of solid organ transplants have highlighted the complex balance of competing ethical principles that underpin attitudes to this challenging issue in the broader populations. For example, in a systematic review of fifteen qualitative and quantitative studies, Tong et al (2010)[32] identified seven themes describing community preferences including maximum benefit, social valuation, moral deservingness, prejudice, 'fair innings', 'first come, first served' and medical urgency. A systematic review by Oedingen et al (2019)[33] used a framework of principles of distributive justice to examine the same issue. They found that whilst studies showed a preference for a rational utilitarian ethical model, this was contradicted by a simultaneous priority to treat the most in need and concluded that "data on public preferences regarding clear trade-offs in donor organ allocation are still lacking".

Deceased donor kidney transplant allocation involves the rationing of a scarce, high value resource in which a number of potentially competing ethical values, human rights principles and a broad range of stakeholder interests must be considered. Any critique or redesign of this system must therefore use a broad lens to consider both the intended and unintended consequences of any intervention to ensure these principles are upheld.

1.3 The current Australian deceased donor kidney allocation algorithm

Responsibility for developing allocation protocols for deceased donor organ allocation in Australia sits with the Transplantation Society of Australia and New Zealand (TSANZ) and is funded by the Australian Government's Organ and Tissue Authority[34]. Although TSANZ has developed patient eligibility criteria and protocols for the allocation of organs for a number of years, these protocols were first published in the "Consensus Statement on Eligibility Criteria and Allocation Protocols" in June 2011 as part of the *National Reform Agenda – A World's Best Practice Approach to Organ and Tissue Donation for Transplantation*[35]. An extensive revision following feedback sought through a targeted consultation process was published as the "Clinical Guidelines for Organ Transplantation from Deceased Donors" in April 2016[36]. The latest version of this guideline is Version 1.3 published in May 2019[34]. Full details of the current deceased donor kidney allocation algorithms are included as Appendix A to this thesis.

Australia has five distinct transplanting regions which all participate in a coordinated nation deceased donor renal transplant program. Two of these regions (Queensland (QLD) and South Australia/The Northern Territory (SA/NT)) have single adult and paediatric transplant centres that coordinate deceased donor transplantation within that region, whereas Western Australia (WA) and the two largest regions (New South Wales/The Australian Capital Territory (NSW/ACT) and Victoria/Tasmania (VIC/TAS)) have multiple adult and 1-2 paediatric deceased donor transplanting centres.

Patient eligibility for activation on the waiting lists is determined by the local transplanting centre performing the clinical assessment and is based on eligibility criteria published by the Transplantation Society of Australia and New Zealand[34]. During the course of this thesis there was a key change to the eligibility criteria for deceased donor kidney transplant wait listing in Australia. Prior to 17/12/2018, in order to be eligible for waitlisting in Australia a person was required to be receiving dialysis for the treatment of ESKD, have a low anticipated likelihood of perioperative mortality, and have an anticipated 80% likelihood of survival at five years post-transplantation[36]. Subsequent to this date the wording of the final condition was changed to remove a specified threshold for predicted post-transplant survival and replace this with the requirement for candidates to have a "high likelihood of significant benefit from kidney transplantation"[34] in order to be eligible for listing.

In addition to being assessed as clinically suitable for transplantation, in order to be activated on the waiting list, patients must have 1) a valid ABO blood group, 2) validated tissue typing, and 3) screening for anti-HLA antibodies. Tissue typing for the purposes of organ allocation is considered at the antigen level and allocation scores are calculated considering mismatches at the HLA -A, -B and -DRB1 loci only. Anti HLA antibodies are assessed using multiplex bead-based immunoassays with unacceptable antigens entered by the local tissue typing laboratory base on these results. (Detailed background on techniques of HLA tissue typing and antibody detection and contained in Chapter 2 and discussion of changes in methods for determining panel reactive antibody (PRA) are explored in detail in Chapter 6).

Allocation of deceased donor kidneys is performed through a national system called OrganMatch which was implemented in 2019 and replaced a previous system known as the National Organ Matching Service (NOMS). Maintenance and operation of OrganMatch is contracted to Australian Red Cross Lifeblood (formerly Australian Red Cross Blood Service) which also provides the tissue typing and immunogenetics services in three of the five transplanting jurisdictions. Allocation lists are generated in OrganMatch by running up to three sequential algorithms for the allocation of kidneys from each donor – the national allocation formula, a regional allocation formula and the national override formula – and ordering recipients according to allocation scores.

Somewhat unique to the Australian context, a prospective complement dependent cytotoxicity (CDC) crossmatch test is performed for all candidates on the allocation lists and patients with a positive T-cell CDC crossmatch are excluded from the list prior to organ offers. This is achieved through a coordinated national program in which sera from patients active on the deceased donor kidney waiting list is distributed to all tissue typing laboratories monthly in ABO blood group specific trays. As part of the donor work up process, the workup laboratory will perform CDC crossmatches for all blood group identical candidates on the active trays and selected additional blood group compatible recipients if required. Crossmatches are only read for potential recipients appearing on the allocation list and patients with a positive CDC T-cell crossmatch are removed from the list prior to organ offers being made. This differs from many international transplanting programs where offers are made and accepted prior to crossmatches being performed locally.

Details of the national allocation formula are shown in Figure 1.1. In facilitating access to a larger donor pool, the national allocation algorithm prioritises transplants meeting the following criteria:

1) Where there are zero HLA mismatches (-A, -B and-DRB1) between donor and recipient
2) Patients with a PRA >80% where there are two or fewer HLA mismatches
3) Patients with PRA ≤80% where there are zero HLA -DRB1 mismatches and two or fewer HLA class I mismatches (subject to inter-regional kidney sharing balances)

The national formula also corrects imbalances of inter-regional shipping that accumulate based on the above prioritisation and provides a relative bonus for paediatric transplant candidates over adult candidates who otherwise meet the same criteria but have longer waiting time. Overall it is intended that around 20% of kidneys are transplanted through the national allocation algorithm[34].

National Allocation formula

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

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

Figure 1.1 National allocation formula for deceased donor kidney transplantation in Australia

Source: TSANZ (Transplantation Society of Australia and New Zealand). Clinical Guidelines for Organ Transplantation from Deceased Donors. http://www.tsanz.com.au/TSANZ_Clinical_Guidelines_Version 1.3%5B6986%5D.pdf. Published 2019. Accessed April 4, 2020.

The regional allocation formulae vary across jurisdictions, but each gives priority for transplants with few HLA mismatches and then, after an HLA mismatch threshold is reached, default to allocation based on waiting time. Overall it is estimated that around one third of kidneys will be allocated based on HLA matching bonuses and two thirds primarily on waiting time[34]. Some regions place stronger emphasis on the value of HLA -DR matching, whereas others treat all mismatches equally. WA differs from other regions in that the points awarded for waiting time are weighted more heavily such that long waiting patients will receive priority over those with more favourable HLA matching, and a bonus is given for long waiting patients who are homozygous at HLA-DR. The two larger transplanting regions (NSW/ACT and VIC/TAS) have formal bonus point systems for paediatric candidates (<18 years of age) which provide priority over adults with the same degree of HLA matching but longer waiting times. Formal paediatric bonuses do not exist in the three smaller transplanting regions but informal prioritisation or routine listing as 'urgent' is reportedly used to facilitate access to transplantation in this population. None of the regional transplanting formulae consider candidate sensitization in calculating allocation scores. Full details of the regional allocation algorithms are contained in Appendix A.

In rare cases where a kidney is not transplanted through allocation based on national or regional algorithms a national override list is generated with the aim of avoiding organ wastage. This most commonly occurs with blood group AB kidneys where there may be few patients on the regional waiting list, or with marginal donors whose organs are not accepted locally. The national override formula includes points for every PRA percentage point over 50, waiting time and a paediatric bonus.

Blood group compatibility rules are not formally published in the TSANZ guideline, however, based on personal correspondence with staff at OrganMatch, the current ABO compatibility rules used for the national formula are as outlined in Table 1.1 below. Most regional allocations are ABO identical, however, some regions elect to allocate to ABO compatible (but not identical) matches in some circumstances. If no suitable ABO compatible receipt is identified on national override allocation, ABO incompatible allocation is considered for patients with low anti ABO titres who have been pre-consented.

Donor Blood Group	Recipient Blood Group (Allocation Levels 1, 2 and 3)	Recipient Blood Group (Allocation Levels 4-7)
A	A, AB	A, AB
B	B, AB	B, AB
AB	AB	AB
O	A, B, AB, O	O

Table 1.1 ABO blood group compatibility rules used in the Australian national allocation formula

A number of authorized deviations in allocation are outlined in the TSANZ guidelines, these include for multiorgan transplants (including simultaneous pancreas and kidney (SPK) transplantation which is considered separately from kidney only transplantation when a suitable pancreas is donated), dual organ allocation when kidneys are assessed to be unsuitable for transplantation as individual organs, and to correct unplanned anomalies in the paired kidney exchange program such as a 'orphaned' recipient. In addition, exceptional circumstance such as prolonged ischaemic time, restored kidneys (that have had a tumour removed of anatomical abnormality corrected) or where an interstate recipient is found to be unfit after shipping, allow for deviations from standard allocation.

The VIC/TAS transplanting region has also introduced dual allocation streams by which donors are classified as either *'standard viral risk'* or *'increased viral risk'*. All patients on the waiting list are eligible for the allocation of organs from standard risk donors, whereas kidneys from increased viral risk donor are only allocated to patients who have pre-consented to this. Increased viral risk is defined as a donor who has a reported history within the last 12 months of a behaviour that has been associated with a higher risk of contracting of blood borne viruses (including hepatitis B, hepatitis C and human immunodeficiency virus (HIV)) and who has a negative nucleic acid test (NAT) for each of these viruses, but who has not yet cleared the relevant viral window period. Behaviours considered higher risk include the use of non-prescription intravenous drugs, working as a sex worker, being incarcerated and having male/male sexual intercourse. Organs from donors who are NAT positive for a blood borne virus are considered for use on a case by case basis.

A summary of all components included in the current deceased donor allocation system in Australia is provided in Table 1.2.

Table 1.2 Summary of factors used for allocating deceased donor kidneys in Australia

Factor	Role in Allocation
Patient Factors	
Waiting Time	Used in all allocation formulas
cPRA	Used in national and override formulas
Age	Used only in defining eligibility for defining paediatric bonus
ABO Blood Group	Determines organ eligibility (based on donor ABO) at various levels
HLA typing	HLA -A, -B, -DR typing used in determining mismatches used in national and regional formula
Homozygosity at -DR	Used in Western Australia regional allocation formula only
Anti-HLA Antibodies (exclusions)	Used to determine pre-allocation HLA antigen exclusions
Anti-HLA Antibodies (lower level)	Used to define donor specific antibodies
Patient risk index (EPTS)	Reported with organ offer but not used in allocation
Location	Determines regional allocation formula used
Donor Factors	
Location	Determines regional allocation formula used
ABO Blood Group	Determines eligible recipient groups (based on recipient ABO) at various levels
HLA typing	Used to determine HLA mismatches used in national and regional formula and define donor specific antibodies
Viral risk history	Used to define increased viral risk donors, allocated separately to standard viral risk patients in some regions
Donor risk index (KDPI)	Reported with organ offer but not used in allocation
Transplant Factors	
Blood Group Compatibility	Permissible blood group matches vary across allocation levels
HLA matching	Used in national and regional formulas. Weighting of mismatches at specific loci differs across various formulae.
Donor Specific Antibodies (exclusions)	Excluded pre-allocation
Donor Specific Antibodies (lower level)	Reported with offer but not used in allocation.
Cross-Match Results	Positive CDC T-cell crossmatches excluded pre-allocation
Special populations	
Paediatric patients	Bonuses applied in national formula, some regional formulae and override formula. Not linked to donor or transplant factors.
Medically urgent patients	Given priority listing in regional allocation
Multi-organ listings	Allocated through separate processes.
Orphaned paired kidney exchange recipient	Given priority listing in national allocation
System Factors	
Inter-regional sharing balance	Used in national allocation formula
Location of donor/recipient	Bonus in national formula

cPRA – calculated panel reactive antibody; HLA – human leukocyte antigen; EPTS – expected post transplant survival; KDPI – kidney donor performance index; CDC – complement dependant cytoxicity

1.4 Comparison to international allocation algorithms

Comparison to deceased donor kidney allocation systems in other national programs can highlight opportunities for improvement in Australia's allocation algorithms. As many of the features used in international allocation systems overlap with those used in the current Australian algorithm rather than presenting a point by point comparison to each international policy, the following review highlights novel allocation strategies that have been implemented in other national programs but are not present in the current Australian allocation rules. Detailed review of publicly accessible allocation policies from the following jurisdictions was conducted: New Zealand[34], US[37], UK[38], France[39], Israel[40], Eurotransplant (Austria, Belgium, Croatia, Germany, the Netherlands, Slovenia)[41], and Scandiatransplant (Denmark, Finland, Norway, Sweden, Iceland)[42]. Secondary sources referencing policies from the following jurisdictions were also reviewed[43–46]: Canada, Catalonia (Spain), Portugal, Italy, Czech Republic, Serbia, Greece, Hungary, Turkey, Lithuania, Spain, Poland, Slovakia, Switzerland and Estonia.

1.4.1 Approach to highly sensitized patients

Pre-formed antibodies to HLA are a major barrier to successful transplantation and transplant candidates with antibodies to a high percentage of the donor pool have difficulty accessing transplantation and have an increased mortality on the waiting list[47,48]. Priority for sensitized patients is typically based on PRA which represents the percentage of the potential donor pool to which a transplant candidate has antibodies that would prevent transplantation. PRA has historically been determined based on results of CDC crossmatch testing of patient sera against a panel of cells designed to present the potential donor

populational. From October 2009, the United Network of Organ Sharing (UNOS) replaced PRA with calculated PRA (cPRA) which is determined by comparing a list of antibody exclusions, typically defined based on multiplex bead based immunoassays, with the HLA frequencies within the potential donor population[49]. Other jurisdictions have subsequently adopted cPRA for defining sensitization[50,51] with Australia doing so in March 2016[34]. Many transplanting jurisdictions use a similar threshold of 80-85%[52] for applying bonuses for highly sensitized patients, however there are a few notable exceptions.

With the introduction of the new kidney allocation system (KAS) in 2014, the US revised their sensitization bonus from a set 4 point bonus for transplant candidates with cPRA ≥ 80% to an exponential bonus[53]. Bonus points awarded for cPRA in the US KAS are shown in Table 1.3. Under these new rules, candidates with cPRA 85-89% continue to receive a bonus of 4.05 points, however, this scales up dramatically to a maximum of 202.1 bonus points for candidates of cPRA of 100%, substantially increasing the priority given to this population. Although not exponential, Israel also provides an incremental bonus point allocation for increasing degrees of sensitization with points increasing for every 25% increase in PRA[40].

Table 1.3 Points allocated for each level of calculated panel reactive antibdody (cPRA) in the US Kidney Allocation System

Calculated Panel Reactive Antibody (%)	Bonus Points Awarded
0	0.00
1-9	0.00
10-19	0.00
20-29	0.08
30-39	0.21
40-49	0.34
50-59	0.48
60-69	0.81
70-74	1.09
75-79	1.58
80-84	2.46
85-89	4.05
90-94	6.71
95	10.82
96	12.17
97	17.3
98	24.40
99	50.09
100	202.10

Source: Organ Procurement and Transplantation Network (OPTN). Allocation of kidneys. https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf#nameddest=policy_08. published 2017. Accessed May 20, 2017.

An alternative approach is demonstrated in the UK's *matchability* points[38] and Eurotransplant's mismatch probability (MMP)[41], both of which combine information on recipient ABO blood group, HLA typing and unacceptable antigens to produce a measure of the likelihood of the individual receiving a transplant with favourable HLA matching given the potential donor pool. Prior to a major revision of UK kidney allocation policy in September 2019[54], the former system, in use from 2006-2019, gave priority to patients with a calculated reaction frequency of ≥85% for kidneys with a high degree of HLA matching[55]. The new system uses a novel metric known as the *matchability,* to assign priority within allocation. A *match score* is calculated based on the candidate's ABO blood group, HLA typing and unacceptable antigens. The number of ABO-identical, HLA compatible patients within a donor pool of 10,000 patients that a given recipient has a HLA mismatch at level 1 (0 -A,-B, -DR mismatches) or level 2 (0 -DR & ≤1 -B or 1 -DR & 0 -B mismatches) is counted and used to determine a *match score* ranging from 1-10 with higher scores indicating increased matching difficulty[56]. The match score is converted to allocation points using the formula $(40*(1+(\text{Match score}/4.5)^{4.7})$ which results in an incremental scale as shown in Figure 1.2. In addition, candidates with a calculated reaction of 100% or a match score of 10 (along with patients with ≥7 years of waiting time) receive addition priority through a separate tier of allocation that sits above standard allocation[38]. Eurotransplant's MMP, used in determining general allocation points, is calculated using similar methods to the UK's matchability score, however, a different approach has been adopted to facilitate access to transplantation for the very highly sensitized.

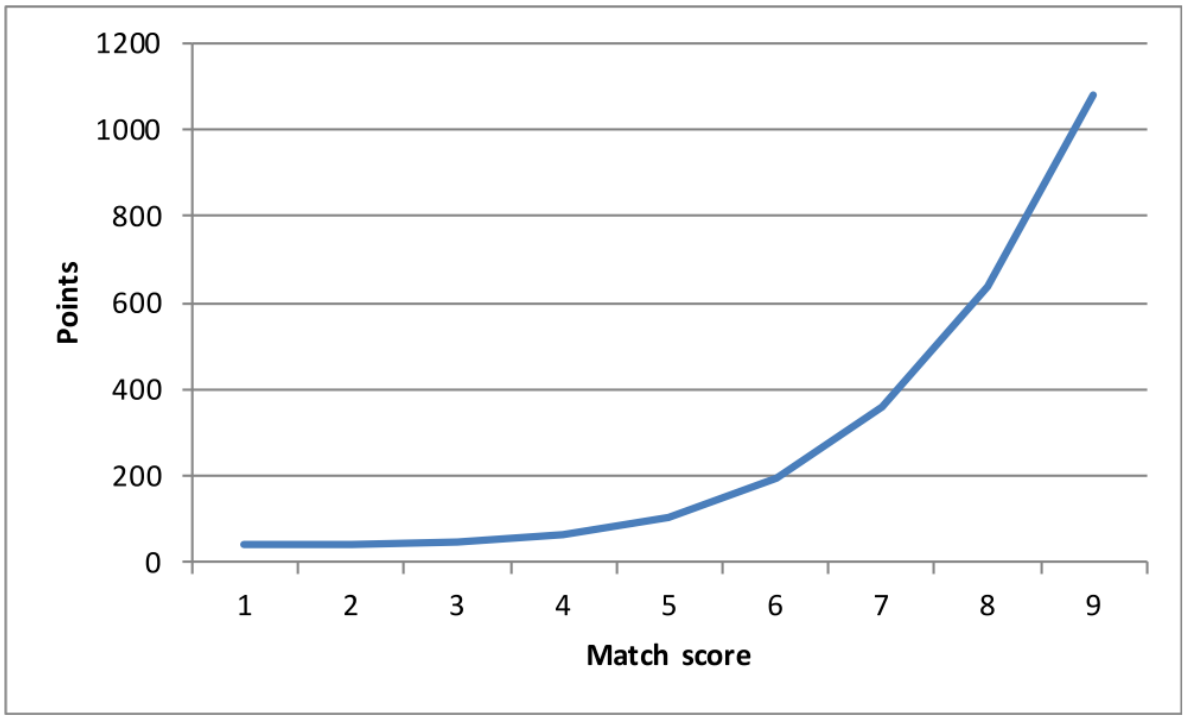

Figure 1.2 Allocation points awarded according to match score in the United Kingdom's deceased donor kidney allocation program

Source: NHS Blood and Transplant. Kidney Transplantation : Deceased Donor Organ Allocation (POLICY POL186/10).; 2019. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/16915/kidney-allocation-policy-pol186.pdf.

Acceptable mismatch programs implemented in Eurotransplant[41] and Scandiatransplant[42] aim to allocate kidneys to patients who are immunologically compromised because of HLA sensitization through a selective program of immunological curation. The anti-HLA antibody profiles of highly sensitized patients with low probability of receiving a matched kidney are reviewed in detail by an HLA immunologist. Various strategies including epitope analysis[57] are used in reviewing the transplant candidate's antibody profile to identify *acceptable antigens,* defined as HLA antigens to which the patients has never made antibodies. If a kidney from a donor with a HLA profile matching the candidate's list of acceptable antigens becomes available, that candidate receives priority for the organ over the standard allocation list[41].

1.4.2 Longevity matching

In addressing the goal of optimising overall utility of the deceased donor kidney transplant system, ideally the maximum number of functioning graft years should be achieved from each available organ. From a utilitarian perspective, the situation in which a patient dies prematurely with a functioning graft that could potentially have provided ongoing replacement of renal function in healthier recipient, should be avoided. Similarly, delaying graft failure in younger patients with better long-term prognosis by transplanting these recipients with the kidneys with the best predicted survival, will reduce the need for re-transplantation (which may be challenging due to the development of sensitization), resulting in benefits for both the individual and the system as a whole. These arguments have led to the introduction of allocation based on longevity matching in some deceased donor transplant programs.

A number of transplant programs have used donor and recipient age as proxies for predicted post-transplant survival and developed specific allocation rules based on donor age or donor/recipient age differences. For example, the historical Share 35 program in the US prioritised paediatric candidates ahead of adult candidates for kidneys from donors aged <35 years[58] and the current French allocation system gives priority to candidates under the age of 18 for kidneys from donors age <18 years nationally, and donors aged <30 years regionally[39], with similar policies in many European countries[45]. Age matching is promoted in the UK by subtracting allocation points for a difference in donor- recipient age[38]. Although designed with the aim of decreasing cold ischaemic time in organs from more marginal donors, the Eurotransplant Senior Program (ESP) which facilitates rapid allocation of organs from older donors (age ≥65 years) to older recipients (aged ≥65 years) also results in donor-recipient age matching for these organs[41]. Kidneys from donors meeting this criterion are allocated to older recipients without the use of HLA typing with the allocation list ranked on urgency and waiting time.

Recognizing that other donor factors, in addition to age, are associated with post-transplant graft survival, a number of donor risk scores have been developed and subsequently adopted in deceased donor transplantation algorithms[59–62]. The Kidney Donor Risk Index (KDRI) was developed by Rao et al (2009) as a comprehensive risk quantification score using donor and transplant factors to estimate the risk of graft survival[59]. A modified version of this index using only donor factors (including: age, ethnicity, creatinine, history of hypertension, history of diabetes, cause of death, height, weight, donation pathway and hepatitis C status) was adopted for donor classification in the 2014 US KAS. The raw KDRI score is used to derive a kidney donor performance index (KDPI) which represents the

percentage of kidney donors in a reference population that have a KDRI less than or equal to the donor's score. Adults on the deceased donor waiting list are also classified in terms of risk of death post-transplant using the Estimated Post-Transplant Survival (EPTS) score. Factors included in the EPTS are: recipient age, time on dialysis, diabetes status and whether or not the candidate has had a previous solid organ transplant. Under the KAS, organs are classified in 4 groups according to KDPI (KPDI ≤20%, KDPI >20 but <35%, KDPI ≥35% but ≤85%, and KDPI >85%). Separate allocation rules are applied to each KDPI with priority given to patients with EPTS≤20% for kidneys with KDPI≤20%[37].

The recently revised UK kidney allocation system also introduces donor and recipient risk indices and presents an alternative method of incorporating these into points allocation[38]. The donor risk score (DRI) is calculated based on: age, height, history of hypertension, donor gender, cytomegalovirus (CMV) seropositivity, estimated glomerular filtration rate (eGFR) and days in hospital. The recipient risk score (RRI) is calculated based on: age, dialysis at registration, waiting time from dialysis and diabetes status. Both scores are classified into four risk groups according to absolute cut-off values defined in the allocation protocol and points are awarded by comparing the donor and recipient risk categories at time of allocation according to Table 1.4. Maximal points are awarded for donor and recipient risk index concordance with points incrementally decreasing with progressive differences in risk categories. Unlike the US system which only prioritises kidneys with the best post-transplant survival to recipients with the best post-transplant survival, the UK program also promotes longevity matching for organs with the poorest post-transplant survival so that these are preferentially allocated to recipients with the poorest post-transplant survival, achieving a similar outcome as Eurotransplant's ESP.

Donor Risk Group	Recipient Risk Group R1	R2	R3	R4
D1	1000	700	350	0
D2	700	1000	500	350
D3	350	500	1000	700
D4	0	350	700	1000

Table 1.4 Points allocated according to donor and recipient risk indices in deceased donor kidney allocation in the UK

Source: NHS Blood and Transplant. Kidney Transplantation : Deceased Donor Organ Allocation (POLICY POL186/10).; 2019. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/16915/kidney-allocation-policy-pol186.pdf.

The use of donor and recipient risk indices is currently being debated in the Australian kidney transplanting community[60,61,63,64] and although not yet used in allocation, the KDPI and EPTS are currently reported with all organ offers[65].

1.4.3 Application of paediatric bonuses

For most children with ESKD, kidney transplantation not only offers a survival benefit when compared with dialysis[66], but also provides improved opportunities for growth[12], neurocognitive development[13], education and social interaction[14], and a superior quality of life[15]. A white paper produced by the OPTN/UNOS Paediatric Transplantation and Ethics Committees set out several philosophical justifications for paediatric priority including the prudential lifespan account, the principles of 'fair innings' and maximising the minimum benefit to the least advantaged, and utility considerations[67]. Recognising the unique needs and potential benefits of transplantation for this population, many transplant programs worldwide have specific deceased donor organ allocation rules aimed at prioritising access to transplantation for children with ESKD[43,45].

In Australia, paediatric bonuses are applied solely based on recipient age (<18 years) and therefore do not consider donor age, predicted organ survival or HLA matching. A comprehensive review of European policies relating to paediatric kidney transplantation in Europe by Harambat and Stralen (2013)[45] showed wide variation in how paediatric bonuses were applied across the continent. The age by which childhood was defined ranged from <15 years in Spain to <21 years in Serbia. While in many countries paediatric bonuses no longer apply after a child reaches the age of maturity, in some jurisdictions such as France[39],Eurotransplant[41] and the US[37] bonuses are continued into adulthood if the candidate commenced dialysis (or was registered on the waiting list, in the case of the US) in childhood but has not yet been transplanted. As outlined in the section above, paediatric priority is achieved in many programs through preferential allocation of donors of a certain age to paediatric candidates. In the US, paediatric priority is only granted for kidneys with KDPI<35% or when KDPI is ≥30% but ≤85% and there are zero -A/-B/-DR mismatches[37].

As well as making paediatric bonuses contingent on donor factors, in some jurisdictions paediatric bonuses are only applied in the setting of favourable HLA matching or bonuses serve to amplify HLA matching points. In Scandiatransplant for example, donors <40 years are offered to recipients <16 years as long as there is DR compatibility and no more than 2 HLA-A or -B mismatches[45]. In Turkey, recipients aged <11 years double their HLA matching points and those aged 11-18 receive a 1.5 fold increase[45].

One of the more novel applications linking paediatric priority to HLA matching is in the current UK allocation algorithm[38]. Paediatric bonuses per se have been removed from the allocation algorithm (except in the case of clinically urgent paediatric listings) and are

replaced with a combined HLA match and age score that is calculated for all patients. All potential combinations of HLA mismatch at -A/-B/-DR have been grouped into four levels, where level one is the most favourable mismatch (ie zero HLA mismatches) and level four is the least favourable (1 -DR and 2 -B mismatches or 2 -DR mismatches). Separate equations are used to calculate allocation points for levels of mismatch according to age. Those equations are:

- Level 1 = 1200*COS(age/18)+2300
- Level 2 = 750*COS(age/18)+1500
- Level 3/4 = 400*Sin(age/50)

Figure 1.3 illustrates these functions and shows how younger patients receive a substantial point allocation for well-matched kidneys (levels 1 & 2) but no priority for poorly matched kidneys compared to older adults. It is noteworthy that in the revised equations introduced in 2019, the allocation points for well-matched kidneys increase with age after a nadir for candidates in their late 50s, in the previous allocation policy points continued to taper with increasing age[68]. The intention of this is not stated in the policy document, however, this may relate to the higher risk of infectious complications in older transplant recipients[69] in that a well-matched transplant may permit a lower burden of immunosuppression, or perhaps may be intended to balance the reduce priority give to older recipients based on the longevity matching system outlined above. Under the UK allocation algorithm, paediatric recipients are not considered for kidneys from donors over 50 years of age.

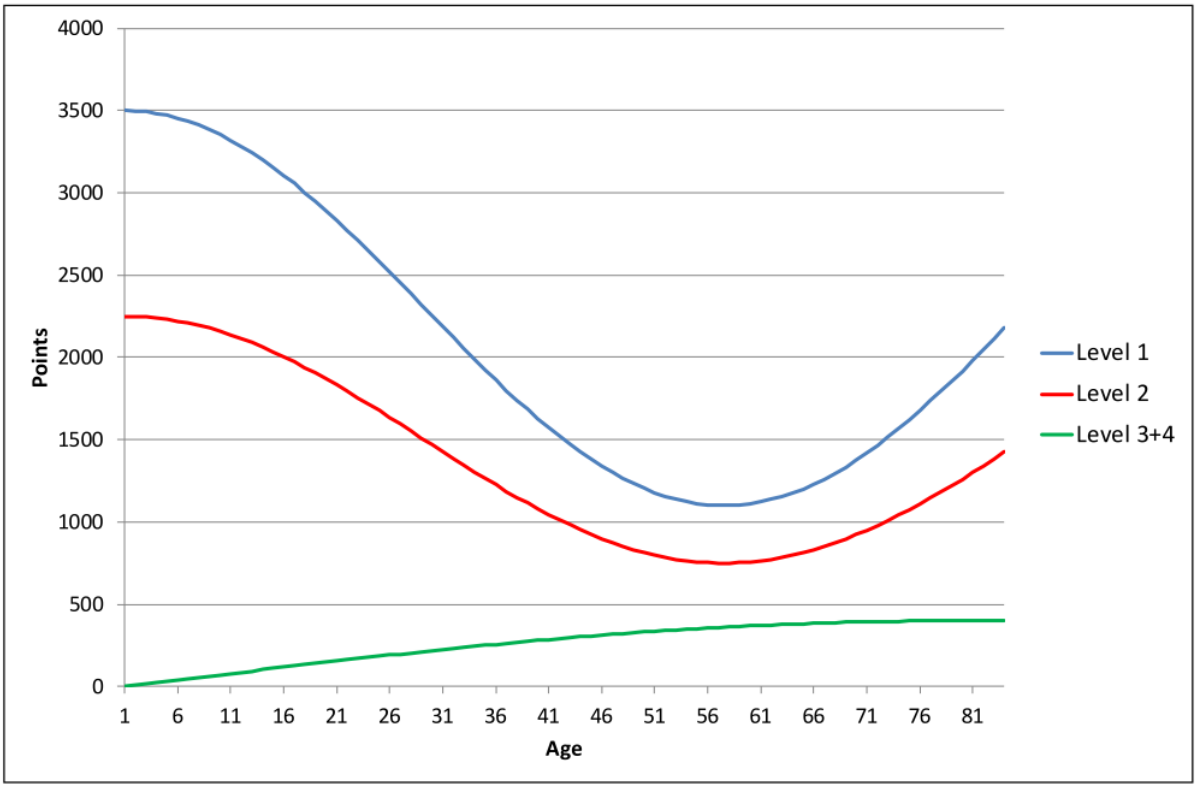

Figure 1.3 Allocations points awarding to age and level of HLA matching in the United Kingdom's deceased donor kidney allocation program

Source: NHS Blood and Transplant. Kidney Transplantation : Deceased Donor Organ Allocation (POLICY POL186/10).; 2019. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/16915/kidney-allocation-policy-pol186.pdf.

Paediatric priority is included in all of the allocation systems reviewed, implying a broad acceptance of the justifications for positive discrimination in this population. In their current form Australia's paediatric bonuses are not contingent on favourable donor characteristics or immunological matching and international comparisons demonstrate examples of how this might be achieved. It is also important to consider the unintended consequences of any priority system, as illustrated by analysis of the Share 35 program, a previous paediatric priority in the US outlined above. Whilst this program achieved its goal of improving access to deceased donor transplantation for paediatric candidates, the expedited access was also associated with a decline in living donor transplant rates and increase in HLA mismatches for this population[70].

1.4.4 Other opportunities

The discussion above outlines three key areas where international practice varies significantly from the current Australian allocation system, and therefore highlights areas that may be considered for improvement. Other examples of novel allocation rules that have been implemented in deceased donor kidney allocation include: priority for registered donors in Israel[46], distinct allocation pathways for HLA homozygous donors in Eurotransplant[41], and the use of HLA-epitope based exclusion in an Australian paediatric transplanting centre[4], to highlight a few. Of course, the redesign of deceased donor kidney allocation in Australia need not be limited to what has been done elsewhere before. Understanding the deficiencies of the current system in Australia is a vital step in considering the opportunities for improvement.

1.4.5 The role of simulation in testing deceased donor organ allocation systems

Recognizing the complexity of organ allocation systems, the need to strike a compromise between equity, efficiency and practicability, and the imperative to detect potential unintended consequences of policy interventions prior to implementation, many have argued for the value of simulation in the development of allocation protocols[53,71–75]. The major revision of deceased donor kidney allocation in the US in 2014 was heavily informed by simulations conducted on a bespoke platform developed by the Scientific Registry of Transplant Recipients (SRTR)[53]. The Kidney Pancreas Simulated Allocation Model (KPSAM) uses historical waiting list and organ donation data to simulate deceased donor kidney and pancreas transplantation using an event sequenced Monte Carlo technique[76]. The model was extensively validated by SRTR and used to test proposals that were eventually implemented as a completely revised allocation protocol[53]. The *Agence de la biomedicine* in France has used a similar approach to SRTR in developing a 'dynamic historical data based simulation' to model allocation proposals and conclude in their initial reporting on the use of these simulations that they have been *"shown to be a helpful tool during the allocation design phase providing objective facts for the debates and increasing the potential for change"* [73]. Likewise, the National Health Service Blood and Transplant (NHSBT) in the UK has developed an event based simulation covering a 4 year period to assist in the design process for the revision of allocation protocols implemented in September 2019[54,77]. There are many challenges in attempting to accurately model the complexity of a deceased donor transplant allocation system and even if simulations were able to perfectly predict the effect of new allocation protocols based on historical patterns of behaviour, they are unable to account for behavioural changes induced by the policy itself[74]. Despite these limitations, the

use of simulation models in the process of policy design and testing internationally has shown them to be a valuable tool in refining and implementing changes.

1.5 Identifying knowledge gaps in Australia's deceased donor kidney program

Australia is fortunate to have a national renal replacement therapy registry which not only has complete capture of transplant activity through direct input from the donation sector, but also collects a rich outcome dataset from all kidney transplanting units[7]. The ANZDATA registry publishes a comprehensive annual report as well as centre specific outcome reports. While these reports often identify trends and patterns, targeted epidemiological analysis is required in order to explore these trends further, determine associations and test hypotheses of causation. In reviewing the data available on the deceased donor kidney allocation system in Australia, several knowledge gaps were identified and are discussed below.

1.5.1 Access to the deceased donor waiting list

ANZDATA reports annually on the deceased donor kidney transplant waiting list including: waiting list dynamics, the proportion of RRT patients on the list by region, waiting list demographics, transplant rate and in more recent years on outcomes after waitlisting[17]. However, an analysis of predictors of deceased donor kidney transplant wait listing in Australia has not be reported. Commentary based on publicly available registry data has questioned the low proportion of prevalent dialysis patients on the renal transplant waitlist

in Australia[78] and qualitative analysis of nephrologists' perspectives on waitlisting has revealed tensions between advocating for the best treatment for their own patients, maintaining professional integrity and protecting centre reputation, and maximising societal benefit[79].

Studies of waitlisting practice in other countries have consistently found inequalities in completion of transplant work up and waitlisting for patients on dialysis based on patient factors including race[80–82], gender[81,83,84], socioeconomic status[80–82] and regional factors[85,86]. Small, single centre audits in Australia have helped identify some barriers to timely transplant waitlisting[87], and previous work has reported reduced access to waitlisting for Australia's Indigenous population[88], however, prior to the work presented in Chapter 3 of this thesis, a comprehensive analysis of waiting list practice in Australia that may identify additional areas of inequality was lacking.

1.5.2 Deceased donor kidney non-utilisation

Reduced availability of deceased donor kidneys for transplantation due to organ non-utilisation has also been a major topic of debate in international literature[89–94] on which local analysis was lacking. The United States in particular saw an increase in kidney non-utilisation from below 10% in the early 1990s to almost 20% in recent years[91] and the United Kingdom saw an increase from 5% to 12% across the first decade of this century[93]. The percentage of kidneys retrieved in Australia, but not transplanted is reported in the ANZOD annual report. Although non-utilisation rates are low compared to international standards, in 2013 this more than doubled from 3.0% in the preceding year to 6.7%, with levels remaining elevated in subsequent years[95].

The heterogeneity of donation, retrieval and allocation systems in different countries, as well as differences in population characteristics limit the relevance of direct international comparisons of the causes of organ non-utilisation. Nevertheless, it is notable that studies in the US have demonstrated a number of predictors of non-utilisation in the local context[90,91,96] and one analysis estimated that 82.5% of the increase in kidney non-utilisation in the US could be explained by changes in donor characteristics, and biopsy and machine perfusion practices over time[91]. Understanding if changes in donor characteristics, organ acceptance patterns or other factors have contributed to the increase in kidney non-utilisation seen in Australia is important when considering the redesign of organ allocation. Not only do utilisation rates directly impact organ availability for transplantation, but allocation protocols are also likely to directly influence organ utilisation.

1.5.3 Impacts of previous changes to the allocation system

The most recent comprehensive review of deceased donor kidney allocation policy in Australia was released in April 2016 and was developed through the TSANZ advisory committee with written feedback sought through a targeted consultation process'[34]. This document, *Clinical Guidelines for Organ Transplantation from Deceased Donors Version 1.0* replaced the previous *Consensus Statement of Eligibility Criteria and Allocation Protocols* that was originally released in June 2011[35]. The structure and components of the current allocation system, outlined in detail above, have not changed substantially since the 2011 protocol, however a number of specific alterations to allocation policy have been implemented over this time period. Although justifications for these changes have been published, little or no analysis of their impacts has been reported. Three key examples of policy revisions for which post implementation analysis has not been reported are: 1) the

introduction of paediatric allocation bonuses in national and regional algorithms, 2) the reporting of KDPI with all kidney offers and 3) the introduction of cPRA to replace PRA in defining sensitization for waiting list candidates. The context in which these changes were introduced, relevant background literature and justifications for analysing their impacts are described in detail in the relevant chapters that follow.

1.6 Summary

A person living with ESKD who is suitable for transplantation but who does not have access to an appropriate living donor is dependent on the deceased donor kidney transplant system to provide them with an organ that has the potential to dramatically improve their quality of life and long-term survival. The system they rely on comprises a number of interconnected processes that all must align in order to achieve a successful transplant. The design of that system must not only consider the needs of each individual, but also achieve balance between competing needs whilst at the same time optimising the overall benefits. Complex interdependencies exist between waiting list practices, organ availability and allocation policies where changes in any of these may influence components of other. Decisions that are made to prioritise one patient group or optimise a particular aspect of the system will result in decreased access to organs for other patient groups or may compromise an alternative goal. It is therefore vital that any attempt to redesign deceased donor kidney allocation takes into account the complexity of these system and uses a multifaceted and comprehensive approach in assessing the impacts of any intervention.

Each of the eight studies presented in this thesis addresses a specific hypothesis relating to the deceased donor kidney transplant system in Australia. Together they present a cohesive argument for how epidemiological analysis, choice experiments and computer-based simulation can be used to assist in the redesign, implementation and assessment of deceased donor kidney transplant allocation policies to ultimately improve the long-term outcomes of people living with ESKD.

Chapter 2 HLA Epitope Matching in Renal Transplantation: An overview for the general nephrologist

2.1 Preface

The content of this chapter has been published in The American Journal of Kidney Diseases (Am J Kidney Dis. 2018; 71(5):720-731) and provides further background and a literature review relevant to the role of human leukocyte antigen (HLA) epitope based matching in kidney transplantation. The text is identical to the published manuscript apart from minor stylistic changes to figure and table titles and legends.

Authors

Matthew P Sypek, Joshua Y Kausman, Steve Holt, Peter Hughes

Author contributions are described in the thesis preface.

2.2 Abstract

Rapid changes in tissue typing technology, including the widespread availability of highly specific molecular typing methods and solid phase assays for the detection of allele specific anti-human leukocyte antigen (HLA) antibodies, make it increasingly challenging to remain up to date with developments in organ matching. Terms such as *epitopes* and *eplets* abound in the transplant literature, but often it can be difficult to see what they might mean for the patient awaiting transplantation. In this review we provide the historical context for current practice in tissue typing and explore the potential role of HLA epitopes in renal transplantation. Despite impressive gains in preventing and managing T-cell mediated rejection and the associated improvements in graft survival, the challenge of the humoral allo-response remains largely unmet and is the major cause of late graft loss. Describing HLA antigens as a series of antibody targets, or epitopes, rather than based on broad seroreactivity patterns or precise amino-acid sequences, might provide a more practical and clinically relevant system to help avoid antibody-mediated rejection, reduce sensitization and select the most appropriate organs in the setting of pre-existing allo-antibodies. We explain the systems proposed to define HLA epitopes, summarize the evidence to date for their role in transplantation and explore the potential benefits of incorporating HLA epitopes into clinical practice as this field continues to evolve towards everyday practice.

2.3 Introduction

Recently, a number of reviews of human leukocyte antigen (HLA) epitopes and their significance in renal transplantation have appeared in the transplant literature [97–103]. For the general nephrologist, keeping track of the ever-increasing complexity of transplant tissue typing, the expanding list of HLA alleles and the significance of allele specific anti-HLA antibodies detected by solid phase assays, has been challenging enough[104,105] without the introduction of new concepts such as epitopes. Added to this complexity are the competing priorities of organ quality matching, improving access to transplantation for sensitized individuals and disadvantaged minority populations, and addressing overall waiting times. In the modern era of highly effective immunosuppression which has led to low rates of T-cell mediated rejection, some have even questioned the ongoing relavance of HLA matching.

In this review we set out to provide a simple overview of the history behind HLA typing and the theory of HLA epitopes. We explain the systems that have been proposed to define HLA epitopes and review the potential benefits of considering HLA compatibility at the epitope level. We aim to assist nephrologists in navigating the increasingly complex world of HLA matching and demonstrate why a shift in the paradigm of how we define tissue matching to an epitope based system may potentially offer long term benefits for our patients.

2.4 A brief history of HLA Discoveries

It is just over 100 years since it was first recognized that the growth of genetically distinct (allogenic) transplanted tumours was a heritable trait[106], suggesting that a system for detecting phenotypically different cells exists. Major discoveries in the field of histocompatibility are highlighted in the timeline in Figure 2.1.

The first human histocompatibility antigens were identified in 1958 by analysing agglutination patterns when white cells were mixed with serum extracted from multiply transfused patients and multiparous women [107–109], these were later named human leukocyte antigens (HLA). Subsequent groups discovered a second[110], and later a third[111], set of distinct histocompatibility antigens termed HLA-B and HLA-C respectively. As more sophisticated serological techniques were developed, it became possible to divide previously serologically defined HLA groups into more specific sub-types[112]. For example, HLA A9 was first described at the 1964 workshop[113], but later subdivided into two distinct groups with different reactivity patterns[114] and in 1972 A9 was superseded by A23 and A24[112].

Further advances were made when it was observed that mixed lymphocyte reactions (MLR) could identify an additional distinct HLA reactivity pattern[115], provisionally named HLA-D. Analysis of antisera that identified antigens present on B cells, but not T cells, revealed antigens closely related to the HLA-D determinants from the MLR. These were named D 'related', or HLA-DR, antigens and subsequent analysis identified that several closely linked genetic loci (DR, DQ, DP) encode proteins for these B cell antigens. Thus, by the mid 1970s,

the overall structure of the HLA system had been mapped, and a set of serologically defined HLA types had been agreed upon though collaborative efforts[116].

The first HLA gene sequence was reported in 1981[117], beginning the era of molecular typing. Modern tissue typing laboratories use a number of molecular technologies to perform HLA typing that are based on determining the sequences of HLA genes rather than on patterns of serological reactivity to leukocytes [98,118]. As techniques of molecular typing have developed, HLA naming conventions have had to be adapted to accommodate proteins that are within the same serological class but differ in their amino-acid sequence or genetic coding.The current system of HLA allele classification is denoted by a letter representing the HLA locus followed by an asterisk to indicate that molecular typing has been performed, and up to four sets of digits represented by separated colons (see Figure 2.2).

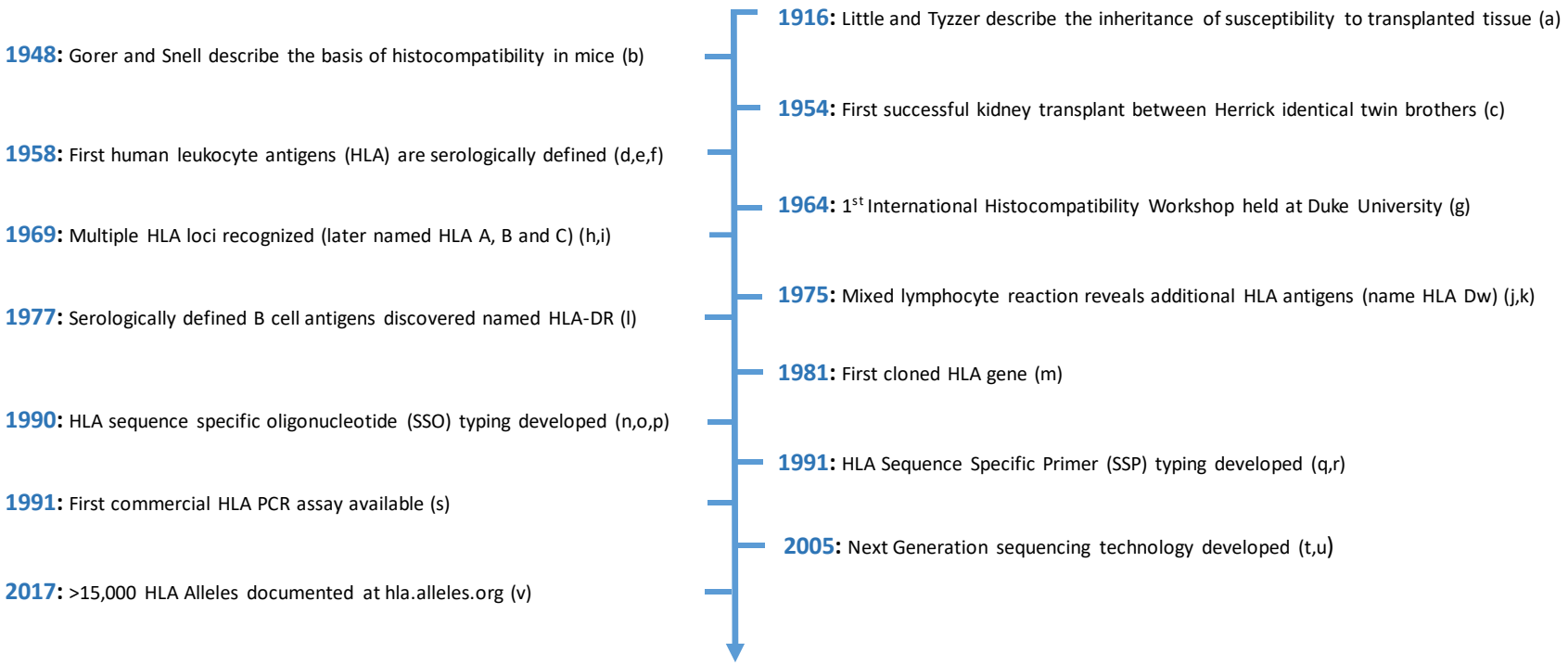

Figure 2.1 Timeline of key discoveries relating to human leukocyte antigens

(References: a[106], b[119], c[120], d[107], e[108], f[109], g[121], h[110], i[111],j[121], k[122], l[123], m[117], n[124],.o[125],.p[126], q[127], r[128], s[118], t[129], u[130], v[131])

2.5 Basic structure and genetics of HLA molecules

Class I HLA molecules consist of a polymorphic alpha chain encoded within the major histocompatibility complex (MHC) region on chromosome 6 and a non-polymorphic beta-2 microglobulin protein encoded on chromosome 15[132]. In contrast, class II HLA molecules are heterodimers formed by alpha (α) and beta (β) glycoprotein chains, both of which can be polymorphic and are encoded within the MHC region[132,133]. The HLA-DQ and HLA-DP regions both contain one functional gene for each of their α and β chains (DQA1 and DQB1, DPA1 and DPB1, respectively). The HLA-DR region, however, encodes one highly conserved DR α chain that is essentially invariant, and either one or two DR β chains. Each haplotype contains one DRB1 gene and may also include a DRB3, DRB4 or DRB5 paralogue (a distinct gene that derives from the same ancestral gene) that is coexpressed with DRB1[133,134]. Thus, molecular typing across the key class I and class II HLA loci in renal transplantation includes sequence information on the following genes: HLA-A, B, C, DRB1, DRB3, DRB4, DRB5, DQA1, DQB1, DPA1 and DPB1.

The resolution of molecular typing methods, that is, their ability to distinguish minor differences in allele sequences, varies according to the technology used and number of alleles at a particular locus. Low resolution or two-digit typing distinguishes allele groups and is roughly equivalent to serological typing, whereas high resolution or four-digit typing is able to distinguish alleles to the protein level (seeFigure 2.2). The HLA nomenclature website currently lists 15,000 HLA alleles, encoding over 10,000 unique proteins[131].

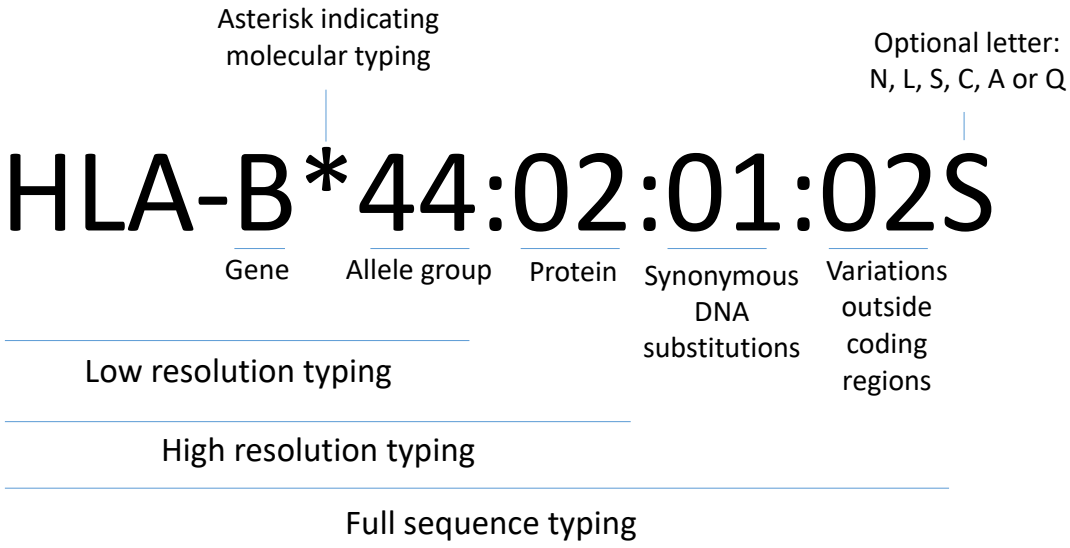

Figure 2.2 Human Leukocyte Antigen Nomeclature

When molecular HLA typing has been performed the gene is denoted by a letter or alpha-numeric combination (eg –B or –DQB1) followed by an asterisk. The first set of digits describe the allele type, which usually (but not always) corresponds to the serological antigen. The next set of digits refers to different alleles within the group that differ by at least one amino acid in the encoded protein. The third set of digits denote alleles that differ only in synonymous substitutions (that is, there is no change in the amino acid sequence of the protein) and the fourth set of digits denote alleles with sequence variations in non-coding regions. These numbers are sometimes followed by a letter that indicates expression status (N= Null allele, S= Secreted molecule not present on cell surface, C= Cytoplasmic protein not present on cell surface, A= Aberrant expression, Q= Questionable expression). Based on nomenclature specified in [135].

2.6 Why HLA matching matters

HLA antigens are the primary alloantigens recognized by a host immune system in ABO blood group compatible organ transplantation, however, the role of HLA matching in kidney transplantation has long been a controversial topic. Early studies showed that class I HLA mismatches were a predictor of clinical outcomes in living donor kidney transplantation [136] but not of great importance in deceased donor kidney transplantation[137,138]. With the discovery of HLA-DR antigens, the impact of HLA mismatches on deceased donor transplantation outcomes was also demonstrated[139,140]. Improvements in immunosuppression have led some to debate the continued importance of HLA matching in renal transplantation. However, a recent study of 189,141 first adult kidney transplants in the US showed that even in the era of calcineurin inhibitor based immunosuppression regimes, a significant linear relationship was seen between HLA mismatches at HLA-A, -B and –DR and graft survival[141]. Most national and regional deceased donor organ allocation algorithms give priority to transplants with no or few HLA mismatches (generally considering only HLA-A, -B and -DR) [37,68,142,143].

Despite advances in avoiding and treating T cell-mediated rejection, little progress has been made in addressing the humoral allo-response[144,145] which is now recognised as the most important cause of chronic allograft loss[1,2,146]. HLA mismatches are associated with an increased risk of developing de novo anti-HLA donor specific antibodies (DSA), which are most commonly anti-HLA DQ, and are in turn associated with poorer graft survival [3,147–150] and increased sensitization. Although not usually considered in routine organ matching, anti

HLA-C and -DP antibodies have also been associated with antibody mediated rejection (AMR)[151,152].

Testing for allele specific anti-HLA antibodies using solid phase assays (see Figure 2.3) is now widely available, with its role in clinical transplantation continuing to evolve[153]. Many jurisdictions use the population frequencies of HLA typing to determine calculated panel reactive antibodies (cPRA) based on the specificity of a potential recipient's anti-HLA antibody profile. This number represents the percentage of the donor pool with whom the recipient is predicted to have a positive cross match[49] and is increasingly being used in organ allocation algorithms.

Tissue typing therefore has several potential roles in renal transplantation. Firstly, it enables strategies to improve donor/recipient HLA matching and therefore reduce the exposure to immunogenic alloantigen. And, for sensitized patients, HLA typing allows the specificity of preformed antibodies to be determined in order to avoid donors with increased risk of AMR or implement therapies to mitigate this risk.

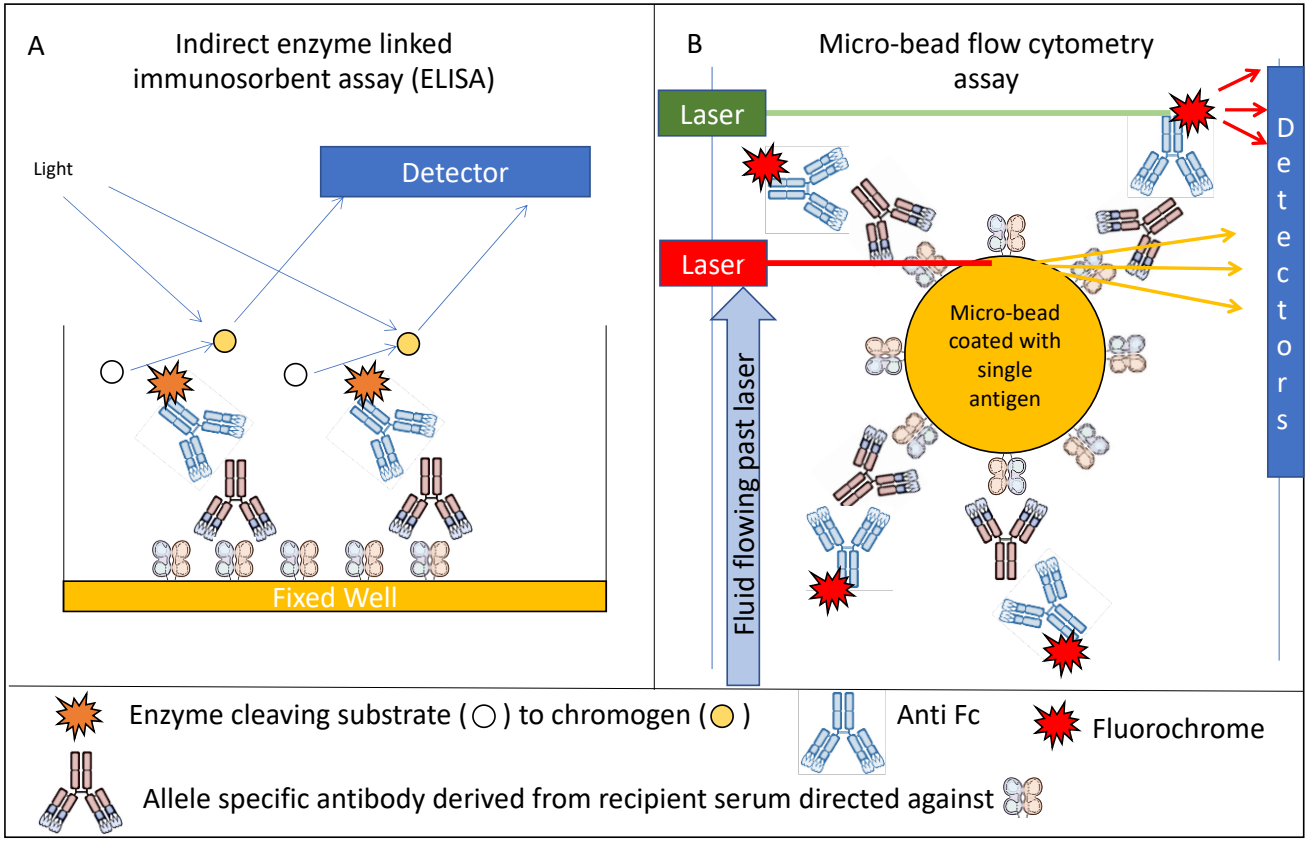

Figure 2.3 Examples of solid phase assays for the detection of anti-HLA antibodies

Panel A shows the principles of indirect enzyme-linked immunosorbent assay. Immunoprecipitated HLA glycoproteins are immobilized in the wells of a microtiter trays, test serum is added and, if present, antigen specific anti-HLA antibodies bind to the glycoproteins. A second, anti-human IgG antibody bound with a reporter molecule is added and binds to Fc portion of the primary antibody. After washing, a substrate is added that is cleaved a chromogen by the reporter molecule and the assay is read. Panel B shows the principles of micro-bead flow cytometry assay. Polystyrene microspheres embedded with flurochromes for dectection are coated in purified HLA molecules. Beads may be coated in multiple different HLA (screening beads) or a specific HLA of interest (single antigen beads). Once again, test serum is added to the beads and then a secondary labeled anti-human IgG antibody. The beads are then passed through a flow cytometer in which both bead identification and the presence of bound secondary antibody are detected. As such, a single micro-bead test can be used to test for multiple specific anti-HLA antibodies by mixing many single antigen beads with the same test serum.

2.7 Limitations of the current system

Currently available methods for defining HLA typing provide either too little or too much information to efficiently achieve these objectives. Serological and low resolution molecular typing is a simplification of the HLA system that risks not providing sufficient detail for matching in transplantation. This is particularly important when excluding potential donors based on pre-formed anti-HLA antibodies[154]. Single antigen bead based testing detects allele specific antibodies that do not necessarily react with an entire serological grouping. For example, a patient may form a high level antibody against A*24:02 that does not interact with A*24:03. Exclusion of the serological A24 group would therefore prohibit offers from a donor with A*24:03 allele, despite no preformed antibody to this antigen[155]. The implications of this are most significant for very highly sensitized patients, whose potential donor pool is already markedly reduced.

Conversely, high resolution typing presents challenges with the sheer number of distinct alleles. The likelihood of achieving prospective HLA matching reduces significantly when considering thousands of alleles across a population, unless a system of grouping is employed. Similarly, it is impractical to assign antibody specificity without a method of grouping alleles. Anti-HLA antibody testing commonly utilises panels of around 100 HLA alleles for each class and antibodies to these specific alleles are presumed to interact with other similar antigens. Testing against thousands of distinct alleles would not be feasible. Thus, current systems use a pragmatic hybrid of molecular and serological typing, where antigens and antibodies are often defined at a high resolution level based on molecular and

solid phase assay testing but converted to low resolution or serologically equivalents for the purposes of matching.

The current system also fails to address two important aspects of prospective HLA matching to improve long term transplant outcomes; the relative immunogenicity of specific mismatches and the potential for cross reactivity of *de novo* antibodies that develop post-transplant. HLA antigens differing from the recipient by only a few amino acids might elicit a very different immune response to those with a large degree of sequence variation or specific highly immunogenic features. Similarly, current systems fail to address the risk of cross reactive antibodies developing following allo-immunisation that can result in broad sensitization and have devastating impacts on re-transplantation opportunities.

2.8 Defining HLA based on Antibody Binding

Epitopes

B cell epitopes (hereafter referred to as *epitopes*, as T cell epitopes are beyond the scope of this review) can be defined as the minimum structural determinants required to bind a specific antibody. The antigen binding site of an antibody is formed by the pairing of the variable (V) regions of its light and heavy chains. Amino acid sequence variability that results from gene recombination and somatic hypermutation is concentrated in three segments of each V region known as hypervariable or complementarity-determining regions (CDRs) [156]. CDRs determine both the specificity and the affinity of antibody/antigen interactions. The configuration of amino acids on the antibody involved in binding an antigen are known as

the *paratope*; the corresponding configuration on the antigen is termed the *epitope*. Epitopes are not an intrinsic property of a protein, but rather they are identified only by their ability to interact with the defining antibody[157,158]. The amino acid residues that constitute an epitope may be contiguous in the peptide chain, or more commonly brought together as a result of peptide folding. X-ray crystallographic studies of antibody/antigen interactions have shown that epitopes consist of around 10-22 amino-acid residues [157,159]. Therefore, a large protein contains multiple amino acid configurations that may represent distinct epitopes, capable of binding a number of specific antibodies.

Serological HLA typing methods led to the early observation that distinct antigens frequently shared common (or public) epitopes that were capable of binding with cross-reactive antibodies[160–162]. These formed the basis of the Cross Reactive Groups (CREGs) that for a time were debated as an alternative to antigen matching for renal transplantation[163]. It has also been demonstrated that exposure to a limited number of foreign HLA can result in sensitization to a broad range of seemingly unrelated HLA antigens. These observations have led to the conclusions that HLA molecules are composed of a number of potentially immunogenic epitopes and that common epitopes are shared across different serological groupings.

HLA epitope matching is based on the principle that if a donor HLA antigen shares a specific epitope with a recipient's HLA antigen, then that epitope will not be recognized as foreign and will therefore not provoke a humoral immune response. By breaking down each HLA into a series of epitopes, matching can be performed on a much more granular level and using a more biologically relevant classification system. If the goal of HLA matching in

transplantation is to reduce the number of foreign targets that antibodies may be raised against, and to avoid the targets of specific preformed antibodies, the logical progression is to define the matching in terms of those antibody targets.

Systems for Defining Epitopes

The first challenge has been to define a complete list of HLA epitopes that includes all potential antibody targets and can been used for matching and assigning antibody specificity. The two primary methods of achieving this have been: 1) analysing a broad range of anti-HLA antibodies and assigning epitope specificity based on reactivity patterns, and 2) using the sequencing and structural data on HLA alleles to predict all potential epitopes based on known features of an epitope and then validate this system by matching the predicted epitopes with observed antibodies.

The development of microbeads coated with single HLA antigens resulted in rapid advancements in the identification and description of HLA epitopes based on antibody analysis. El-Awar and colleagues used single antigen beads to analyse both monoclonal anti-HLA antibodies and antibodies derived from adsorption/elution of allosera using recombinant HLA single antigen cell lines, and described 103 class I, 60 DR and 18 DQ epitopes, which they termed TerEps in honour of Paul Terasaki(48).

Eplets

Rene Duquesnoy and colleagues have used an alternative, in silico, approach to devise a list of all potential HLA epitopes. The structural analysis of crystalized antibody/antigen complexes has indicated that binding specificity is primarily determined by a cluster of

between 2-5 amino acids, termed the *functional* epitope, that lies centrally within a larger *structural* epitope, consisting of around 15-20 amino acids, all of which are involved in antigen/antibody binding[164–166] (Figure 2.4). In order to be immunogenic, the *functional* epitope must contain at least one polymorphic residue on the molecule's surface. Using the sequences of all common HLA alleles and 3D protein modelling, Duquesnoy's group determined a list of all surface exposed polymorphic residues and the amino acid clusters associated with them that could define a potential functional epitope[167]. Initially the group only included linear amino acid sequences, termed *triplets*, however, later iterations also include discontinuous sequences brought together as a result of protein folding. They have consolidated overlapping clusters shared by the same allele grouping and derived a list of all potential functional epitopes which they term *eplets*.

Eplets are denoted with a number representing the sequence position of the defining polymorphic amino acid followed by a list of letters representing the associated polymorphic residues (eg 82LR, which contains a leucine in position 82 and an arginine in position 83). Figure 2.5 Three views of the 3D crystallographic structure of HLA-A*01:01 with the position of 3 eplets highlightedshows the crystallographic structure of HLA-A*01:01 with the amino acid residues that define three different eplets highlighted. Using freely available software (HLAMatchmaker) the number of eplet mismatches between a donor and recipient or the eplet specificity of an anti-HLA antibody can be determined based on 4 digit HLA typing. Table 2.1 shows an example of HLA and eplet matching between a kidney transplant candidate and two potential donors, demonstrating how eplet based matching can provide additional detail over antigen based matching.

Each of these systems for defining HLA epitopes has its drawbacks. TerEps are determined using a limited number of antibody samples and thus may not describe the full repertoire of epitopes. Whereas eplets, as a list of all theoretical epitopes, might include polymorphic structures of no biological relevance or fail to include all antigenic targets. A collaborative effort is ongoing to document all eplets that denote antibody confirmed epitopes[168] and the current version of HLAMatchmaker gives information on these separate from non-verified or theoretical eplets. A comparison between these two systems found that 90% of TerEps could be defined by eplets, however, not all antibody verified eplets are accounted for in the TerEps repertoire[169]. Others have suggested novel methods including assessment of HLA physicochemical properties and machine learning techniques to predict HLA class II binding, to enhance the analysis of epitopes[170,171]. One of the primary objectives of the 17th International HLA Immunogenetics Workshop to be held in September 2017 is to map the HLA serological epitopes contributing to AMR.

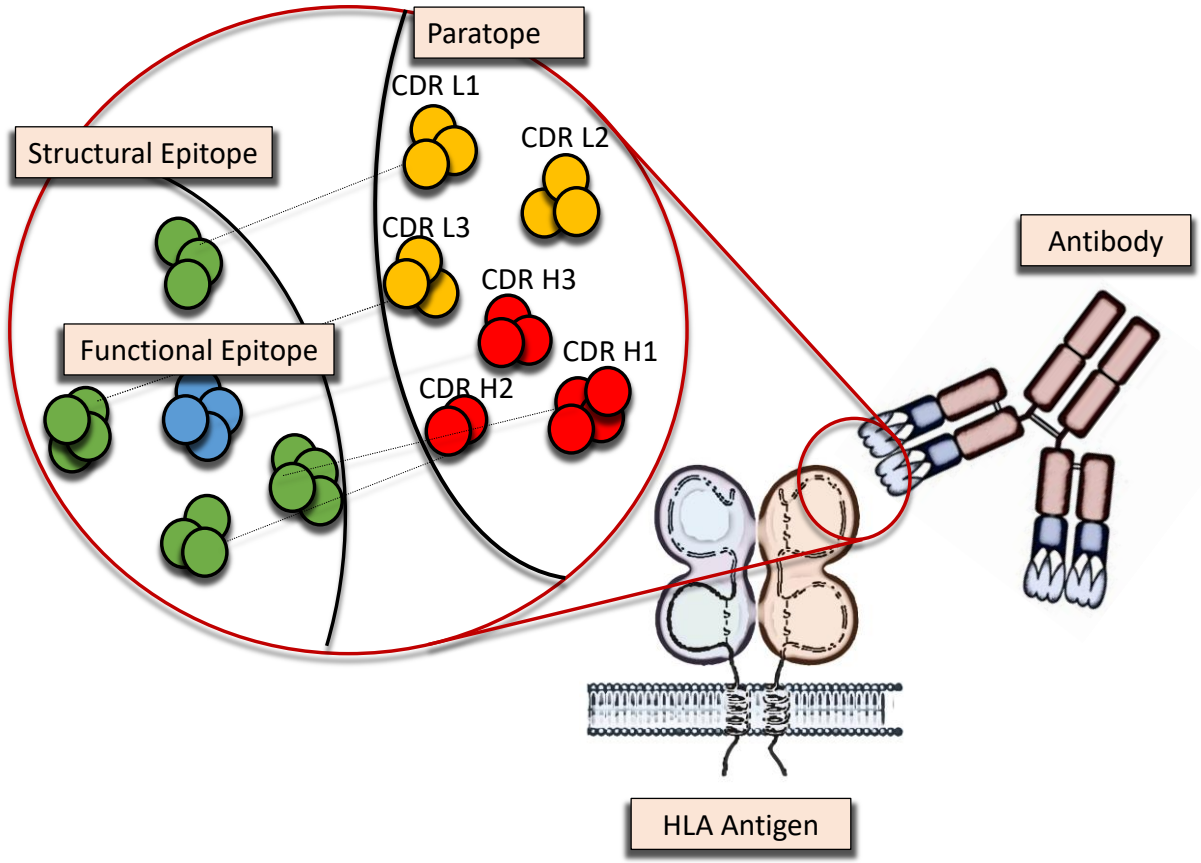

Figure 2.4 Simplified illustration of the interface between an antibody paratope and antigen epitope

The paratope incorporates the three complementarity determining regions (CDR) on each light (L1-3) and heavy (H1-3) chain that contact the epitope. There are around 10-22 contact residues on the antigen that make up the structural epitope. Central to this is a cluster of amino acid residues that are the key determinants of antibody binding specificity that has been termed the functional epitope or eplet. Note that not all CDRs are involved in binding a specific epitope. Colored circles represent amino acid residues. Dotted lines represent hydrophobic, van der Waals and hydrogen bonds, and salt bridges between contact residues. Reproduced from Paediatric Nephrology (Sypek et al, 2016) [6] with permission.

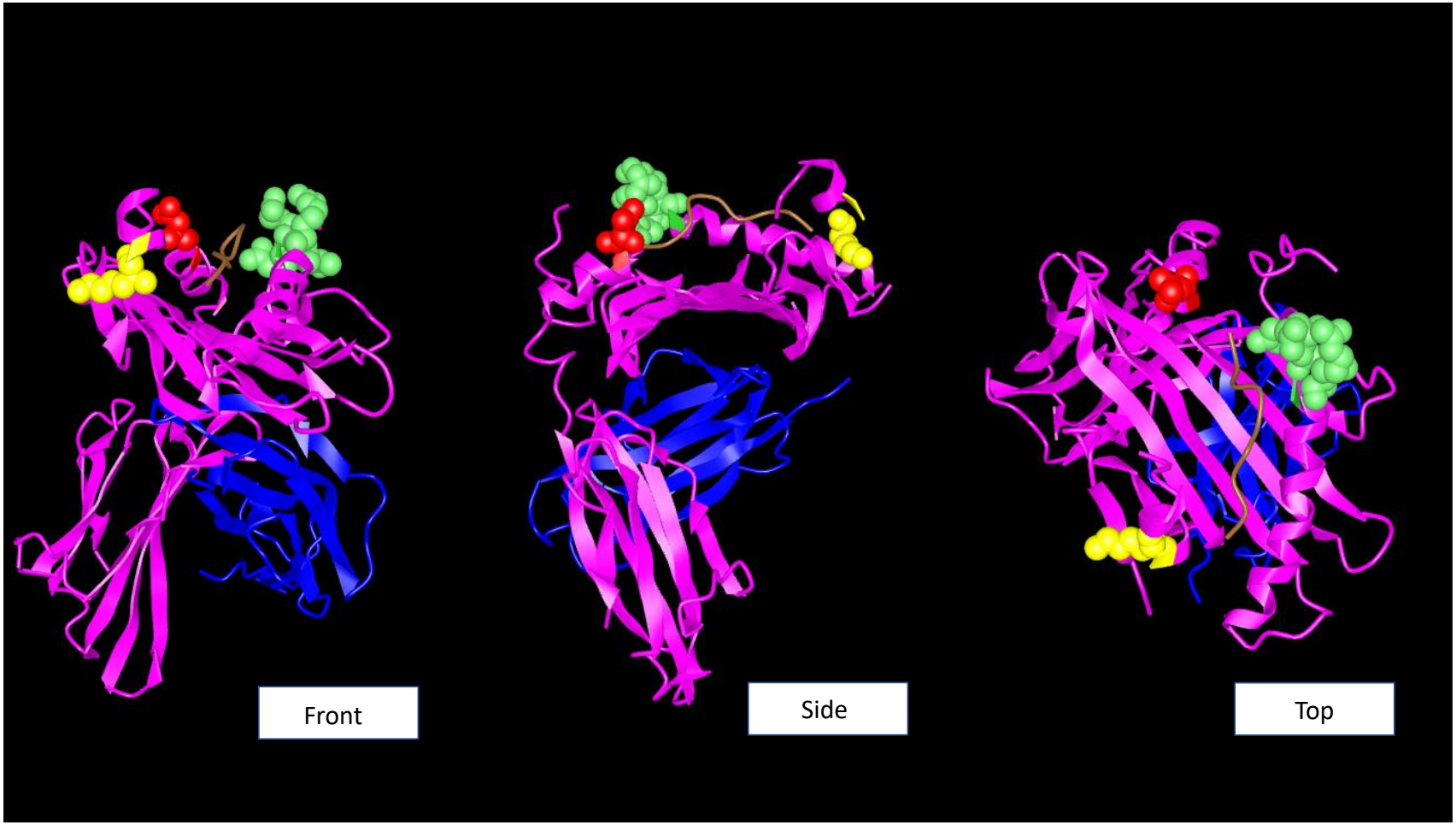

*Figure 2.5 Three views of the 3D crystallographic structure of HLA-A*01:01 with the position of 3 eplets highlighted*

*The alpha glycoprotein chain is shown in pink, the non-polymorphic beta-2 microglobulin chain in blue and the protein binding groove is shown in brown. The positions of three eplets are highlighted by coloured spheres: 62QE (green), 144KR (yellow) and 166DG (red). Note that the current HLA epitope registry database (http://www.epregistry.com.br) includes 54 eplets for HLA-A*01:01, only three of which are shown here. Image created using NCBI's Cn3D macromolecular structure viewer[172].*

Table 2.1 Example comparing human leukocytes antigen (HLA) and eplet mismatches

Recipient HLA typing: A*02:01 A*32:01 B*18:01 B*35:01						
Donor HLA Typing	HLA (antigen) mismatches	Mismatched eplets		HLA (eplet) mismatches		
		Verified	Unverified	Verified	Unverified	Total
Donor 1						
A*03:01	1	144KR, 161D	71QS[#], 182TDP[†], 276L[^]	2	3	5
A*30:01	1	17RS, 56R	71QS[#], 182TDP[†], 276L[^]	2	3	5
B*08:01	1	156DA, 180E	177DT	2	1	3
B*49:01	1	41T	76EN, 152RE	1	2	3
Total	4			7	6	13
Donor 2						
A*01:01	1	44KM, 76ANT, 90D[‡], 144KR, 163R, 163RG, 166DG	151HA, 182TDP, 276L	7	3	10
A*25:01	1	62RR, 90D[‡], 149TAH, 163R, 163RW	156WA	5	1	6
B*07:02	1	65QIA, 69AA, 70IAQ, 163EW, 180E	66IY, 152RE, 156RA, 177DK	5	4	9
B*44:03	1	41T, 80TLR	76EN	2	1	3
Total	4			18	9	27

Table 2.1 shows human leukocyte antigen (HLA) and eplet mismatches between 2 potential donors and a potential recipient. Eplet mismatches are separated into eplets that have been confirmed to represent antibody binding epitopes (Verified) and those that remain theoretical descriptions of epitopes (Unverified). Both donors have a 4/4 HLA class I antigen mismatch (considering HLA -A and -B only). However, the recipient has fewer eplet mismatches with Donor 1 compared to Donor 2, both when considering only antibody verified eplets (7 vs 18 mismatches) and all eplets (13 vs 27). According to the theory of quantitative eplet matching, Donor 1 has fewer potential antibody targets and therefore might pose a lower risk of eliciting a humoral immune response. Eplet mismatches that share a symbol (#, †, ^ or ‡) are present on more than one donor antigen, but are only counted once towards the mismatch total. Eplet matching performed using HLAMatchmatcher 'HLA-ABC matching for up to 1000 cases (v02)' available from www.epitopes.net/downloads.html, downloaded 14 Jan 2017.

2.9 Clinical use of epitope based matching

Duquesnoy's eplets have received the most attention in the clinical transplant world and a number of publications have highlighted the usefulness of this system in both prospective identification of low risk mismatches for highly sensitized patients and in the role of eplet matching in determining long term outcomes in solid organ transplantation.

The Eurotransplant Acceptable Mismatch program aims to prioritize appropriate kidneys to highly sensitized patients who would otherwise experience poor access to transplantation and long waiting times. For highly sensitized patients, mismatched at HLA A/B antigen level, a zero class I triplet mismatch is strongly predictive of a negative flow cross match[170]. HLAMatchmaker has been used in this program to identify organs that, although mismatched at the antigen level, have very few eplet mismatches and are therefore of lower immunological risk, significantly expanding the potential donor pool for this population[57]. It has been shown that for recipients matched at HLA-DR, 5 year outcomes are similar for those with a low number of class I triplet mismatches and those with zero class I antigen mismatches[173].

A similar approach has been used identifying lower risk platelet infusions for HLA allo-immunized thrombocytopenic patients[174]. It was recognized as early as 1969 that platelet increments for refractory patients could be improved by using cells from HLA compatible donors[175], and the CREG system has been used to identify potential platelet donors for almost 40 years[176]. Recent publications have validated Duquesnoy's eplet matching program

as a tool for selecting donors for refractory patients[177,178]. Many tissue typing laboratories have included eplet analysis into their algorithms to identify donor platelets for highly sensitized, refractory patients, and a double-blind, randomized, non-inferiority crossover trial is currently underway in the UK to validate this approach[179].

Table 2.2 summarises the clinical studies examining the association between eplet mismatches and clinical outcomes in solid organ transplantation. An early study by Dankers et al found a strong positive correlation between the number of class I triplet mismatches and the percentage of individuals producing anti-HLA antibodies following both failed renal transplantation and pregnancy[180]. Wiebe et al have demonstrated that class II locus specific eplet mismatches are an independent risk factor for class II de novo DSA formation [181]. They identified thresholds for eplet mismatches that were associated with low risk of de novo DSA formation, 10 for HLA-DR and 17 for HLA-DQ. In a later study, the group showed that higher eplet mismatch and poor adherence acted synergistically to determine the risk of rejection and graft loss[182]. Kosmoliaptsis and colleagues also showed that eplet mismatch scores were an independent predictor of class II de novo DSA formation, however, their novel electrostatic mismatch score (EMS) based on additional physicochemical properties of mismatched HLA amino acid residues was a better predictor of class I de novo DSA formation and sensitization[183]. Another group did find that HLA-DQβ1 eplet mismatches were an independent risk factor for becoming highly sensitized following graft failure, but not HLA-DRβ1/3/4/5 or HLA DQα1 eplet mismatches[184]. And in a nested case control study, class II eplet mismatches were associated with an increase in the odds of transplant glomerulopathy both when modelled as a continuous variable and when threshold cut offs were used[185].

In other solid organ transplantation, it has been shown that class II eplet mismatches are predictive of chronic lung allograft dysfunction (CLAD) in lung transplant recipients[186] and class I eplet mismatch is associated with risk of graft failure for paediatric cardiac allograft recipients[187].

These studies suggest that strategies to reduce eplet mismatches in solid organ transplantation might result in a reduction in the rate of anti-HLA antibodies and potentially in the negative sequelae of AMR, graft failure and reduced re-transplantation rates due to sensitization. A major limitation of these studies is that analysis has been conducted using total number of eplet mismatches including both eplets that describe antibody verified epitopes and eplets that remain theoretical epitopes. However, even with this important caveat, strong associations with eplet mismatch and the humoral allo-response have been demonstrated.

Table 2.2 Summary table of clinical studies examining eplet mismatches in solid organ transplantation

Author	Year	Organ	Outcome Measure	Study design	Key Findings
Dankers et al (89)	2006	Kidney	De novo donor specific antibody (de novo DSA) formation	Retrospective cohort study	-Strong correlation between number of class I triplet mismatches and the percentage of patients producing DSA (r^2=0.99, p<0.0001) -no patients with zero triplet mismatches produced de novo DSA compared with 94% of patients with >10 mismatches
Wiebe et al (90)	2013	Kidney	De novo DSA formation	Prospective cohort study	- Locus specific eplet mismatches (EpMM) were more numerous in patients who developed de novo DSA (HLA-DR 21.4 v 13.2, HLA-DQ 27.5 v 17.3 - EpMM thresholds for low risk of de novo DSA were identified (10 for HLA-DR and 17 for HLA-DQ) - In a multivariate model, locus specific EpMM were an independent preditor of de novo DSA (OR 1.06 per mismatch)
Sapir-Pichhadze et al (91)	2014	Kidney	Transplant glomerulopathy (TG)	Nested case-control study	-Increased odds of TG with higher EpMM (OR 2.84 and 4.62, for mismatch 27-43 and >43 vs <27 respectively) -OR for TG was 1.25 (95%CI 1.04-1.50) for every 10 EpMM when modeled as a continuous variable
Kosmoliaptsis et al (92)	2015	Kidney	de novo DSA and sensitization	Prospective cohort study	-EpMM score was associated with risk of developing class II de novo DSA but not class I de novo DSA or sensitization -Electrostatic mismatch score was associated with class I and class II de novo DSA formation and sensitization
Wiebe et al (93)	2015	Kidney	Rejection and graft loss	Prospective cohort study	Higher EpMM and poor adherence acted synergistically to determine risk of rejection and graft loss -Graft loss 33% vs. 8% for HLA-DR EpMM >10 and poor adherence vs <10 with good adherence
Singh et al (94)	2016	Kidney	Sensitization	Retrospective cohort study	-HLA-DQβ1 EpMM (but not DQα1 or DRβ1/3/4/5 eplet mismatch) was associated with becoming highly sensitized following graft failure (OR 1.14, 95%CI 1.01-1.33)
Walton et al (95)	2016	Lung	Chronic Lung Allograft Dysfunction (CLAD)	Retrospective cohort study	-Class II EpMM was a significant predictor of CLAD (HR 3.77, 95%CI 1.71-8.29, for top quartile vs bottom quartile). This association was not seen for class I EpMM.
Sullivan et al (96)	2016	Heart (Paediatric)	Graft failure	Retrospective cohort study	-Recipients with 10-20 or >20 class I EpMM experienced increased graft loss compared with recipiets with <10 class I eplet mismatches (HR 1.23, 95% CI 1.06-1.42 and 1.27, 95%CI 1.08-1.50, respectively).

2.10 The potential role of HLA epitopes in renal transplantation

The aim of kidney transplantation for each individual patient is to access the best quality organ, with the lowest immunological risk either prior to onset of end-stage kidney disease, or as soon as possible thereafter. Hence a number of priorities in organ allocation, including fair access and the overall utility of this scarce resource must be balanced. The population likely to benefit the most from improved HLA matching is younger patients whose long term survival means that maximising graft longevity, minimising immunosuppression burden and maintaining future transplantation opportunities are key priorities. A retrospective analysis of DR mismatched organ offers to paediatric waitlisted patients in the US showed that 40% of 1 DR mismatched offers and 64% of 2 DR mismatched offers were above the low risk eplet thresholds for developing de novo DSA as defined by Wiebe et al[181,188]. A pilot program that uses analysis of eplet mismatches to prospectively exclude deceased donor organs carrying HLA antigens with high eplet mismatch loads has been introduced at The Royal Children's Hospital, Melbourne, Australia with early outcomes appearing promising and with minimal impact on access to transplantation[4].

The planned nature and large live donor pools of kidney donor exchanges offer an opportunity to explore the benefits of eplet based matching[189]. Simulations of the impact of entering HLA mismatched but otherwise compatible pairs into the Australian paired kidney exchange program have demonstrated that this would not only increase match rates for incompatible pairs in the exchange, but can also lead to better matching at an eplet level if the compatible pairs entering have >65 eplet mismatches[190].

It is not only paediatric patients and live donor organ recipients who stand to benefit from reduced rates of de novo DSA formation and it has been argued that epitope based deceased donor organ allocation systems could potentially improve overall transplant outcomes[97,100,191]. However, there are several challenges that must be addressed before effecting such a change. Firstly, high resolution, extended HLA typing is an essential requirement for determining HLA epitopes. With the rapid advancements in gene sequencing technology and reducing costs over the last decade, this is fast becoming standard of care. More importantly, a robust system for defining a complete repertoire of epitopes is required. Duquesnoy's eplets are an attractive candidate as the system is designed to include all potential antibody targets and user friendly software makes calculating mismatches simple, however, the biological relevance and relative immunogenicity of all eplets are yet to be completely determined. The collaborative efforts of the 17th International HLA and Immunogentics Workshop aim to better define serologic epitopes contributing to AMR and will hopefully assist in identifying clinically relevant eplets[192]. Furthermore, epitope matching is only one priority in organ allocation and robust simulation of changes to national organ allocation systems is required to ensure that the benefits can be maximised without unintended consequence such as inequitable assess to organs for minority populations or extended waiting times.

2.11 Conclusions

Many have argued that in the current era of highly effective immunosuppression, HLA matching in renal transplantation is now obsolete. However, prevention and control of the

humoral allo-response remains one of the greatest unsolved challenges in solid organ transplantation. Understanding and improving HLA matching through the lens of antibody recognition offers an opportunity to prevent the devastating consequences of *de novo* DSA formation and reduce the risks of transplantation in the face of pre-existing anti-HLA antibodies. Epitopes are defined by their ability to bind antibodies, and therefore a system of epitope based matching is the logical step toward addressing the allo-antibody response. A great deal of progress has been made in defining HLA epitopes, with the systems of eplets achieving popularity due to its sound theoretical basis, verification with the documentation of eplet specific antibodies, ease of use and association with clinical outcomes. While rejection remains the leading cause of graft loss, the role of HLA in renal transplantation is far from over and we believe that HLA epitope based matching is an important part of the answer to the unmet challenge of the humoral allo-response. However, further collaborative efforts are required to confirm the benefits of this approach before it can be recommended for widespread use in clinical practice.

Chapter 3 Access to waitlisting for deceased donor kidney transplantation in Australia

3.1 Preface

The content of this chapter has been published in the journal *Nephrology (*2019;24(7):758-766). The text is identical to the published manuscript apart from minor stylistic changes to figure and table titles and legends.

Authors

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Author contributions are described in the thesis preface.

3.2 Abstract

Background: A detailed analysis of waitlisting for deceased donor kidney transplantation in Australia has not previously been reported. We aimed to determine if patient characteristics associated with waitlisting identify areas of potential inequality in access to transplantation in Australia. Methods: A competing risk time-to-event model was used to determine predictors of waitlisting for all adult incident renal replacement therapy patients in Australia between 2006-2015. Secondary analysis was performed to determine predictors of overall access to transplantation (using a combined outcome of waitlisting and living donor transplantation). Results: The cohort consisted of 21,231 patients with a median age of 63 years. Overall, 4,361 (20.5%) were waitlisted and 1,239 (5.8%) received a living donor transplant without being previously waitlisted. Primary analysis revealed that medical comorbidities, older age, smoking status and body mass index, were all significant predictors of waitlisting and that and there was variation in waitlisting practice across states Despite adjustment for the above factors, demographic characteristics including Indigenous ethnicity (SHR 0.46, [95%CI 0.38-0.55]), female gender (SHR 0.46, [95%CI 0.38-0.55]), and residence in a regional area (SHR 0.88 [95%CI 0.81-0.95]) were also associated with a lower likelihood of waitlisting. Secondary analysis showed younger age and higher socioeconomic advantage were additional predictors of overall access to transplantation, driven by higher rates of living donor transplantation. Conclusion: Demographic as well as clinical characteristics are associated with reduced likelihood of waitlisting for kidney transplantation in Australia. Further analysis and auditing should be considered to determine if this reflects other, unmeasured factors or highlights a need to address inequality.

3.3 Background

For many patients with end stage kidney disease (ESKD), transplantation offers superior survival and quality of life compared to dialysis, and is associated with reduced burden of health care costs [8–11]. In Australia, around 75% of renal transplants come from deceased donors[193]. The Australia and New Zealand Dialysis and Transplantation Registry (ANZDATA) publishes annual waitlist stock and flow data [194], however, a detailed analysis of the predictors of transplant waitlisting for incident renal replacement therapy (RRT) patients in Australia has not been previously reported.

Studies in the United States[81,82], United Kingdom[80,195], Canada[84], France[83,85] and other transplantation jurisdictions[86] have consistently found inequalities in completion of transplant work up and waitlisting for patients on dialysis based on patient factors including race, gender, socioeconomic status and regional factors. Commentary based on publicly available registry data has questioned the low proportion of prevalent dialysis patients on the renal transplant waitlist in Australia[78] and qualitative analysis of nephrologists' perspectives on waitlisting has revealed tensions between advocating for the best treatment for their own patients, maintaining professional integrity and protecting centre reputation, and maximising societal benefit[79]. Although small, single centre audits have helped identify some barriers to timely transplant waitlisting[87], a review of national practice is required to understand current waitlisting practices and identify potential areas of inequality that may require targeted interventions.

The Transplantation Society of Australia and New Zealand (TSANZ) provides guidance on recipient eligibility criteria for deceased donor kidney transplant waitlisting[143]. In order to be eligible for waitlisting in Australia a person must be receiving dialysis for the treatment of ESKD, have a low anticipated likelihood of perioperative mortality, and have an anticipated 80% likelihood of survival at five years post-transplantation. It is acknowledged that based on these criteria, some patients who might benefit from a kidney transplant will be deemed ineligible for listing.

The National Health and Medical Research Council's (NHRMC) *'Ethical guidelines for organ transplantation from deceased donors'* state that there must be no unlawful or unreasonable discrimination against potential recipients based on a number of factors including, but not limited to; race, cultural beliefs, gender, age, disability, social status, sexual preference, location of residence or capacity to pay for treatment[196].

We aimed to provide a detailed description of access to waitlisting for renal transplantation in Australia for incident RRT patients and determine if patient factors associated with access to transplantation identify potential inequalities that may require further investigation or targeted interventions.

3.4 Methods

Data Sources

A de-identified data extract from the ANZDATA registry was used in the analysis. ANZDATA is a binational clinical quality assurance registry that collects data on all patients receiving

RRT for ESKD in Australia and New Zealand. Waitlist data from the National Organ Matching System (NOMS), an Australia wide database and application used in maintaining the kidney waitlist, organ donor testing and organ allocation is incorporated into the ANZDATA database for auditing and reporting purposes. ANZDATA collects data from all patients receiving RRT in Australia and New Zealand under an opt-out consent process approved by the Central Adelaide Local Health Network Human Research Ethics Committee. Data on waitlisting in New Zealand were not available for this analysis.

Inclusion/exclusion criteria

All incident RRT patients in Australia during the 10-year period from 1^{tst} July 2006 to 30th June 2015 were included in the analysis. Patients aged less than 18 years at the time of commencing RRT were excluded. Patients who were waitlisted for multi-organ transplants were excluded, as were those who had recovery of native renal function sufficient to cease RRT. Patients who received deceased donor kidney transplants prior to waitlisting (n=7) were excluded, these may include data errors or exceptional clinical circumstances.

Outcome

The primary outcome was time to first active waitlisting for deceased donor transplantation. Death and living donor transplantation were considered competing events. Patients were censored at 31st December 2015 or date of last follow up. Secondary analyses were conducted both with living donor transplant as the outcome of interest and with a combined endpoint of deceased donor waitlisting or living donor transplantation.

Predictors

The following predictor variables were examined: year of commencing RRT, age at commencing RRT, gender, primary cause of ESKD, comorbidities at time of commencing RRT (vascular disease (a composite of ischaemic heart disease, peripheral vascular disease and cerebrovascular disease), chronic lung disease, diabetes as a comorbid condition (i.e. presence of diabetes in patients whose primary renal disease is not diabetic nephropathy), smoking status, history of non-skin cancer), body mass index (BMI), late referral to a nephrologist (commencement of RRT within 90 days of referral), Indigenous ethnicity, state in which RRT was commenced, quintile of socio-economic disadvantage (derived from the Australia Bureau of Statistics (ABS) Socio-Economic Indexes for Areas (SEIFA))[197] and remoteness based on postcode of residence (collapsed to three categories)[198].

Statistical analysis

Characteristics of the cohort are reported. The observed first outcome for patients with sufficient follow up time at specified time points (6 months, 1, and 5 years) post commencing RRT is reported by age group.

Survival analysis was conducted using competing risk time to event regression models using methods described by Fine and Gray[199], with results presented as subdistribution hazard ratios (SHR). Continuous variables (age and BMI) were categorised into clinically relevant groupings. SHR for states are presented relative to the balanced grand mean of all states. Predictors were considered for inclusion in the multivariate model if significant on univariate analysis using a p value threshold of <0.2. The proportional subhazard assumption was tested using visual inspection of plotted Schoenfeld residuals. Where there

were violations of this assumption, time dependent covariates were introduced to create a piecewise model. Time varying covariates were created for 3 predictor variables, non-skin cancer, smoking history and late referral, with separate subhazard ratios estimated for each time period.

Tests were considered to be statistically significant at a p value <0.05. Analyses were conducted in Stata/IC 15.1 (StataCorp, College Station TX, USA).

3.5 Results

3.5.1 Population

A total of 21,213 incident RRT patients were included in the analysis. The median age was 63 years old (IQR 51-73) and 38.2% of patients were female. Table 3.1 shows the characteristics of the overall cohort. The median follow-up time was 3.02 years (IQR 1.46-5.25). At the completion of the follow up period a total of 4,361 patients (20.6%) had been waitlisted, 1,239 (5.8%) had received a living donor (LD) transplant without being listed and 7,800 (36.8%) had died without being ever waitlisted (Table 3.2).

Table 3.1 Demographics and clinical characteristics of Australian adult incident renal replacement therapy patients (2005-2015)

Characteristic	Levels	N (%)
Total Number of Incident Patients		21,213
Age at RRT, median (IQR)		63 (51, 73)
Age Category	18-24	385 (1.8%)
	25-39	1694 (8.0%)
	40-54	4501 (21.2%)
	55-64	4812 (22.7%)
	65-74	5263 (24.8%)
	>=75	4558 (21.5%)
Gender	Female	8102 (38.2%)
Primary Renal Disease	GN	4690 (22.2%)
	PKD/VUR	1945 (9.2%)
	Diabetes	7422 (35.1%)
	Other	7075 (33.5%)
Ethnicity	Non-Indigenous	18895 (89.8%)
	Indigenous	2153 (10.2%)
Body Mass Index	Underweight	602 (2.9%)
	Normal	6537 (31.3%)
	Overweight	6802 (32.6%)
	Obese	6913 (33.1%)
Comorbidities at Commencing RRT	Vascular Comorbidity	10673 (50.5%)
	Comorbid diabetes	2444 (11.6%)
	Chronic Lung Disease	3503 (16.6%)
	History of non-skin Cancer	3503 (16.6%)
Smoking History	Never Smoked	9660 (46.1%)
	Current Smoker	2547 (12.1%)
	Former Smoker	8761 (41.8%)
Referral Timing	Late Referral	4304 (20.5%)
State of Residence	NT	758 (3.6%)
	NSW	6652 (31.4%)
	VIC	5018 (23.7%)
	QLD	4061 (19.1%)
	SA	1568 (7.4%)
	WA	2273 (10.7%)
	TAS	420 (2.0%)
	ACT	463 (2.2%)
SEIFA	1st Quintile	5042 (23.9%)
	2nd Qunitile	4173 (19.8%)
	3rd Quintile	4195 (19.9%)
	4th Quintile	3912 (18.6%)
	5th Quintile	3739 (17.8%)
Remoteness	Major city	14025 (66.5%)
	Regional	5805 (27.5%)
	Remote	1255 (6.0%)

Table 3.2 First observed outcome and median time to event for adult incident renal replacement therapy patients (2005-2015)

First Observed Outcome	Number	Percentage	Median time to event, Days (IQR)
Waitlisted	4361	20.6	296 (139, 572)
Living donor transplant without being waitlisted	1239	5.8	0 (0, 205)
Death without being waitlisted	7800	36.8	774 (318, 1364)
Censored	7813	36.8	1074 (554, 1839)
Total	21213	100	

Censored patients are those who were lost to follow up prior to experiencing an event or who remained on dialysis at the conclusion of the follow up period. Note that 54% of living donor transplants performed without patients being waitlisted were pre-emptive, hence median time to event is 0 days. IQR interquartile range.

3.5.2 Observed outcome at specified timepoints

Overall, 6.7% of patients were waitlisted by 6 months after commencing RRT, this increased to 12.1% at 1 year and 21.3% at 5 years for patients with a sufficient duration of follow up time to observe all outcomes. An additional 4.3%, 5.0% and 6.6% had received a living donor transplant without previously being waitlisted by 6 months, 1 year and 5 years respectively. There was a substantial difference in outcome a specified time points between age groups (Figure 3.1). By 1 year post commencing RRT, 33.0% of 18-24 year-old patients had been waitlisted, with 22% having received a LD transplant without being listed and 2.2% dying without being listed or transplanted. This compares with 15.3% of 55-64 year-old patients being listed, 5.1% receiving a LD transplant and 8% dying prior to other endpoints. Only 2 of the 4,301 patients over the age of 75 years at time of commencing RRT prior to 2015 were waitlisted by 1 year.

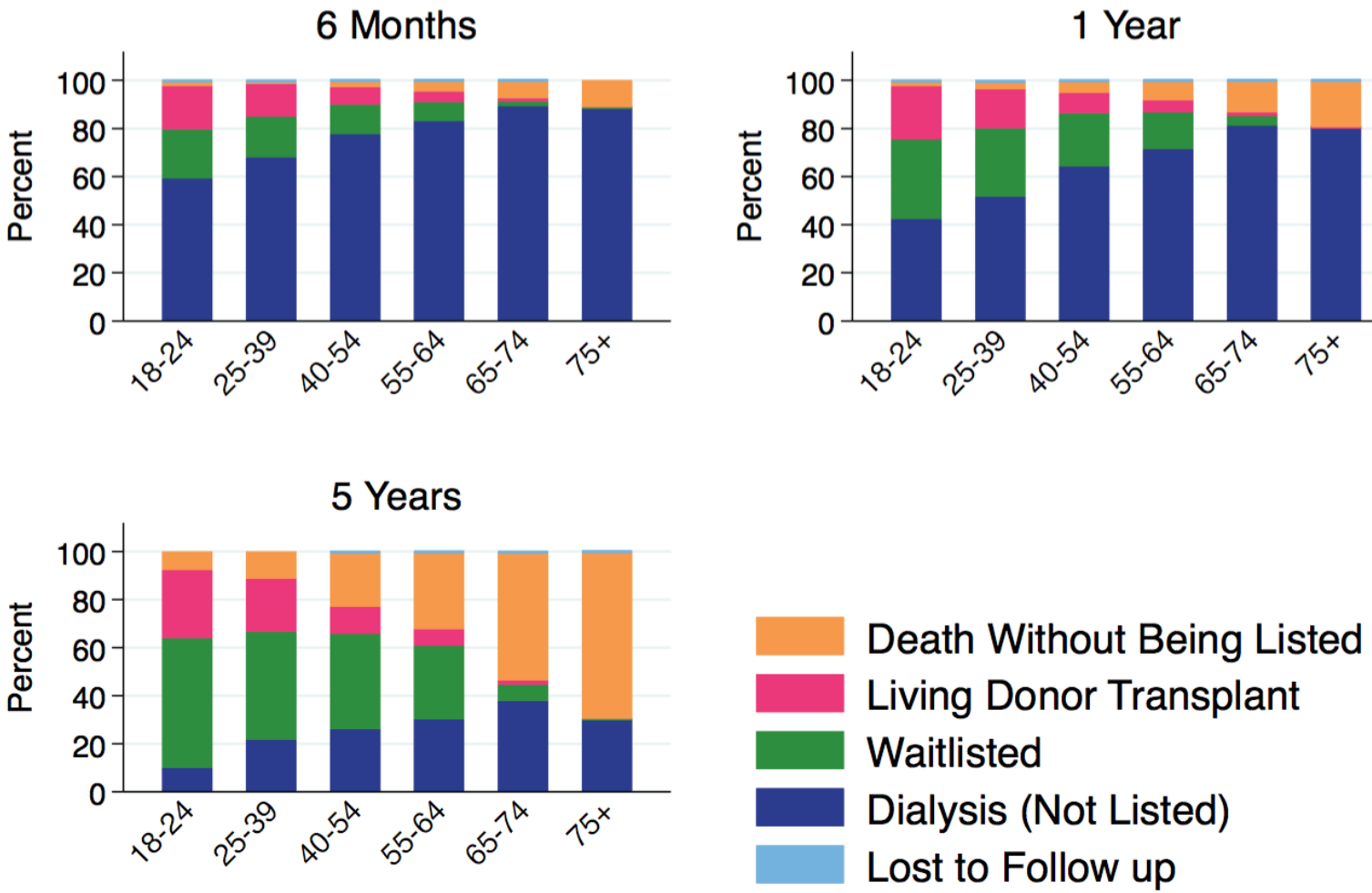

Figure 3.1 First observed outcome at specified timepoints after commencing RRT, by age group

Note that only patients with sufficient duration of follow up to capture all events are included. RRT renal replacement therapy

3.5.3 Survival Analysis

The cumulative incidence for each competing outcome by age group is shown in Figure 3.2. The results of univariate and multivariate models are shown in Table 3.3. All predictor variables, with the exception of year of commencing RRT, were significantly associated with the primary outcome of deceased donor waitlisting on univariate analysis. In the fully adjusted model, all comorbidities included (diabetes, vascular disease, respiratory disease, history of cancer) were associated with a lower likelihood of waitlisting, as were older age groups. There was a difference in waitlisting practice across a number of Australian states, although some significant associations seen on univariate analysis were attenuated in the multivariate model.

Indigenous patients were less likely to be waitlisted or transplanted compared to non-indigenous patients (SHR 0.46, [95%CI 0.38-0.55]), as were female patients compared to males (SHR 0.85, [95%CI 0.80-0.91]). Residing in a regional area was associated with a reduced likelihood of waitlisting compared to urban patients (0.88, [95%CI 0.81-0.95]), however, remote location did not have a significant association in the adjusted model. The association of socioeconomic disadvantage and reduced likelihood of waitlisting seen on univariate analysis was not seen in the fully adjusted model.

Both underweight and obese patients were less likely to be waitlisted or transplanted compared to patients in the normal BMI range (SHR 0.81 [95%CI 0.67-0.97], 0.83 [95%CI 0.76-0.89], respectively). The association between cigarette smoking at time of commencing RRT and waitlisting was only seen in the first 12 months of RRT, and was stronger for current smokers than for former smokers (SHR 0.47 [95%CI 0.41-0.55] and 0.81 [95%CI 0.75-0.88],

respectively, comparisons to the non-smoking group). The negative effect of late referral to a nephrologist was most pronounced in the first six months after starting RRT (SHR 0.45 [95%CI 0.39-0.53]) and was actually associated with increased waitlisting in the period later than 12 months after starting RRT (SHR 1.22 [95%CI 1.09,1.37]).

Secondary analyses of overall access to transplantation (a composite endpoint of deceased donor waitlisting and living donor transplantation) and of living donor transplantation are also reported in Table 3.3 (models 2 and 3, respectively). Of note, in the combined model, younger age groups (18-24 and 25-39) and patients with higher socioeconomic advantage (SEIFA 4th and 5th quintiles) were more likely to receive living donor transplants and had greater overall access to transplantation compared to the reference populations (age 40-54 and SEIFA 3rd quintile, respectively).

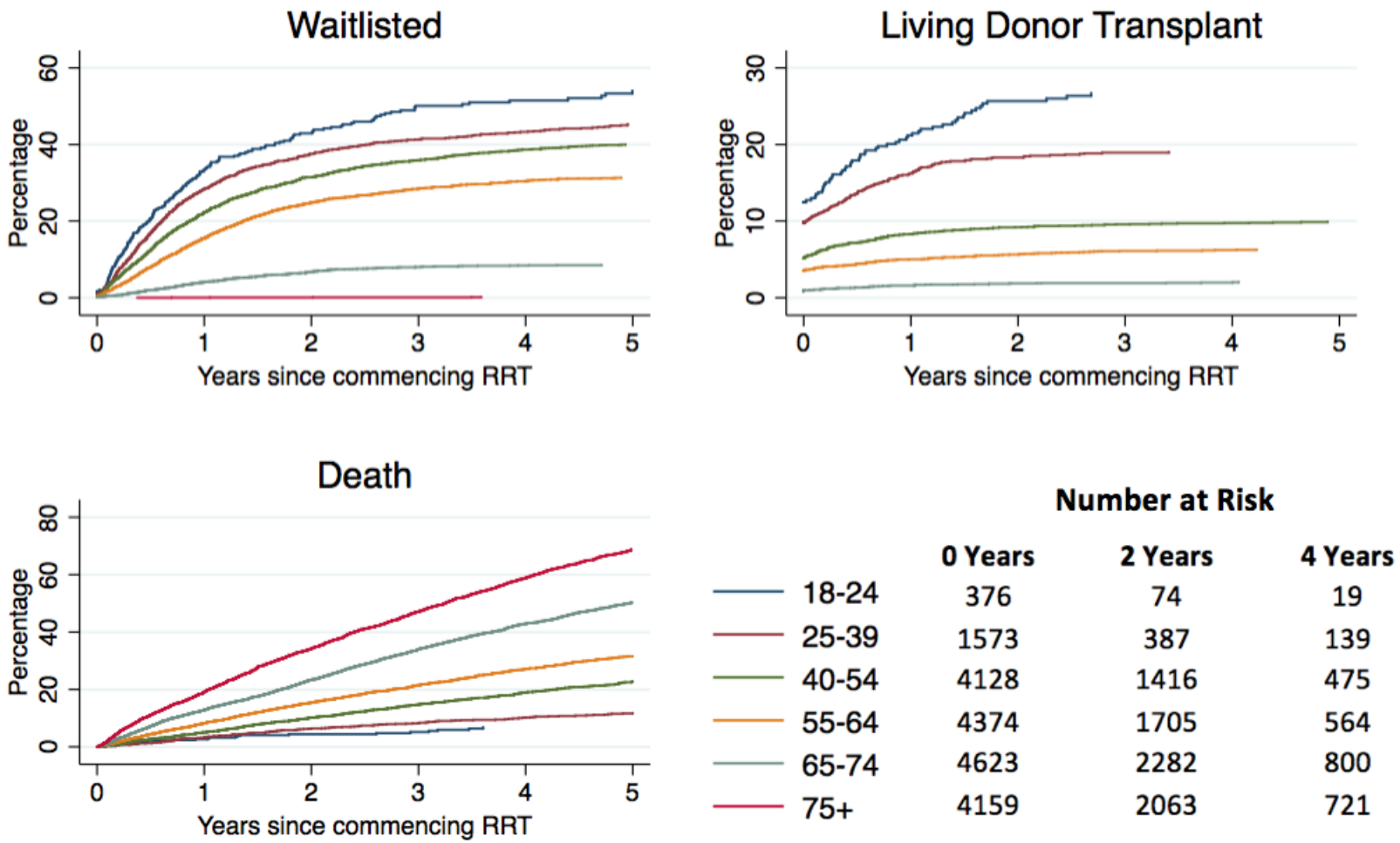

Figure 3.2 Cumulative incidence of competing outcomes, by age group

Cumulative incidence of each competing outcome for all adult patients commencing renal replacement therapy in Australia July 2006-July 2015 by age group. Note differences in Y axes. RRT, renal replacement therapy.

Table 3.3 Results of competing risk regression univariate and multivariate models of access to kidney transplantation in Australia

	Univariate		Model 1		Model 2		Model 3	
	Outcome: Waitlisting Competing Risk: LDTx, Death		Outcome: Waitlisting Competing Risk: LDTx, Death		Outcome: LDTx Competing Risk: Waitlisting, Death		Outcome: Waitlisting or LDTx Competing Risk: Death	
	SHR	**95% CI**	**SHR**	**95% CI**	**SHR**	**95% CI**	**SHR**	**95% CI**
Age Category								
18-24	**1.98****	1.71,2.30	**0.91**	0.77,1.08	**2.17****	1.75,2.68	**1.36****	1.18,1.58
25-39	**1.41****	1.30,1.54	**0.93**	0.85,1.02	**1.57****	1.36,1.83	**1.18****	1.09,1.28
40-54				Reference				
55-64	**0.69****	0.65,0.74	**0.83****	0.77,0.90	**0.74****	0.64,0.87	**0.76****	0.71,0.81
65-74	**0.16****	0.14,0.18	**0.2****	0.18,0.22	**0.24****	0.19,0.30	**0.16****	0.15,0.18
>=75	**<0.01****	0.00,0.01	**<0.01****	0.00,0.01	**<0.01****	0.00,0.02	**<0.01****	0.00,0.01
Gender								
Female	**0.91****	0.85,0.96	**0.85****	0.80,0.91	**0.84****	0.75,0.95	**0.81****	0.77,0.86
Ethnicity								
Non- Indigenous				Reference				
Indigenous	**0.36****	0.31,0.41	**0.46****	0.38,0.55	**0.11****	0.05,0.24	**0.36****	0.31,0.43
Body Mass Index								
Underweight	**0.88**	0.74,1.06	**0.81***	0.67,0.97	**0.81**	0.58,1.13	**0.75****	0.64,0.88
Normal				Reference				
Overweight	**0.96**	0.89,1.03	**1.06**	0.98,1.14	**1.07**	0.94,1.22	**1.07**	1.00,1.14
Obese	**0.76****	0.70,0.81	**0.83****	0.76,0.89	**0.61****	0.52,0.71	**0.69****	0.64,0.74
Primary Renal Disease								
Glomerulonephritis				Reference				
PKD/VUR	**1.66****	1.53,1.80	**1.12***	1.03,1.22	**1.32****	1.15,1.51	**1.28****	1.19,1.38
Diabetes	**0.22****	0.20,0.23	**0.38****	0.34,0.41	**0.32****	0.26,0.41	**0.33****	0.30,0.36
Other	**0.3****	0.28,0.33	**0.68****	0.62,0.74	**0.69****	0.59,0.81	**0.64****	0.59,0.69
Comorbidities								
Vascular Comorbidity	**0.22****	0.20,0.23	**0.54****	0.50,0.58	**0.54****	0.45,0.64	**0.48****	0.45,0.52

Comorbid Diabetes	**0.43****	0.38,0.49	**0.56****	0.49,0.64	**0.77**	0.60,1.00	**0.56****	0.49,0.63
Chronic Lung Disease	**0.32****	0.29,0.36	**0.62****	0.55,0.69	**0.49****	0.37,0.65	**0.57****	0.51,0.64
History of Cancer (1st Year)	**0.17****	0.13,0.22	**0.28****	0.22,0.36	**0.51****	0.36,0.73	**0.3****	0.25,0.38
History of Cancer (After 1st Year)	**0.59****	0.49,0.71	**0.76***	0.63,0.93	**1.1**	0.63,1.94	**0.62****	0.52,0.74
Smoking Status								
Current Smoker (1st Year)	**0.6****	0.52,0.69	**0.47****	0.41,0.55	**0.19****	0.14,0.27	**0.35****	0.30,0.40
Current Smoker (After 1st Year)	**1.15***	1.00,1.31	**1**	0.86,1.15	**0.96**	0.57,1.62	**0.57****	0.50,0.65
Former Smoker (1st Year)	**0.68****	0.63,0.73	**0.81****	0.75,0.88	**0.7****	0.62,0.81	**0.83****	0.77,0.89
Former Smoker (After 1st Year)	**1.03**	0.94,1.14	**1.67****	1.50,1.86	**2.29****	1.63,3.23	**1.1**	1.00,1.22
Late Referral								
Late Referral (1st 6 months)	**0.38****	0.33,0.45	**0.45****	0.39,0.53	**0.17****	0.13,0.24	**0.32****	0.28,0.37
Late Referral (6-12 months)	**0.8****	0.69,0.92	**0.86**	0.74,1.00	**0.77**	0.51,1.17	**0.63****	0.55,0.73
Late Referral (After 12 months)	**1.31****	1.17,1.46	**1.22****	1.09,1.37	**1.74****	1.23,2.47	**0.94**	0.85,1.05
Socioeconomic Disadvantage								
SEIFA 1st Quintile	**0.85****	0.78,0.94	**0.98**	0.88,1.08	**0.66****	0.53,0.80	**0.85****	0.78,0.93
SEIFA 2nd Quintile	**1.08**	0.98,1.18	**1.15***	1.04,1.27	**0.91**	0.75,1.10	**1.08**	0.99,1.18
				Reference				
SEIFA 4th Quintile	**1.15****	1.04,1.26	**1.02**	0.92,1.13	**1.33****	1.11,1.58	**1.16****	1.06,1.26
SEIFA 5th Quintile	**1.22****	1.11,1.34	**1.01**	0.91,1.12	**1.52****	1.28,1.81	**1.24****	1.13,1.35
Remoteness								
Urban				Reference				
Regional	**0.83****	0.78,0.89	**0.88****	0.81,0.95	**1.33****	1.15,1.53	**1.01**	0.94,1.08
Remote	**0.41****	0.35,0.49	**0.81**	0.63,1.04	**0.86**	0.47,1.59	**0.89**	0.71,1.12
State								
Northern Territory	**0.5****	0.41,0.61	**0.83**	0.65,1.07	**0.64**	0.35,1.16	**0.72****	0.57,0.90
New South Wales	**1.14****	1.07,1.23	**1.13****	1.04,1.22	**0.79****	0.68,0.91	**1.01**	0.95,1.09
Victoria	**1.43****	1.33,1.53	**1.22****	1.12,1.32	**1.07**	0.93,1.23	**1.22****	1.14,1.30
Queensland	**1.01**	0.93,1.09	**1**	0.92,1.09	**0.6****	0.51,0.72	**0.82****	0.76,0.89
South Australia	**1.45****	1.31,1.61	**1.37****	1.22,1.53	**1.2**	0.99,1.46	**1.42****	1.28,1.56

Western Australia	**0.82****	0.74,0.91	**0.76****	0.68,0.85	**1.16**	0.98,1.38	**0.82****	0.75,0.90
Tasmania	**0.91**	0.74,1.12	**0.77***	0.62,0.97	**2.24****	1.74,2.87	**1.21***	1.03,1.42
Australian Capital Territory	**1.13**	0.95,1.35	**1.08**	0.89,1.31	**0.99**	0.71,1.38	**0.97**	0.81,1.16
Year of Commencing RRT								
Per Year	**1**	0.99,1.02						

*Results of competing risk regression univariate and multivariate models. Note that subhazard ratios for States are referenced to the balanced grand mean for all states. LDTx living donor transplantation; SHR sub hazard ratio; PKD polycystic kidney disease; VUR vesicoureteric reflux; SEIFA socioeconomic indexes for area; RRT renal replacement therapy. *p value <0.05 **p value <0.01*

3.6 Discussion

We present the first detailed description of kidney transplant deceased donor waitlisting practice for adults with incident ESKD in Australia and report factors associated with waitlisting in this population. This study confirms a number of expected findings, including that increased comorbid burden and older age are strongly associated with a decreased likelihood of waitlisting, and also highlights variations across specific populations that require further exploration to determine if these observed differences represent inequities that may require targeted interventions.

Although age is not a specific criterion for kidney transplant waitlisting in Australia, there is an association between older age and risk of death as well as age and comorbid burden. The decreased rate of waitlisting for older patients may represent appropriate implementation of TSANZ guidelines on excluding patients with <80% anticipated 5-year survival post-transplant from the waiting list. However, numerous studies have demonstrated that transplantation confers a survival advantage for elderly patients compared to remaining on dialysis for those deemed suitable for transplantation[9,200–202], albeit in a highly selected cohort. Furthermore, although studies are limited, there are likely to be quality of life and economic benefits of transplantation for this population also[203].

Patients aged 65 years and older accounted for 46% of all new incident RRT patient in Australia in 2015[204] but made up only 7.3% of patients active on the transplant list at the end of that year[205]. By contrast, older people represent a growing proportion of the kidney transplant waiting list in many countries with the percentage of patients aged 65 years and

older on the US waitlist increasing from 14.5% in 2005 to 22% in 2015[206]. International practice varies widely with a 2012 study showing transplant listing rates for patients starting RRT aged >65 years of up to 24% in Norway, compared to ~6% in Austria, Scotland and the Netherlands[86]. Of note, a study of elderly patients transplanted in Norway between 1990-2005 reported an 5 year actuarial survival post-transplant of 56% in patients aged 70 years and older and 72% in patients aged 60-69 years[207], suggesting that a substantial number of older patients listed in Norway would not meet the criterion for listing used in Australia. As the number of older persons reaching ESKD continues to increase, it is important that patients are educated about all treatment options, including supportive care and transplantation, and that decisions regarding waitlisting for transplantation are based on consideration of the individual's best interests as well as appropriate resource utilisation whilst avoiding discrimination based on age.

Australia's Indigenous population experiences a disproportionally high burden of chronic disease compared to non-indigenous Australians[208], including kidney disease, with rates of RRT eightfold higher in the Indigenous population[209]. Reduced access to transplant waitlisting and transplantation for Indigenous people has previously been reported[210] and post-transplant outcomes are poorer for Indigenous recipients[211] . Recent qualitative research examining the views of Indigenous patients on kidney transplantation has highlighted an intense interest in transplantation within this community, undermined by limited knowledge about transplantation and multiple barriers to effective communication with health professionals[212]. Efforts to improve equity in access to transplantation for Indigenous Australians not only require a better understanding of the factors that predict

outcomes in this population, but will also rely on developing collaborative partnerships with Indigenous communities to address specific barriers to access.

We found significant differences in waitlisting and transplantation practice based on geographical location in Australia, similar to many other countries[80,82,83,195]. A number of factors vary across states including patient demographics, health system structure and the clinical cultures that individuals work within. For example, the Northern Territory (NT) has the highest percentage of Aboriginal and Torres Strait Islander people (25.5% compared with the national average of 2.8%[213]) many of whom live remotely; following adjustment for these factors, commencing RRT in the NT was not associated with reduced access to waitlisting. The variation across other states may reflect other, unmeasured population differences. In our secondary analysis, we found that two states (Western Australia and Tasmania) that were less likely to waitlist patients were associated with higher rates of living donor transplantation. Each geographical region comprises multiple autonomous parent renal units, and practice may vary between units in the same region. Further centre level analysis that was beyond the scope of this study is required to determine if variation in waitlisting practice across Australia represents appropriate implementation of national guidelines based on local population characteristics or whether interventions may be required to standardize opportunities for patients across the country.

In access to kidney transplantation, as in many aspects of health care and broader society, women experience a systemic disadvantage compared to men. Our finding that after adjustment for other factors, women remained 15% less likely to be waitlisted is consistent with international experience[83,214,215]. And our observed lower likelihood of living donor

transplantation for women is consistent with the well documented higher proportion of female-to-male compared to male-to-female living donors[216]. These gender discrepancies likely represent a complex of biological and sociocultural determinants[217–219]. Segev et al reported that age and comorbidities were effect modifiers of gender disparities in access to renal transplantation in the US population, concluding that there was no disparity for women in general but rather marker disparity for older women and those with comorbidities[215]. We saw the effect size of female gender increase in our multivariate model compared with univariate analysis (SHR 0.85 vs 0.91), however, the exploration of effect modifiers was beyond the scope of this paper. Further analysis, clinical auditing and patient engagement is needed to identify and work towards eliminating any systematic or cultural gender-based discrimination that is contributing to these observed differences.

While there was no association between younger age groups (18-24 and 25-39, compared with the reference group 40-54) or more socioeconomically advantaged groups and waitlisting on our primary analysis, secondary analysis using a composite endpoint of waitlisting or living donor transplantation showed significant advantages for these groups. This is consistent with our previously reported finding that socioeconomic status is associated with lower rates of living, but not deceased donor kidney transplantation in Australia[220]. Studies in the United States have also reported an association between markers of socio-economic prosperity such as insurance status and successful completion of transplantation work up[81,221]. This finding highlights the importance of considering all potential pathways to transplantation for incident RRT patients when assessing equity of access and targeting interventions to address this.

As with any registry-based study, our conclusions are limited by the variables available. We chose to include only the major comorbidities reported to ANZDATA which are more universally collected than the free text 'other comorbidity' field. We also used only comorbidities reported at time of commencing RRT rather than those that developed whilst on dialysis but prior to listing to simplify our models. Information about reasons for not listing was not available and in many cases, may have reflected patient choice or other unmeasured factors such as additional comorbidities or adherence to medical therapy. Our dataset was also unable to accurately identify other vulnerable population groups such as recent migrants or persons with mental health conditions, who may also be at risk of reduced access to transplantation. Our analysis provides a broad overview of factors that predict access to transplantation; further analysis such as multilevel modelling, detailed exploration of variable interactions and clinical auditing that was beyond the scope of this paper, may yield further insights into waitlisting practice.

3.7 Conclusion

We present the first detailed description of kidney transplant waitlisting practices in Australia. It is expected that factors associated with poor outcome post transplantation such as comorbid medical conditions and older age would also be associated with lower likelihood of waitlisting, and these finding likely represent appropriate implementation of current guidelines. However, we also highlight differences in access to waitlisting based on a number of additional demographic factors including gender, ethnicity and location of residence. Further analysis and clinical audit are required to determine if these differences

represent other, unmeasured factors or whether targeted interventions are required to improve equity in access to waitlisting in Australia.

Chapter 4 Examining the increased rates of deceased donor kidney non-utilisation in Australia: what has changed?

4.1 Preface

The content of this chapter has been published in the journal *Transplantation* (2019;103(12):2582-2590). The text is identical to the published manuscript apart from minor stylistic changes to figure and table titles and legends.

Authors

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Author contributions are described in the thesis preface.

4.2 Abstract

Background: From 2013, Australia has experienced a sustained increase in the proportion of deceased donor kidneys that are retrieved but not utilised for transplantation. We aimed to determine whether this could be explained by changes in donor characteristics over time.

Methods: Registry data were used to examine predictors of kidney non-utilisation over the period 2005-2017. Multi-level mixed effect logistic regression modelling and propensity score analysis were used to determine if era of donation (2013-2017 vs 2005-2012) was an independent predictor of organ non-utilisation after controlling for donor characteristics.

Results: A total of 7,810 kidneys were retrieved for the purpose of transplantation with 334 (4.3%) not utilised. The non-utilisation rate was 5.8% in 2013-2017 compared to 2.7% in 2005-2012. Despite adjustment for donor characteristics, donation in the more recent era remained a significant predictor of kidney non-utilisation (adjusted OR 1.98, 95%CI 1.54-2.54, $p<0.001$). This finding was confirmed in the propensity score analysis.

Conclusion: Kidneys retrieved in Australia since 2013 were more likely not to be utilised for transplantation even after adjusting for changes in donor characteristics. The abrupt increase may be explained by increased clinical risk aversion, changes in unmeasured donor factors or logistical issues. Although non-utilisation rates in Australia remain low by international standards, further clinical auditing of the reasons for offer decline may help to optimise resource utilisation and maximise transplant opportunities.

4.3 Introduction

Despite the increasing number of deceased donor kidney transplants performed each year in Australia, around one thousand patients remain on the waiting list[222] and demand for organs far exceeds supply. Australia has historically had low rates of organ non-utilisation compared with other countries for which reliable numbers are publicly available[91,223,224]. However, like other jurisdictions, the proportion of kidneys retrieved from deceased donors but not utilised for transplantation has increased in recent years[225]. The Australia and New Zealand Organ Donor Registry (ANZOD) reported a more than doubling in the percentage of kidneys retrieved for the purpose of transplantation but not utilised in 2013, from 3.0% to 6.7%[95].

In July 2008 the Australian Government announced a national reform program to implement a world's best practice approach to organ and tissue donation for transplantation[21] which resulted in the formation of the Organ and Tissue Authority (OTA) in 2009, an independent statutory agency within the Australian Government health portfolio that manages the implementation of the government's transplantation reform program. Since this time Australia has seen a steady increase in the numbers of deceased organ donors each year[226]. During this period Australia, like many other countries, has also seen a change in the characteristics of deceased organ donors with increases in mean donor age, increasing numbers of donations after circulatory death and changes in donor comorbidity profile [91,227,228].

In order to maximise the number of transplants performed and minimise resource wastage, ideally all kidneys retrieved for transplantation would be utilised for this purpose. Non-utilisation may reflect either that kidneys that are not suitable for use in transplantation are being retrieved – with inappropriate consumption of resources in this process – or that suitable kidneys are not being effectively allocated to appropriate recipients. We aimed to determine if the observed increase in deceased donor non-utilisation rates in Australia could be explained by changes in donor characteristics over time.

4.4 Methods

Data Sources and definitions

De-identified data from the ANZOD registry were used to analyse deceased donor kidney utilisation in Australia. All kidneys retrieved for the purpose of transplantation in Australian from January 2005 to December 2017 were included in the analysis.

Data on the number of intended donors, actual solid organ donors and donors from whom at least one kidney was retrieved are also presented for context. Intended donors are included in the ANZOD database if consent for donation has been signed and a blood sample has been sent for tissue typing. Actual organ donors are defined as donors who proceeded to the operating theatre for the purpose of organ or tissue retrieval for transplantation.

The outcome of kidney non-utilisation was defined as organs that were retrieved but not transplanted into a recipient. Where kidneys were transplanted en-bloc or as double kidney transplants, both kidneys were considered to have been transplanted. The primary exposure was donation in the period 2013-2017 compared to the period 2005-2012 based on the observed step wise increase in non-utilisation rates during this era.

Donor characteristics considered as potential confounders included: age, gender, body mass index (BMI), ABO blood group (AB vs non-AB), comorbidities (diabetes, hypertension, hepatitis C (either serological or nucleic acid testing positive) , hepatitis B core antibody positive, smoking status), the use of maintenance inotropes, admission and terminal serum creatinine, cause of death (stroke vs non-stroke), donation pathway (donation after brain death (DBD) vs donation after controlled circulatory death (DCD)) and weekend organ retrieval.

Statistical Methods

Donor characteristics in the two eras were compared using the Wilcoxon rank-sum test for non-normally distributed continuous variables and the Pearson's chi-squared test for categorical variables.

Due to variations in organ non-utilisation rates across Australian transplantation jurisdictions, a multilevel mixed effect logistic regression model with transplant jurisdiction included as a random intercept was used to determine the predictors of kidney non-utilisation. The linear association of continuous predictors was assessed by plotting continuous variables against log odds for non-utilisation. Where non-linear relationships

were observed, either linear splines or categorisation into clinically meaningful groups were used.

Donor characteristics in the Australian Kidney Donor Performance Index (KDPI)[65] were included a priori in the multivariate model, as well as predictors significant at a p value of <0.2 on univariate analysis. Additional backward selection of variables was used to optimise the model fit and discrimination (based on Akaike's Information Criterion (AIC) and Receiver Operating Characteristic (ROC) curve analysis). Predicted kidney non-utilisation rates using the full model and a model including only donor characteristics were plotted against observed non-utilisation rates by year.

Models were refit with assumed values at each extreme for the 159 (2%) observations excluded from the multivariate model due to missing values to assess the potential influence of missing data. Additional exploratory analyses were conducted to assess the impact of including performance of a kidney biopsy, changes in regional waiting list numbers and transplantation rate (number of transplants per 100 active waiting years in the preceding year by ABO blood group in each transplanting region) in the multivariate model (note that data on transplantation rate was only available for the years 2008-2017). In order to highlight potential changes in clinical behaviour over time, all donor characteristics were screened for interactions with era of donation.

To complement our primary analysis, a propensity score was developed to define the probability of each kidney being retrieved in either era 1 or era 2 based on donor characteristics. One-to-one nearest neighbour matched cohorts were created using a

calliper of one quarter of the propensity score standard deviation with replacement, and used to assess the independent association of era with non-utilisation in a logistic regression model weighted according to control matching. Adequacy of matching was assessed by comparing the distributions of propensity score before and after matching and comparing donor characteristics in the matched cohort using the methods outlined above. Sensitivity analyses were conducted using different matching methodologies to define the control cohort including one to one matching without replacement and radius matching. Free text documented reasons for non-utilisation were mapped to 8 categories for descriptive analysis. A p value of <0.05 was considered statistically significant. Analyses were conducted in Stata/IC 15.1 (StataCorp, College Station TX, USA).

4.5 Results

There were a total of 5,127 intended organ donors in Australia between 2005-2017 of whom 4,327 were actual donors and 3,947 had at least one kidney retrieved for the purpose of transplantation. Figure 4.1 shows the trend in donor numbers over the study period. The number of donors from whom at least one kidney was retrieved ranged from 198 in 2005 to 452 in 2017.

Between 2005-2017, a total of 7,810 kidneys were retrieved for the purpose of transplantation in Australia. Overall, 334 (4.3%) were not utilised for transplantation. Of these, 135 (40.4%) were cases of unilateral non-utilisation in which the paired kidney was used for transplantation, and 199 (59.6%) were cases in which all kidneys retrieved from the

donor were not utilised . Figure 4.2 shows the change in total number of kidneys retrieved each year over the study period, the total number of active patients on the Australian kidney transplant waiting list at December 31s each year, and the step-wise increase in the percentage of kidneys not utilised in 2013 from 2.7% in 2005-2012 to 5.8% in 2013-2017. The percentage of kidneys not utilised in each transplanting jurisdiction in Australia by era is shown in Figure 4.3.

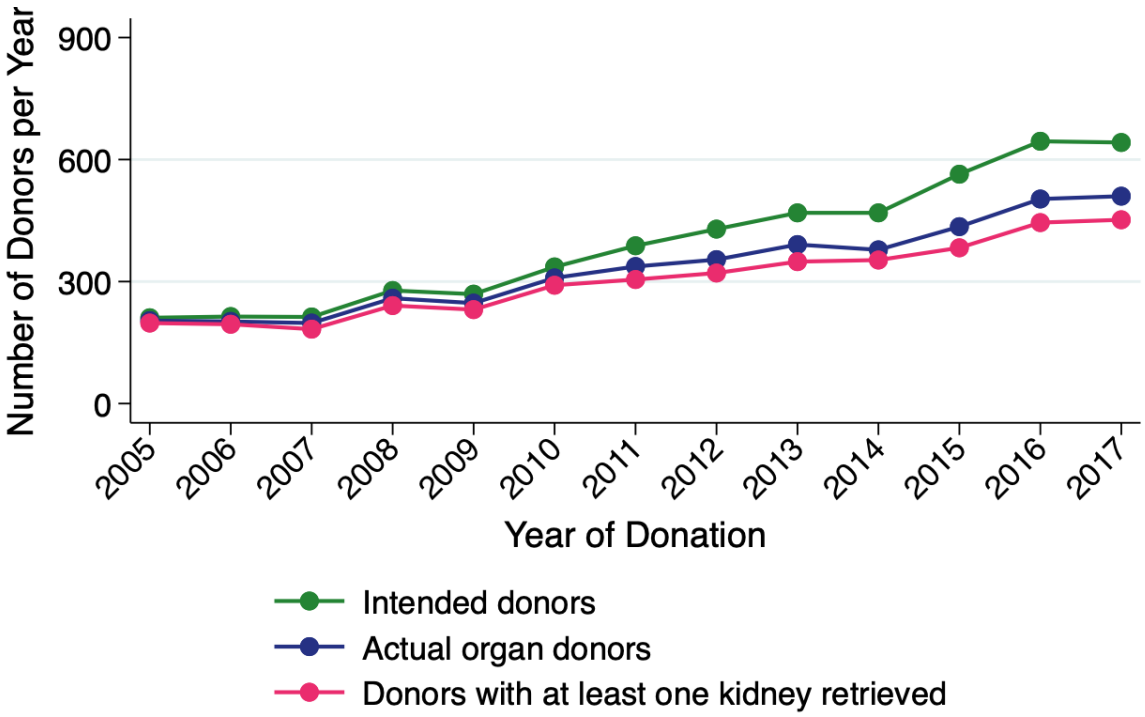

Figure 4.1 Intended and actual organ donors in Australia, 2005-2017

Trends in organ and kidney deceased donors in Australia per year 2005-2017. There has been a continuous increase in the number of organ donors each year in Australia since a national reform program was launched in 2009. Note that in recent years the gap between the number of intended and actual donors has widened.

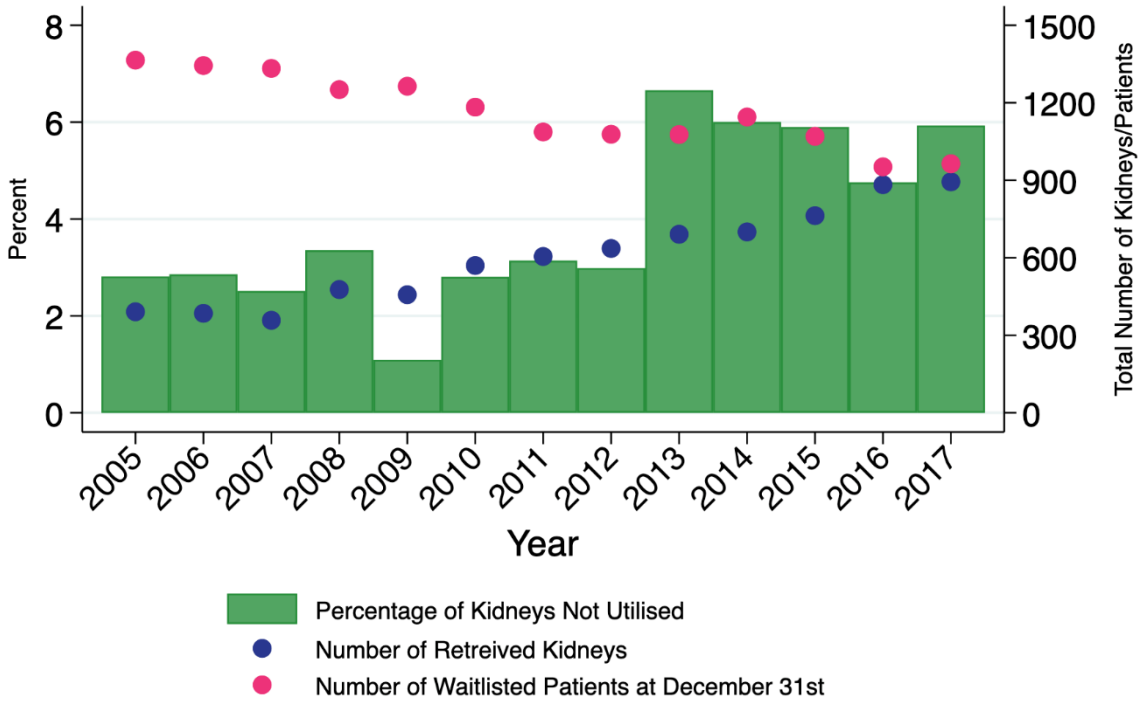

Figure 4.2 Kidney non-utilisation in Australia, 2015-2017

Trend in the number of kidneys retrieved not utilised for transplantation in Australia 2005-2017. A step wise increase in kidney non-utilisation was observed in 2013 and has remained consistently above historical levels since. The total number of kidneys retrieved per year and number of patients on the kidney transplant waiting list at December 31st each year and shown for context. Waiting list numbers are taken from the Australia and New Zealand Dialysis and Transplant Registry Annual Report: Chapter 6 Waiting List, available at http://www.anzdata.org.au/v1/annual_reports_download.html.

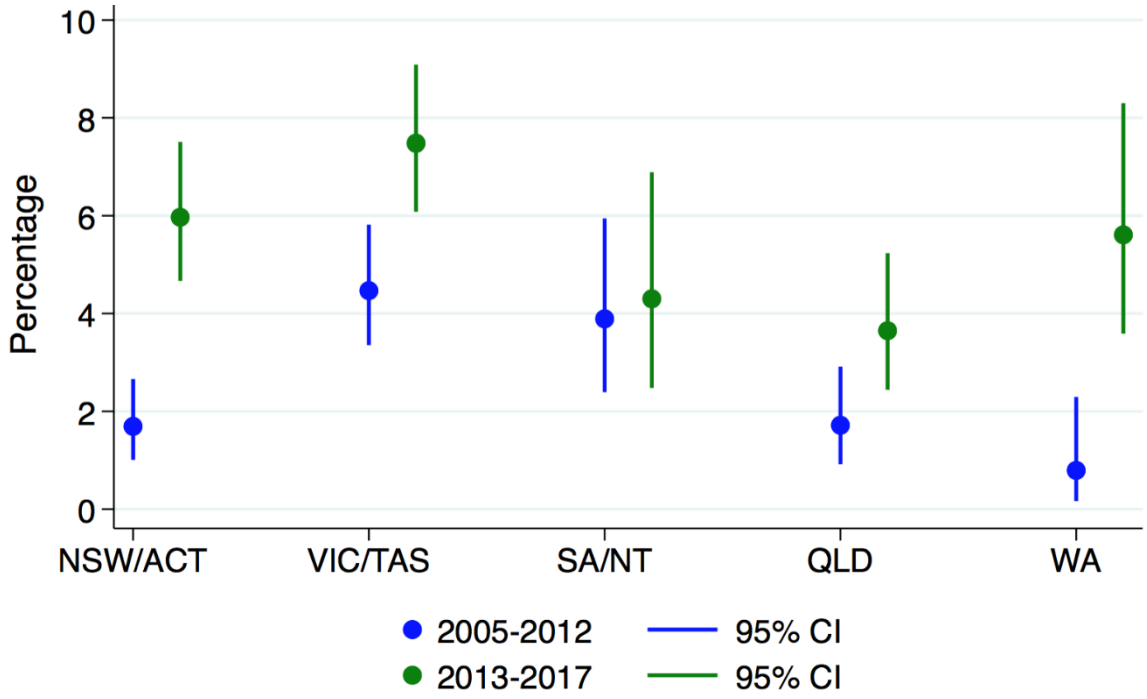

Figure 4.3 Kidney non-utilisation rate by transplant region, by era of donation

Percentage of kidneys retrieved but not utilised for transplantation in each Australian transplant jurisdiction comparing eras 2005-2012 and 2013-2017. There is significant variation in kidney non-utilisation rates across transplant jurisdiction. All jurisdictions saw an increase in non-utilisation in the more recent period, however, the magnitude of this varied considerably. NSW/ACT – New South Wales/Australian Capital Territory; VIC/TAS – Victoria/Tasmania; SA/NT – South Australia/Northern Territory; QLD – Queensland; WA – Western Australia.

Table 4.1 compares the donor characteristics between the two eras for all retrieved kidneys. Donors in 2013-2017 were older (median age 49 vs 47, p=0.002), with an increase in the percentage of donors aged 65 years or older (13.1% vs 15.6%, p=0.002). A higher percentage of kidneys were from donation after circulatory death (26.7% vs 15.6%, p <0.001), however, donors were less likely to have had maintenance inotropes (74.2% vs 86.2%, p<0.001) or have died as the result of a stroke (42.9% vs 50.9%, p<0.001). The proportion of donors with diabetes did not differ between the two eras (7.0% vs 7.3%, p=0.39). There was a small increase in the number of kidneys in which procurement biopsies were performed across the eras (11.5% to 13.5%, p=0.007). The trends over time for selected donor characteristics are shown in Figure 4.4. Note there was a fall in median donor age in 2015 and 2016 on the background of a trend of increased donor age over the preceding decade.

Table 4.1 Donor characteristics for kidneys retrieved for transplantation in Australia between 2005-2017, by era of donation

Donor Characteristic	2005-2012 (n= 3879)	2013-2017 (n=3931)	p-value
	n (%)	n (%)	
Age [median (IQR)]	47.0 (31.0, 59.0)	49.0 (33.0, 60.0)	0.002
Donors Aged ≥ 65	509 (13.1%)	614 (15.6%)	
Gender (Female)	1684 (43.4%)	1780 (45.3%)	0.097
BMI (kg/m^2)			0.30
Underweight (<18.5)	94 (2.4%)	103 (2.6%)	
Normal (18.5-<25)	1504 (38.8%)	1483 (37.7%)	
Overweight(25-<30)	1410 (36.3%)	1396 (35.5%)	
Obese(≥30)	871 (22.5%)	949 (24.1%)	
Diabetes	284 (7.3%)	276 (7.0%)	0.62
Hypertension	897 (23.4%)	993 (25.5%)	0.028
Donor Blood Group			0.056
O	1827 (47.1%)	1900 (48.3%)	
A	1506 (38.8%)	1496 (38.1%)	
B	397 (10.2%)	424 (10.8%)	
AB	149 (3.8%)	111 (2.8%)	
Hepatitis B Core Ab Positive	185 (4.8%)	157 (4.0%)	0.11
Hepatitis C Antibody Positive	24 (0.6%)	43 (0.9%)	0.20
Hepatitis C NAT Positive	5 (0.1%)	8 (0.2%)	0.42
Current smoker	1466 (37.8%)	1567 (40.0%)	0.048
Donation Pathway			<0.001
DBD	3275 (84.4%)	2883 (73.3%)	
DCD	604 (15.6%)	1048 (26.7%)	
Cause of death			<0.001
Non-stroke	1906 (49.1%)	2244 (57.1%)	
Stroke	1973 (50.9%)	1687 (42.9%)	
Inotropes	3345 (86.2%)	2915 (74.2%)	<0.001
Admission Creatinine			0.10
0-120µmol/L	3272 (84.4%)	3308 (84.2%)	
121-180µmol/L	528 (13.6%)	514 (13.1%)	
181-240µmol/L	45 (1.2%)	70 (1.8%)	
>240µmol/L	30 (0.8%)	37 (0.9%)	
Terminal Creatinine			<0.001
0-120µmol/L	3280 (84.6%)	3284 (83.5%)	
121-180µmol/L	361 (9.3%)	320 (8.1%)	
181-240µmol/L	97 (2.5%)	111 (2.8%)	
>240µmol/L	141 (3.6%)	216 (5.5%)	
Donation Region			<0.001
NSW/ACT	1064 (27.4%)	1139 (29.0%)	
VIC/TAS	1164 (30.0%)	1243 (31.6%)	
SA/NT	514 (13.3%)	372 (9.5%)	
QLD	758 (19.5%)	767 (19.5%)	
WA	379 (9.8%)	410 (10.4%)	
Biopsy performed			0.007
No	3432 (88.5%)	3398 (86.5%)	
Yes	447 (11.5%)	532 (13.5%)	

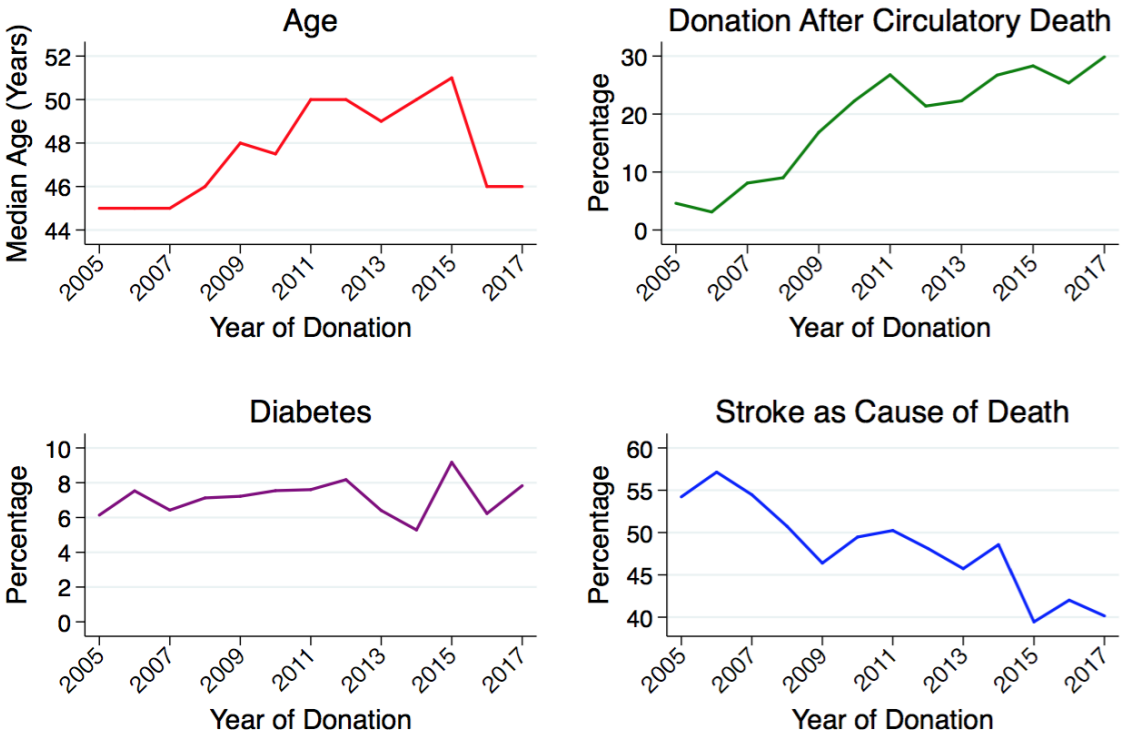

Figure 4.4 Changes in selected donor characteristics over time

Trends in selected donor characteristics for kidneys retrieved for transplantation in Australia 2005-2017. After steady increase in median donor age over the preceding decade, this fell in 2016 and remained lower in 2017. During this period there has been a substantial and ongoing increase in the number of kidneys from donors who have donated after circulatory death, no significant change in the portion of kidneys from donors with diabetes was observed and there has been a gradual decline in percentage of donors with stroke as their cause of death.

On univariate analysis, donation in the later era (2013-2017) was strongly associated with organ non-utilisation (OR 2.19, 95%CI 1.73-2.77, p<0.001). Although there was a downward trend in the non-utilisation rate between 2013-2016 which reversed in 2017, when year after 2013 was modelled as a continuous variable in univariate analysis, there was no significant association with non-utilisation (OR 0.95, 95%CI 0.87-1.05, p=0.331). The results of all univariate analyses are shown in Figure 4.5. Donor age was associated with a 7% increase in odds of non-utilisation per year over the age of 50 years (OR 1.07, 95%CI 1.06-1.09, p<0.001). Donor AB blood group and all donor comorbidities apart from history of smoking were associated with an increased odds of non-utilisation, as was DCD pathway (OR 2.13, 95%CI 1.69-2.69, p <0.001). The only factor associated with a lower odds of non-utilisation was the use of maintenance inotropes (OR 0.64, 95%CI 0.50-0.82, p<0.001). Weekend retrieval was not associated with an increased odds of non-utilisation (OR 1.06, 95% CI 0.83-1.35, p=0.641).

After adjustment for all clinically and statistically significant donor characteristics and model optimisation, era of donation remained a significant predictor of organ non-utilisation with an almost 2-fold increase in the odds for donors in the period 2013-2017 (adjusted OR 1.98, 95%CI 1.54-2.54, p<0.001). The factors included in the final multivariate model are shown in Figure 4.6; this multilevel model also included a random intercept for transplant region. The area under the ROC curve for the final model was 0.792, compared to an AUC of 0.775 for the model when era was omitted. Figure 4.7 compares the observed and predicted kidney non-utilisation rates using the model containing only donor factors and with the addition of era of donation.

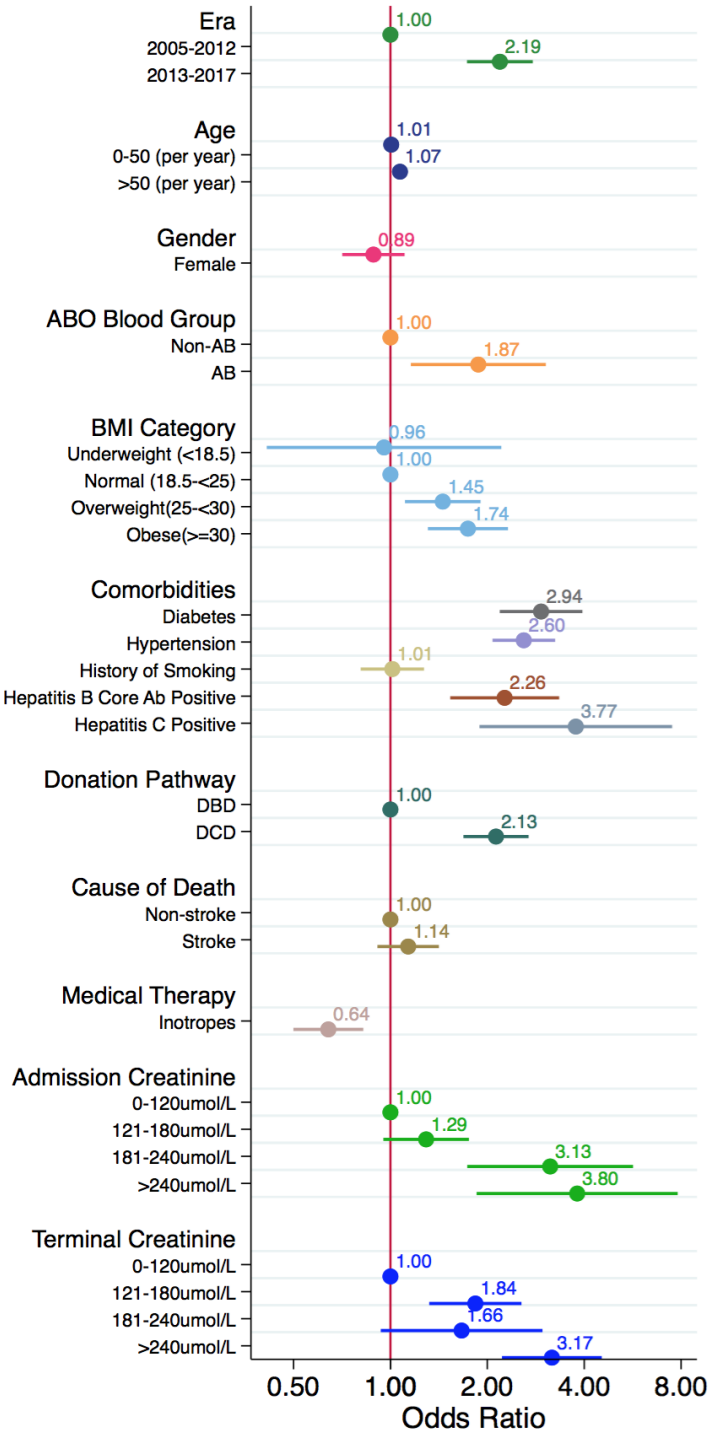

Figure 4.5 Predictors of kidney non-utilisation, univariate analysis

Multi-level mixed effect logistic regression models for kidney non-utilisation. This figure shows the odds ratios (OR) with 95% confidence intervals (CI) for donation era and donor characteristics on univariate analysis. All models include a random intercept from transplant jurisdiction. DBD – donation after brain death; DCD – donation after circulatory death.

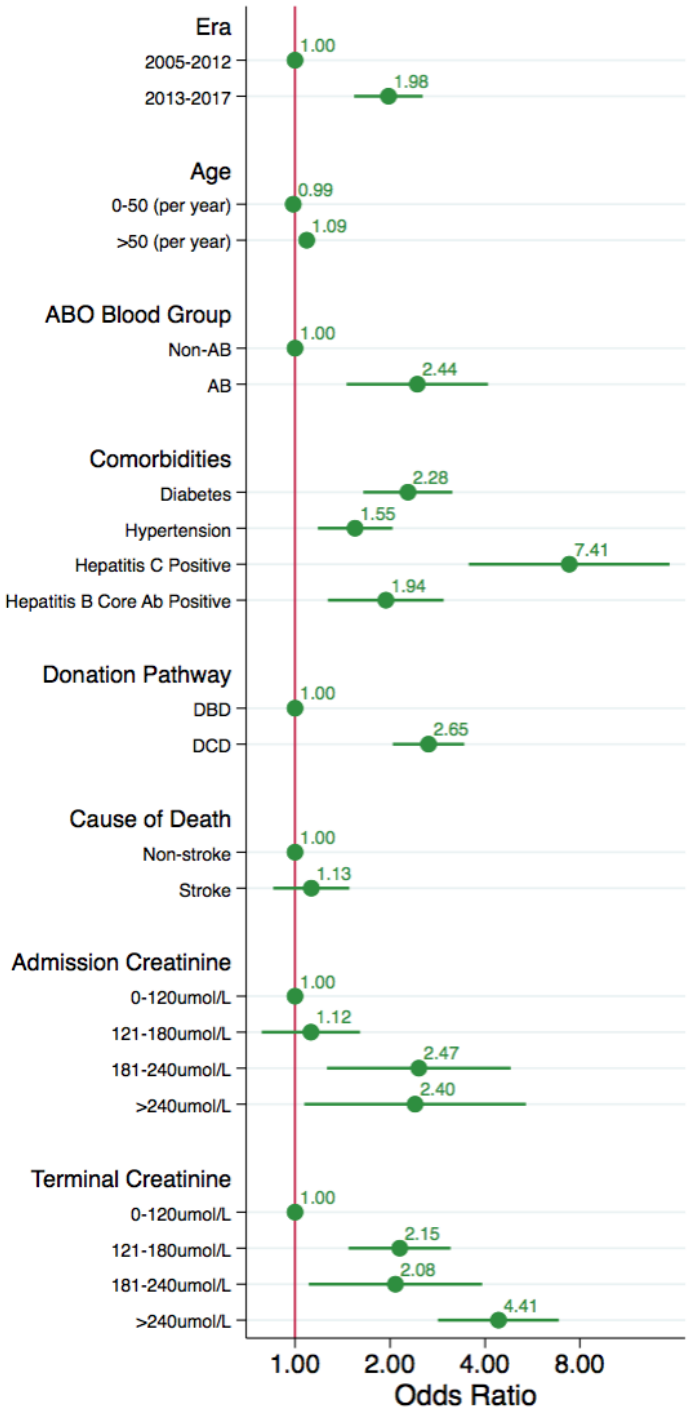

Figure 4.6 Predictors of kidney non-utilisation, multivariate analysis

Multi-level mixed effect logistic regression models for kidney non-utilisation. This figure shows the adjusted OR and 95% CI for multivariate analysis. The adjusted model includes all components of the Australian kidney donor performance index (KDPI) as well as donor variables that were statistically significant at a p value of <0.2 on univariate analysis with some variables removed after addition backward selection to optimise the model fit and discrimination. All models include a random intercept from transplant jurisdiction. DBD – donation after brain death; DCD – donation after circulatory death.

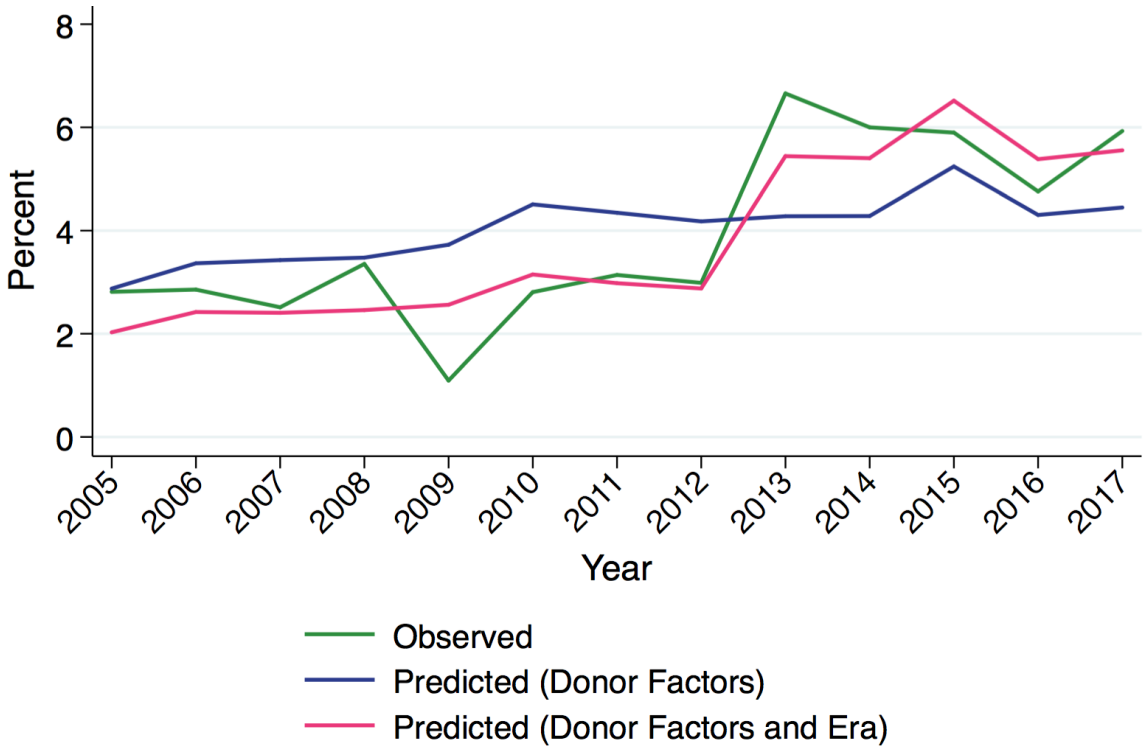

Figure 4.7 Observed vs predicted kidney non-utilisation rate

Comparison of observed and predicted kidney non-utilisation rates using multilevel mixed effect logistic regression models. The donor factors only model includes donor age, ABO blood group (AB vs other), diabetes, hypertension, hepatitis C, hepatitis B core antibody positivity, donation pathway (donation after brain death vs donation after circulatory death), cause of death (stroke vs non-stroke), admission creatinine and terminal creatinine with a random intercept for transplant jurisdiction. The donor factors and era model includes all of the above and era of donation (2005-2012 vs 2013-2017).

A total of 159 (2%) of observations were excluded from the final model due to missing data. On review the pattern of missing data did not appear to be systematic. Refitting the multivariate model with missing data assumed at extremes did not significantly alter the estimate of era effect, therefore observations with missing values were excluded from the analysis.

Having had a biopsy performed was highly significant on univariate analysis as a predictor of non-utilisation (OR 6.27, 95%CI 4.95-7.95, p <0.001), however, including this variable in the final model did not substantially alter the association of era (2013-2017) and non-utilisation (OR 2.01 for model including biopsy variable vs 1.98 for the base model). Similarly, change in the number of patients active on the regional transplant waiting list at the end of the year in which a kidney was retrieved was a significant predictor of non-utilisation on univariate analysis (OR 1.03 per 10 fewer waitlisted patients, 95%CI 1.02-1.05, p<0.001). However, when this variable was included in the multivariate model, there was only a small attenuation in the effect size of for the primary exposure of donation era (2013-2017) (adjusted OR 1.92 compared to 1.98 in the base model, p values both <0.001). Transplant rate in the preceding year for patients in the same region with the same blood group as a retrieved organ was not a predictor of organ non-utilisation on univariate analysis (OR 1.00, p=0.210) and did not have a significant impact on the primary outcome in the adjusted model.

Screening for interactions between era of donation and donor characteristics in the non-utilisation model revealed a single significant interaction between era and donor diabetes

(p-value for interaction term 0.044). The adjusted odds ratio for era (2013-2017) in donors without diabetes (93% of the cohort) was 2.3 (95%CI 1.68-2.94, p <0.001), whereas there was no significant association between era and non-utilisation in donors with diabetes (adjusted OR 1.16, 95%CI 0.66-2.06, p=0.604). Of note, there was no interaction between era of donation and donation pathway (p value for interaction term 0.912).

Propensity matching produced well matched cohorts with no statistically significant differences in baseline characteristics between the two cohorts. A total of 1,000 unique controls were matched to 3,831 cases. Analysis of matched cohorts found that era of donation remained a significant predictor of non-utilisation with a similar effect size to the primary analysis (OR 1.99, 95%CI 1.23-3.20, p =0.005) supporting the finding of our multivariate logistic modelling. Alternative matching methodologies including one to one matching without replacement (3,150 controls and 3,150 controls included) and radius matching (3,831 cases and 3,830 controls included) produced similar results for the association of era and non-utilisation (OR 1.85, 95%CI 1.42-2.41, p<0.01; OR 1.90, 95%CI 1.47-2.47, p <0.001, respectively).

The documented reasons for non-utilisation, with free text mapped to 8 categories, are shown in Table 4.2 by era. The largest increases in documented reason for non-utilisation across eras were in ‘Not Medically Suitable – Poor perfusion/Organ Ischaemia’ and ‘Not Medically Suitable – Other’ (9.4% to 16.2% and 17.9% to 32.9% respectively). ‘Anatomical/Surgical’, ‘Cancer Risk’ and ‘Viral Risk’ were each less common reasons for non-utilisation in the more recent era.

Table 4.2 Documented reasons for kidney non-utilisation in Australia by era (2005-2012 compared to 2013-2017)

Era	2005-2012	2013-2017
Not Medically Suitable - Poor Perfusion/Organ Ischaemia	10 (9.4%)	37 (16.2%)
Not Medically Suitable - Biopsy Result	10 (9.4%)	21 (9.2%)
Not Medically Suitable - Other	19 (17.9%)	75 (32.9%)
Anatomical/Surgical	28 (26.4%)	30 (13.2%)
Cancer Risk	12 (11.3%)	13 (5.7%)
Viral Risk	6 (5.7%)	4 (1.8%)
Recipient/Logistic	17 (16.0%)	39 (17.1%)
Not Reported	4 (3.8%)	9 (3.9%)
Total	106 (100%)	228 (100%)

Note that for each kidney a single free text reason for non-utilisation is documented by the donation co-ordinator. These reasons were mapped to eight categories according to the clinical discretion of the authors.

4.6 Discussion

Efforts in Australia to increase deceased donor organ availability have seen a steady and ongoing rise in the number kidney deceased donors with particular growth in the number donating via the controlled DCD pathway (Australia does not have a program for the retrieval of organs following uncontrolled DCD). Although, at 20.7 donors per million population Australia was ranked only 18th globally in 2017 by the International Registry in Organ Donation and Transplantation, below both the US and the UK[229]. At the same time, a more than doubling of kidney non-utilisation rates in 2013 that has largely been sustained over a five year period raises concerns about resource wastage and potential missed transplant opportunities. Our study demonstrates that changes in recorded donor characteristics alone are not sufficient to explain this abrupt rise in non-utilisation and other explanations must be sought.

Our analysis is limited by the availability of donor information and the inability of individual donor characteristics to capture the complexity of the specific clinical situation for each donor. Efforts in Australia to expand the donor pool are likely to have increased the number of donors with comorbidities unmeasured in our cohort. It is possible that the increase in non-utilisation represents an abrupt change in unmeasured donor characteristics, however it is unclear why there should be a sudden change in these when recorded characteristics have seen only incremental changes over the time period.

The un-explained observed increase in non-utilisation may represent increased reluctance of clinicians and patients to accept kidney offers which are perceived to be of higher risk. The physician must balance the benefits of accepting a sub-optimal organ against the risks of remaining on dialysis for the individual patient and their responsibility to the overall health system to maximise the use of available organs. Recent studies have shown that kidneys from expanded criteria or DCD donors may have poorer graft survival, particularly when combined with other risk factors such as prolonged ischaemic times or donor specific antibodies[230,231], which may encourage clinicians to be more cautious in accepting non-standard organ offers. We screened for interactions between donor characteristics and era of donation in an attempt to identify if acceptance patterns related to specific variables differed between the two eras, however, we did not identify any specific comorbidities or characteristics associated with increased non-utilisation in the later era compared to the earlier.

With a plateau in the incidence of renal replacement therapy and increasing numbers of transplants in recent years, the number of patients active on the renal transplant waiting list in Australia at the end of 2016 was the lowest of any year in the preceding decade[222,232]. The fall in waiting list numbers may result in the lack of a suitable recipient for a specific kidney, contributing to the increase in non-utilisation in recent years. This likely explains the higher rate of non-utilisation for blood group AB kidneys for which there were only 23 actively waitlisted potential recipients at the end of 2016[222]. Although the national organ allocation protocol should result in kidneys that cannot be allocated locally being shipped to a suitable recipient elsewhere in the country, it is notable that the transplant jurisdiction with the smallest waiting list[222] saw the largest increase in non-utilisation rates across eras. With

fewer patients on the waiting list and the associated reduction in expected additional waiting time before another organ offer, physicians may also become more discerning about the organs they choose to accept. However, despite being a significant predictor of non-utilisation on univariate analysis, when regional waiting list numbers were included in the multivariate model there was only a small attenuation of the effect of era, and no association was seen between transplant rate in the preceding year for patients in the same state with the same blood group as a retrieved organ and non-utilisation, indicating that these changes are not sufficient to explain the observed increase.

Our analysis of documented reason for non-utilisation is limited by the fact at only a single reason is recorded for each organ, rather than unique reasons for each individual offer decline, and challenges in mapping free text documentation. A substantial increase in 'poor perfusion/tissue ischaemia' as the reason for non-utilisation was seen. It has been suggested that an increase in kidney pumping in other jurisdictions may have helped curb increases in kidney non-utilisation [91]. Although data were not available on pumping of kidneys in Australia, anecdotally this practice remains rare with the vast majority of kidneys transported in cold storage. Recent advances in kidney machine perfusion technology offer a potential approach to increase organ utilisation in Australia, however, the long term benefits of these therapies remain uncertain[233–235]. The largest increase in documented reason for non-utilisation was in 'Not Medically Suitable – Other' (17.9% to 32.9%) indicating that more detailed and systematic auditing of the reasons for each organ offer decline may help provide insights on how clinician attitudes concerning donor suitability influence non-utilisation rates.

We were unable to identify any clear policy or procedural changes occurring in 2013 that may have resulted in the abrupt increase in non-utilisation due to data collection or definition changes. However, an important event to note is the introduction of the Electronic Donor Record (EDR) in mid 2014[236]. Prior to the implementation of the EDR, donor workup was completed on paper forms and submitted manually to the ANZOD registry changing to automatic data transfer following introduction of the EDR. Changes in the data available to clinicians at the time of organ offer may influence organ utilisation rates, for example, concerns have been raised in the United States around the potential for KDPI reporting to discourage acceptance of higher risk kidneys and thus result in increased non-utilisation[237,238]. KDPI is not currently used in kidney allocation in Australia but has been reported with all kidney offers since November 2016.

The increasing rate of kidney non-utilisation has been an international trend and a number of reports have examined the potential causes of this in other jurisdictions[89–94]. The United States in particular saw an increase in kidney non-utilisation from below 10% in the early 1990s to almost 20% in recent years[91] and the United Kingdom saw an increase from 5% to 12% across the first decade of this century[93]. The heterogeneity of donation, retrieval and allocation systems in different countries, as well as differences in population characteristics, limit the usefulness of direct international comparisons. However, multiple studies in the US have identified similar donor factors associated with non-utilisation as were seen in our study including donor age, comorbidities, positive blood borne virus testing, AB blood group and higher serum creatinine[90,91,96]. In contrast, whilst Stewart et al estimated that 82.5% of the increase in kidney non-utilisation in the United States during the 2000's could be explained by changes in donor characteristics, and biopsy and pumping practices over

time[91], we found that adjustment for donor characteristics only partially attenuated the association between donation era and non-utilisation highlighting the presence of other, unmeasured factors that are associated with this increase.

Commentators in the US have also speculated that regulatory oversight of kidney transplant outcomes may also encourage risk adverse practices that contribute to the high rate of organ non-utilisation[239,240]. In Australia, transplant hospital performance reports are published annual by the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), comparing 12 month graft and patient survival between centres[241]. However, centre performance is not subject to regulatory oversight and does not impact funding of health services, and therefore is much less likely to influence organ acceptance behaviour in the Australian context. Organ donation in Australia is co-ordinated and funded nationally through the Organ and Tissue Authority[242] which may help to address some of the financial and regulatory barriers contributing to organ non-utilisation that have been highlighted in other regions[243].

Despite the observed jump in kidney non-utilisation reported here, Australia remains below rates reported in the US and UK, yet one and five year allograft and patient survival is better in Australia compared to both the US and Europe[244]. A possible explanation for this low non-utilisation rate is the close working relationship between the donation and transplant sectors in Australia where pre-retrieval consultation with transplant surgeons and physicians may prevent organs that would be deemed unsuitable for transplantation from being retrieved. This is supported by the observation that the lowest non-utilisation rates in 2013-17 were in the two transplant jurisdictions with a single transplanting unit responsible

for both local organ retrieval and transplant implantation. It is interesting to observe that after a decade long trend of increasing median donor age, this actually fell in 2016 and remained at levels similar to 10 years earlier in 2017 possibly reflecting a response within the donation sector to clinician acceptance behaviour, although further studies are needed to test this hypothesis.

Like any registry based study, our analysis is limited to available data and by the quality of reporting. Overall, there was only a small amount of missing data with 2% of observations excluded from the final model, and we found that this did not impact our overall conclusions. Data on the number of offers declined and donation coordinator time spent on offers would be valuable to analyse but was unavailable.

4.7 Conclusion

Australia's abrupt increase in deceased donor kidney non-utilisation in 2013 is not fully explained by changes in recorded donor characteristics during this time period. Whilst it is possible that other unmeasured donor characteristics account for some of the residual era effect in our models, changes in organ acceptance behaviour should also be considered as a potential driver of the observed increase in kidney non-utilisation in Australia. More detailed documentation of non-utilisation reasons, auditing of clinical practice and ongoing communication between the donation and transplantation sectors are required to minimise resource wastage and ensure that all kidneys that are suitable for transplantation are used to improve outcomes for patients.

Chapter 5 Insights into the labelling effect of KDPI reporting: the Australian experience.

5.1 Preface

The content of this chapter has been published in the journal *The American Journal of Transplantation (*2020;20(3):870-878). The text is identical to the published manuscript apart from minor stylistic changes to figure and table titles and legends.

Authors

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Author contributions are described in the thesis preface.

5.2 Abstract

In 2016 Australia began reporting the Kidney Donor Performance Index (KDPI) with all deceased donor kidney transplant offers despite this not being used in organ allocation rules, offering a unique opportunity to explore the 'labelling effect' of KDPI reporting. We reviewed all kidneys retrieved for transplantation in Australia from 2015-2018 and analysed the association of KDPI reporting with organ non-utilisation, number of offer declines and donor/recipient age and longevity matching. Analyses were stratified by organ failure risk: higher risk (KDPI>80%), standard risk (KDPI 20-79%) and lower risk (KDPI 0-20%). There was no significant difference in organ non-utilisation post KDPI reporting either overall or for higher risk kidneys. KDPI reporting was associated with an increase in offer declines for both higher risk (IRR 1.45, p=0.007) and standard risk (IRR 1.22, p=0.021) kidneys, but not for lower risk organs. There was a significant increase in recipient age and Expected Post-Transplant Survival score for higher risk kidneys but no differences amongst other groups. We conclude that whilst KDPI reporting in Australia has been associated with an increased number of offer declines for higher risk kidneys, this has not resulted in increased non-utilisation and may have contributed to more appropriate use of these organs.

5.3 Background

In November 2016, Australia introduced reporting of the kidney donor profile index (KDPI) with all deceased donor kidney offers[65]. The KDPI is a population scaling of the Kidney Donor Risk Index (KDRI) that was designed by the US Scientific Registry of Transplant Recipients to quantify the risk of graft failure associated with a given donor kidney[59] and has subsequently been validated as a prediction tool in the Australian Context[63]. KDPI is not used in the algorithm for organ allocation in Australia[36], but is calculated and reported to "provide an objective measure of kidney quality when making decisions on organ acceptance"[65] and for future auditing purposes. The detailed donor clinical information available to clinicians at the time of organ offer through the Electronic Donor Record did not change during this period and already contained all of the individual components used to calculate the KDPI.

Concerns have been raised about the potential labelling effect of KDPI reporting in Australia: that clinicians may be more reluctant to accept offers of kidneys with high KDPI resulting in resource wastage in donation coordinator time to allocate kidneys and potentially even increased organ non-utilisation. Similar issues have been debated in the US following the introduction of KDPI use in the Kidney Allocation System[53,237,238]. It is also possible that increased awareness of kidney quality at the time of organ offer may result more discerning use of marginal kidneys, and directed use of lower KDPI kidneys, resulting in improved matching between predicted recipient survival and predicted organ survival.

We aimed to undertake a retrospective review of the impact of KDPI reporting with deceased donor kidney offers in Australia on organ acceptance behaviour, organ non-utilisation and explore if this has resulted in improved recipient/organ longevity matching.

In Australia, deceased donor kidney allocation is coordinated nationally through the OrganMatch system according to a uniform allocation protocol developed by the Transplantation Society of Australia and New Zealand (TSANZ)[36]. To briefly summarize, the country is divided into five transplanting regions comprising 17 adult and 6 paediatric renal transplanting services. All kidneys are first offered in a National Allocation which prioritises well matched highly sensitized patients, zero HLA mismatch transplants, paediatric recipients and addresses organ sharing imbalances between regions. If the kidney is not accepted through National Allocation it is offered within the same region as the donor according to region specific allocation rules that consider both HLA matching and waiting time as well as paediatric and other bonuses. If no recipient can be found locally (as is sometimes the case for blood group AB kidneys for example), the organ is once again allocated nationally according to recipient sensitization and waiting time. Around 20% of kidneys are allocated through the national system, and 80% regionally.

5.4 Methods

Population

A retrospective analysis of all kidneys retrieved for the purpose of transplantation in Australia from January 2015 to December 2018 was conducted using a de-identified data set

from The Australia and New Zealand Organ Donor Registry (ANZOD), The Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) and the National Organ Matching Service (NOMS). Kidneys used for multi-organ transplantation (including simultaneous kidney pancreas transplant) were excluded from the analysis.

The Australian KDRI[63] was used to determine the KDPI on a scale of 1-100% based on the characteristics of deceased donor kidney used for transplantation in the preceding 3 years.

Australian KDRI Formula
Exp(-0.0194 x minimum(donor age-18,0)
+ 0.0128 x (donor age-40)
+ 0.0107 x maximum(donor age-50,0)
+ 0.126 if the donor had a history of treated hypertension
+ 0.130 if the donor had a history of diabetes
+ 0.220 x ((donor terminal creatinine (in μmol/L))/88.4)-1)
- 0.209 x ((donor terminal creatinine (in μmol/L))/88.4)>1.5) if ((donor terminal creatinine (in umol/L))/88.4)>1.5
+ 0.0881 if donor cause of death stroke
- 0.0464 x ((height(in cm)-170)/10)
- 0.0199 x (weight(in kg)<80) if weight <80kg
+ 0.133 x if planned donation pathway DCD)

Kidneys were categorised according to risk of graft failure based on KDPI for stratified analysis: higher risk (KDPI>80%), standard risk (KDPI 21-80%), lower risk (KDPI≤20%).

Outcomes and Exposure

Two primary outcomes were considered to assess the impact of KDPI reporting: 1) organ non-utilisation and 2) number of offer declines prior to acceptance. Non-utilisation was defined as a kidney that was retrieved for the purpose of transplantation but not transplanted into a recipient. Number of declines was calculated using the allocation rankings generated by NOMS according to Australia's national kidney allocation algorithm[36].

Prospective cytotoxic T cell cross matching is performed for all potential kidney transplants in Australia using standardized recipient serum trays across all tissue typing laboratories in the country and organs are not offered in the presence of a positive cytotoxic T cell crossmatch. As such, all potential recipients with a positive cytotoxic T cell crossmatch on current serum were excluded from the list of offers and the number of declines was calculated based on the number of potential recipients ranked higher than the eventual recipient who did not receive a kidney from that donor. The number of offer declines prior to organ discard could not be determined for kidneys not utilised for transplantation and therefore these were excluded from this analysis.

Secondary outcomes included mean recipient age and mean Expected Post Transplant Survival (ETPS) score, by KDPI groupings. EPTS was calculated according to the following formula[61] and scaled to a reference population of all patients active on the Australian deceased donor transplant waiting list at 31st December 2014.

Raw EPTS Score Formula
0.047 x maximum ((age at transplant-25),0)
- 0.015 x max((age at transplant-25),0) if history of diabetes
+ 0.398 if prior solid organ transplant
- 0.237 if prior solid organ transplant and history of diabetes
+ 0.315 x log(years on dialysis'+1)
- 0.099 x log(years on dialysis'+1) if history of diabetes
+ 0.130 if years on dialysis = 0
- 0.348 if years on dialysis = 0) and history of diabetes
+ 1.262 if history of diabetes

The primary exposure was donation before or after 8th November 2016, the point at which KDPI reporting to the recipient clinician was introduced.

Statistical Methods

Donor characteristics before and after KPDI report were compared using two sample T test for normally distributed continuous variables, Wilcoxon rank-sum for non-normally distributed continuous variables and Pearson's chi-squared test for categorical variables. Trends in all outcomes across the period are shown graphically with smoothed quarterly rates.

A multilevel logistic regression model with random intercepts for kidneys clustered within donors, clustered within transplant regions was used to test for a difference in odds of non-utilisation before and after KDPI reporting. A multilevel negative binomial model was used to test a difference in the number of offer declines between the two eras. Due to the high number of zero declines in the dataset, a zero inflated negative binomial model was considered, however, there was no clinical or statistical justification to use this model in preference to the standard negative binomial model.

In all models the assumption of a linear relationship between continuous independent variables and the linear predictor was tested by comparing the fit of alternative fractional polynomial models and by plotting the linear predictor against the mean of quantiles of each independent variable. Where significant violations were found, linear splines or clinically meaningful categorisations were used. All potential confounders with a p value of <0.2 on univariate analysis in the entire cohort were included in the adjusted models.

Models significant on univariate analysis were sequentially adjusted for 1) log KDRI, 2) individual donor factors and 3) regional transplant waiting-list of the first of each month to

adjust for changes in the length of waiting lists over time. Donor factors considered for inclusion in the models were: age, gender, body mass index, ABO blood group, cause of death (stroke vs non-stroke), donation pathway (brain death vs circulatory death), diabetes, hypertension, history of smoking, hepatitis C antibody positivity, and terminal creatinine.

Changes in the mean age and EPTS before and after KDPI reporting by KDPI grouping were assessed graphically and tested for difference using a Wilcoxon rank-sum test. Correlation between donor and recipient age and KDPI/EPTS before and after KDPI reporting were assessed using Spearman's rank-order correlation coefficient and tested for difference across the two eras using Bootstrapping methods.

Exploratory analysis was conducted examining time as a continuous variable with a spline knotted at the time of KDPI reporting to test for significant trends pre and post reporting.

Statistical analysis was performed using Stata/IC 15.1 (StataCorp, College Station TX).

5.5 Results

A total of 3,451 kidneys were retrieved for the purposes of transplantation during the study, 232 (6.7%) were used for multi-organ transplants and excluded from the analysis. Of the remaining 3,219 kidneys, 198 (6.2%) were not utilised for transplantation. Thirty-four recipients (1.1%) did not have a match rank recorded in the NOMS dataset and these

transplants were excluded from the subsequent analysis. These may have represented data errors, linkage errors or transplants that occurred in exceptional circumstances.

Donor characteristic of all kidneys retrieved for transplantation in the period prior to and since KDPI reporting are shown in Table 5.1 (excluding those used for multi-organ transplant). Donors in the post-KDPI report era were younger (median age 48 vs 51 years, p 0.015), less likely to have died from stroke (30% vs 43.8%, p0.028) and more likely to be hepatitis C antibody positive (2.4% vs 0.6%, p<0.001). There was a slight reduction in both median KDRI (1.29 vs 1.32, p=0.006) and median KDPI (51% vs 53%, p=0.042) in the latter period (note that multiorgan transplants were excluded from this population and that KDPI in Australia is based on characteristics of kidneys transplanted in the preceding 3 years). Other characteristics were similar, although there was a difference in the geographical distribution of donors between the two periods.

Table 5.1 Donor characteristics of kidneys retrieved prior to and after KDPI reporting

	Pre-KDPI Reporting	Post KDPI Reporting	p-value
N	1362	1857	
Donor Age, median (IQR)	51 (37, 61)	48 (35, 60)	0.015
Gender			0.34
Male	753 (55.3%)	1058 (57.0%)	
Female	609 (44.7%)	799 (43.0%)	
BMI (kg/m2)			0.57
Underweight (<18.5)	30 (2.2%)	53 (2.9%)	
Normal (18.5-<25)	496 (36.4%)	642 (34.6%)	
Overweight(25-<30)	459 (33.7%)	652 (35.1%)	
Obese(>=30)	364 (26.7%)	488 (26.3%)	
Unknown	13 (1.0%)	22 (1.2%)	
Donor Blood Group			0.067
O	609 (44.7%)	908 (48.9%)	
A	558 (41.0%)	702 (37.8%)	
B	156 (11.5%)	185 (10.0%)	
AB	39 (2.9%)	62 (3.3%)	
Cause of death			0.028
Non-stroke	765 (56.2%)	1115 (60.0%)	
Stroke	597 (43.8%)	742 (40.0%)	
Donation Pathway			0.32
DBD	972 (71.4%)	1295 (69.7%)	
DCD	390 (28.6%)	562 (30.3%)	
Donor Diabetes			0.21
	116 (8.5%)	136 (7.3%)	
Hypertension			0.10
	386 (28.6%)	478 (26.0%)	
Smoker (Current or Former)			0.76
	859 (63.1%)	1181 (63.6%)	
Donation Region			<0.001
NSW/ACT	414 (30.4%)	541 (29.1%)	
VIC/TAS	431 (31.6%)	655 (35.3%)	
SA/NT	143 (10.5%)	121 (6.5%)	
QLD	250 (18.4%)	366 (19.7%)	
WA	124 (9.1%)	174 (9.4%)	
Hepatitis C Antibody Positive			<0.001
	8 (0.6%)	44 (2.4%)	
Procurement Biopsy Performed	206 (15.1%)	227 (12.2%)	0.017
KDRI, median (IQR)	1.32 (1.05, 1.76)	1.29 (1.02, 1.67)	0.006
KDPI, median (IQR)	53 (29, 78)	51 (27, 75)	0.042

KDPI – Kidney Donor Performance Index IQR – interquartile range; BMI – body mass index; DBD - donation after brain death; DCD – donation after circulatory death; NSW – New South Wales; ACT – Australian Capital Territory; VIC – Victoria; TAS – Tasmania; QLD- Queensland; SA – South Australia; NT – Northern Territory; WA – Western Australia.

5.5.1 Non-Utilisation

Figure 1.1 shows a non-linear relationship between KDPI and kidney non-utilisation across the entire study period. There was no difference in the overall non-utilisation rate in the pre and post KDPI reporting eras (5.8% vs 6.4%, p =0.478). Figure 1.2 shows the trends in non-utilisation across the study period separated by KDPI categories. There was no significant increase in the odds of non-utilisation for kidneys retrieved after KDPI reporting in Australia (OR 1.1, 95% CI 0.82-1.47, p=0.53). There was a trend towards increased non-utilisation in kidneys with KDPI >80% however, this did not reach statistical significance (OR 1.57,95% CI 0.98-2.51, p=0.06) and may have represented long term fluctuations in non-utilisation rates in this group (Figure 1.5, supplementary figure). Table 1.2 shows the odds of non-utilisation post KDPI reporting across risk categories.

Figure 1.1 Non-utilisation rate by KDPI deciles, Australia 2015-2018

Percent of kidneys retrieved but not used for transplantation but kidney donor performance index (KDPI) deciles.

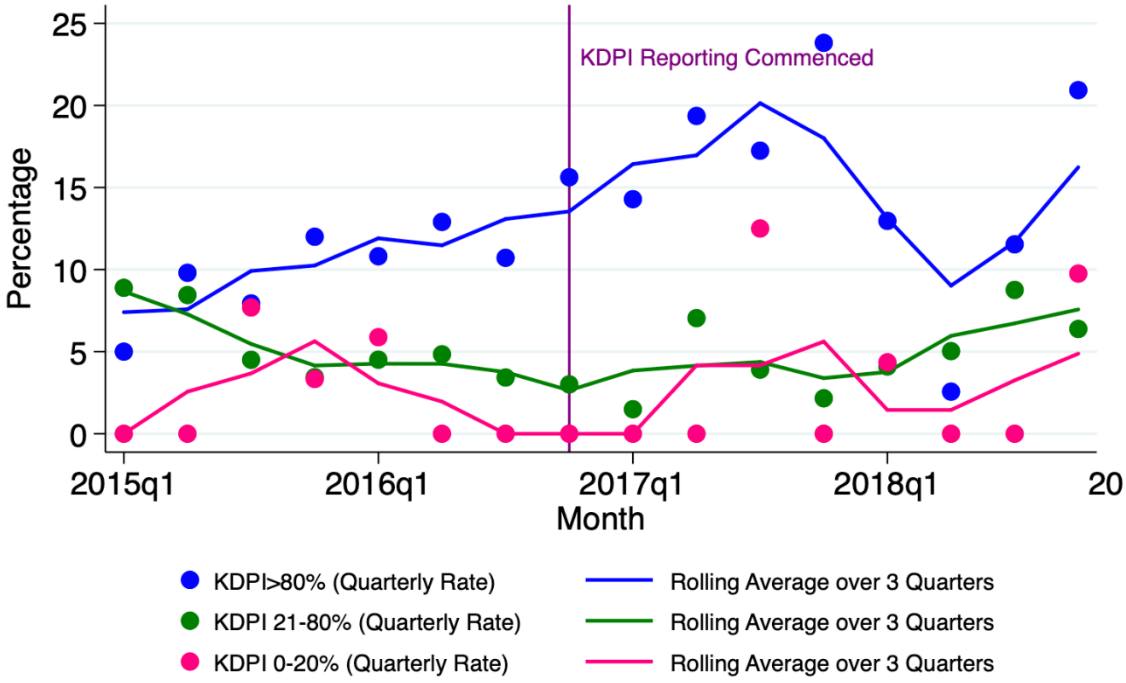

Figure 1.2 Kidney non-utilisation by KDPI, Australia 2015-2018

Percentage of kidneys retrieved for transplantation but not utilised over time stratified by graft failure risk. Quarterly rates and three quarterly rolling averages are shown. The purple line signifies when kidney donor performance index (KDPI) reporting with organ offers commenced.

Table 1.2 Changes in organ non-utilisation following KDPI reporting stratified by graft failure risk group

Organ Group	N	Odds Ratio	95% CI	P Value
All	3219	1.10	[0.82]-[1.47]	0.53
KDPI >80%	664	1.57	[0.98]-[2.51]	0.06
KDPI 21-79%	2026	0.92	[0.61]-[1.40]	0.71
KDPI 0-20%	529	1.42	[0.49]-[4.14]	0.52

Odds ratio for non-utilisation in post KDPI vs pre KDPI era. Multilevel models with kidneys clustered within donors, clustered within transplant regions. KDPI –.Kindey Donor Performance Index. *N – number of kidneys retrieved; OR – odds ratio; CI – confidence interval.*

5.5.2 Offer Declines

The distribution of offer declines was highly skewed with a median of one for lower and standard risk kidneys and three for higher risk kidneys, and a large number of outliers. Distribution of offer declines by KDPI groupings are shown in Figure 1.1.

On univariate analysis, there was no change in offer declines after KDPI reporting when considering all kidneys (IRR 1.13, 95%CI 0.98-1.30, p=0.086). When stratifying by KDPI grouping, there was a significant increase for both higher risk kidneys and standard risk kidneys (IRR 1.45, 95%CI 1.11-1.89, p=0.007 and IRR 1.22, 95%CI 1.03-1.45, p=0.021, respectively) but the number of offer declines per kidney did not differ across the two periods for lower risk kidneys (IRR 0.8, 95%CI 0.57-1.12, p=0.194) see Table 1.3.

Table 1.3 also shows the results of adjusted models. For higher risk kidneys, the increase in offer declines after KDPI reporting persisted after sequential adjustment for log KDRI (model 1), donor factors (model 2), waiting list numbers (model 3), and donor factors and waitlist numbers (model 4) (adjusted IRR range 1.38-1.51, $p<0.05$ for all). However, for standard risk kidneys, the increase in offer declines was attenuated by adjustment for individual donor factors and waiting list numbers.

Exploratory analysis showed that for higher risk kidneys there was no trend in increased offer declines prior to KDPI reporting (IRR 1.00 per month, 95%CI 0.98-1.02, p=0.965), however, after KDPI reporting there was a significant ongoing increase over time (IRR 1.03 per month, 95%CI 1.01-1.05, p=0.006).

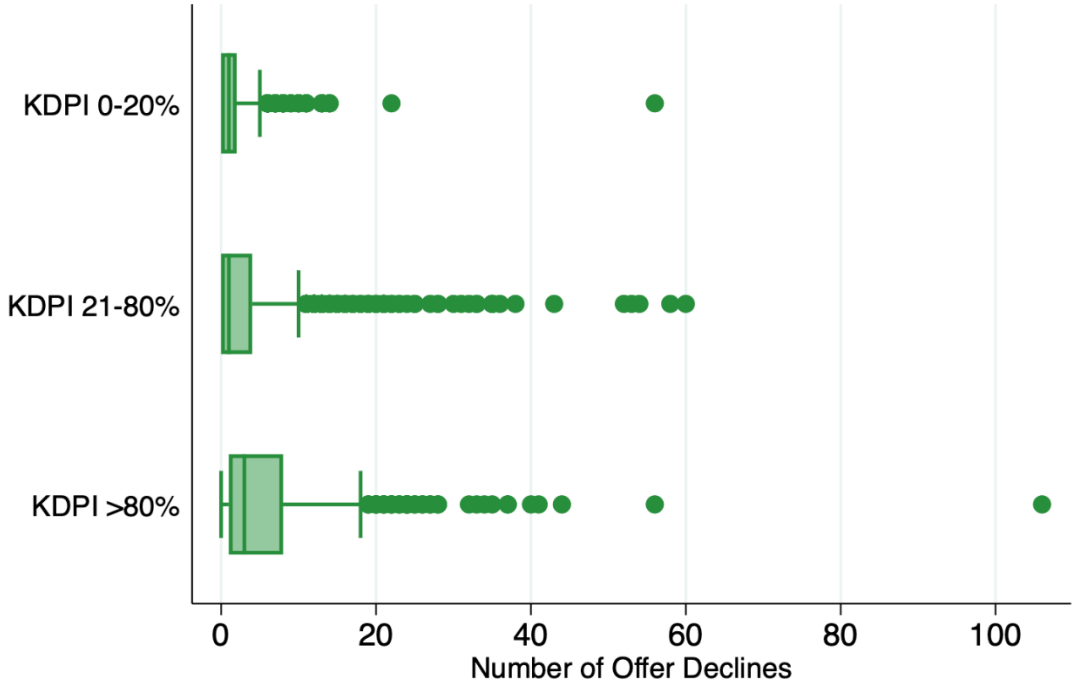

Figure 1.3 Distribution of kidney offers declines by KDPI grouping, kidney only transplants, Australia 2015-2018

Number of organ offer declines prior to acceptance stratified by graft failure risk.

Table 1.3 Changes in number of offer declines following KDPI reporting stratified by graft failure risk group

		Univariate			Model 1			Model 2			Model 3			Model 4	
Organ Group	n	IRR	95% CI	P Value	aIRR	95% CI	P Value	aIRR	95% CI	P Value	aIRR	95% CI	P Value	aIRR	95% CI	P Value
KDPI >80%	574	1.45	[1.11]-[1.89]	0.007	1.51	[1.16]-[1.95]	0.002	1.46	[1.13]-[1.87]	0.003	1.4	[1.07]-[1.83]	0.015	1.38	[1.05]-[1.82]	0.023
KDPI 21-80%	1911	1.22	[1.03]-[1.45]	0.021	1.22	[1.03]-[1.44]	0.022	1.16	[0.98]-[1.36]	0.085	1.16	[0.97]-[1.39]	0.106	1.1	[0.92]-[1.32]	0.298
KDPI 0-20%	502	0.8	[0.57]-[1.12]	0.194	0.79	[0.56]-[1.11]	0.166	0.8	[0.57]-[1.13]	0.206	0.75	[0.53]-[1.06]	0.104	0.77	[0.55]-[1.08]	0.131
All Kidneys	2987	1.13	[0.98]-[1.30]	0.086	1.19	[1.05]-[1.36]	0.008	1.16	[1.02]-[1.32]	0.026	1.08	[0.92]-[1.26]	0.349	1.07	[0.91]-[1.24]	0.409

Changes in number of offer declines following Kidney Donor Performance Index (KDPI) reporting stratified by graft failure risk. Multilevel models with kidneys clustered within donors, clustered within transplant regions. Multivariate models adjusted for: Model 1: exponentiated kidney donor risk index; Model 2: donor factors: age (with linear spline knotted at age 50), ABO blood group, cause of death (stroke vs non-stroke), donation pathway (donation after brain death vs donation after circulatory death), diabetes, hypertension, history of smoking, hepatitis C antibody positivity and terminal creatinine; Model 3: number of patients of the regional waiting list on the first of the month; Model 4: donor factors in model 2 and waiting list numbers. IRR – incidence rate ration; aIRR – adjusted IRR; CI – confidence Interval

5.5.3 Changes in Recipient Characteristics

Overall there was no difference in mean recipient age or EPTS across the two periods, however for higher risk kidneys there was a significant increase in both recipient age and EPTS in the period after KDPI reporting (median age 62 vs 59 years, p <0.001; median EPTS 61% vs 54% p =0.035) (Table 1.4). There were no significant differences in recipient age or EPTS across the two periods for standard or lower risk organs.

Figure 1.4 shows the correlation between donor and recipient age and KDPI/EPTS before and after KDPI reporting for the entire cohort. There was no significant change in the correlation between donor age and recipient age following KDPI reporting (rho 0.318 vs 0.260, difference 0.059, p=0.082) however there was a modest but significant increase in the correlation between KDPI and EPTS (rho 0.286 vs 0.217, difference 0.069, p=0.037).

Table 1.4 Changes in recipient characteristics post KDPI reporting by graft failure risk group

	Pre KDPI Reporting	Post KDPI Reporting	P Value
Recipient Age, Median (IQR)			
KDPI >80%	59.0 (50.0, 65.0)	62.0 (55.0, 67.0)	<0.001
KDPI 21-80%	53.0 (41.5, 61.5)	54.0 (43.0, 62.0)	0.13
KDPI 0-20%	48.0 (41.0, 57.0)	47.0 (34.0, 58.0)	0.24
All Kidneys	54.0 (43.0, 62.0)	55.0 (43.0, 63.0)	0.18
Recipient EPTS, Median (IQR)			
KDPI >80%	54.0 (32.0, 73.0)	61.0 (41.0, 77.0)	0.035
KDPI 21-80%	41.0 (16.0, 67.0)	42.0 (19.0, 69.0)	0.29
KDPI 0-20%	31.5 (14.0, 56.0)	27.0 (7.0, 53.0)	0.086
All Kidneys	43.0 (21.0, 68.0)	43.0 (20.0, 69.0)	0.76

Median recipient age and expected post-transplant survival (EPTS) score prior to and following kidney donor performance index (KDPI) reporting stratified by graft failure risk. IQR -interquartile range.

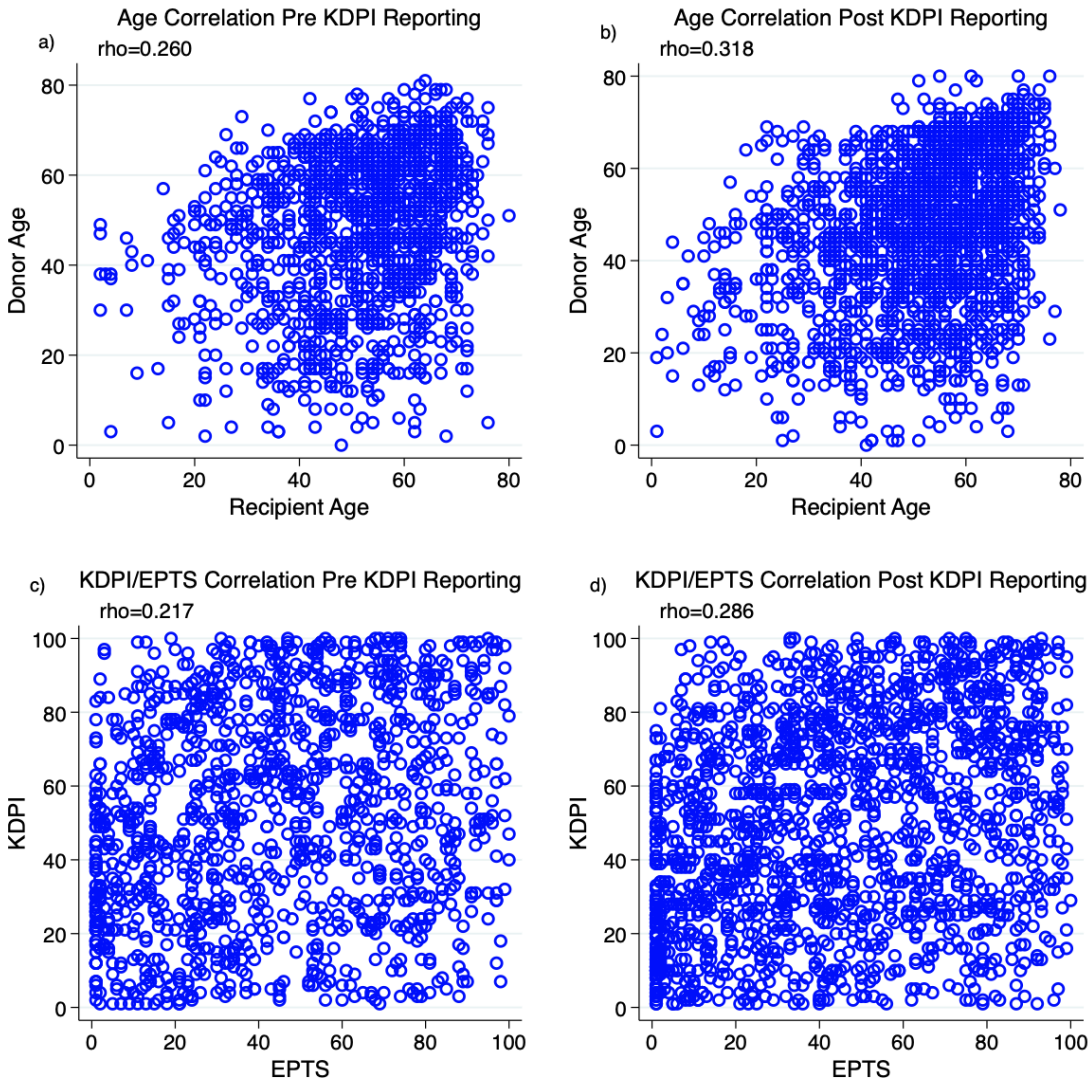

Figure 1.4 Donor/Recipient age and KDPI/EPTS correlations, Australian deceased donor transplants 2015-2018

Panels a and b show the correlation between donor and recipient age before and after kidney donor performance index (KDPI) reporting. Panels c and d show the correlation between KDPI and expected post-transplant survival (EPTS) score before and after KDPI reporting. Each circle represents a single transplant event.

5.6 Discussion

In the wake of the United States' redesign of their Kidney Allocation System in 2014, there has been growing interest globally surrounding the role of recipient/organ longevity matching in kidney transplant allocation[52,64,245]. Following validation of a modified version of the US KDPI[63], Australia began reporting this score with all kidney offers despite it not being incorporated into local allocation algorithms and without changes to the clinical information available to accepting clinicians, offering an opportunity to assess for potential labelling effects associated with the reporting of this organ quality index. We found that KDPI reporting has been associated with a 45% increase in the number of organ offer declines for higher risk (KDPI>80%) kidneys without a significant increase in the rate of non-utilisation. Although there was no formal change in allocation policy, the significant increase in the median age and EPTS of recipients receiving higher risk kidneys and a modest improvement in KDPI/EPTS correlation following KDPI reporting suggests that these kidneys may be being directed to recipients with lower expected survival.

Our results suggest there is a degree of labelling effect in KDPI reporting, given that the component donor information was available prior to the introduction of KDPI reporting. This is consistent with previous studies in the US. Examining changes in the kidney non-utilisation rate after the introduction of KDPI use in the US, Bae et al[246] found that although there was no overall increase in in non-utilisation rates, amongst kidneys that were previously labelled as 'standard criteria' that were reclassified as 'high risk' (KDPI>85%) there was a significant increase in odds of non-utilisation (aOR 1.42, 95%CI 1.07-1.89,

p=0.02). In an opportunistic study, Stewart et al[238] reported on the impact of KDPI labelling when the index was incorrectly calculated for a 30 day period in the US due to a programming error, resulting in erroneously high KDPI values being displayed with organ offers. During this period the kidney non-utilisation rate did increase, but not to the degree that would have been predicted based on the usual relationship between KDPI and organ non-utilisation. The authors concluded that although the elevated non-utilisation rate was "most likely attributable to the erroneously high KDPIs" the findings suggested that "clinicians and patients did not rely heavily on this single number".

Unlike these studies, we did not find a significant increase in organ non-utilisation but rather saw an association between KDPI reporting and the more sensitive measure of offer declines. This may reflect that, despite an unexplained increase in 2013, Australia's non-utilisation rate remains low compared to other countries[247], likely reflecting a number of systemic factors including a close working relationship between the donation and transplantation sectors. Alternatively, due to smaller number of organ retrievals, our study may have been underpowered to detect a true increase in non-utilisation. The absence of a significant impact on organ non-utilisation, even for higher risk kidneys, is reassuring that an unintended labelling effect has not resulted in a major increase in organ wastage. In fact, rather than detrimental impacts, there is a suggestion that it has been associated with the potential benefit of more appropriate organ allocation, although longer term outcome data is required to confirm this hypothesis.

The major limitation to our study is its retrospective, observational nature. It is not possible to state whether the observed changes were caused by KDPI reporting or represent broader

cultural changes in the kidney transplant sector that coincided with KDPI reporting. Since the launch of a coordinated national reform program in 2008 to implement a "world's best practice approach to organ and tissue donation for transplantation"[21] Australia has seen a more than doubling of the annual number of deceased organ donors[20]. As a result, the number of patients active on the deceased donor kidney transplant waiting list has been gradually falling, down to 39 patients per million population at the end of 2017[248,249]. The associated reduction in waiting times may motivate clinicians or patients to decline a higher risk offer and await a more suitable organ. Although the KDRI shows only moderate discrimination of death censored graft survival in the Australian population (Harrel's C statistic 0.63)[63] it may provide an additional tool to assist clinicians in making decisions regarding offer acceptance.

Unlike the US, the kidney allocation system in Australia does not currently address organ and recipient longevity matching. Clinical discretion provides a mechanism to ensure that higher risk kidneys are not transplanted into patients who would benefit from waiting for a better organ offer, however, there is no system for prioritising the use of kidneys with the best predicted survival. Maximising the total benefit is one of a number of competing ethical principles that should be considered when deciding on the optimal use of a scarce resource such as organs for transplantation but this must be weighed against the imperative to ensure equitable access to organs across the population[23]. There was a marginal increase in the correlation between KDPI and recipient EPTS following the introduction of KDPI reporting. This finding was primarily driven by the increase in ETPS for recipients of kidneys from higher risk donors whereas for the 20% of kidneys with be best predicted survival, we did not observe any significant difference in recipient age or EPTS. This highlights the need

for ongoing monitoring to ensure that the quality of outcomes for higher risk recipients who are receiving higher risk kidneys are maintained and supports the argument that allocation rules prioritising the use of lower risk kidneys to patients with the best predicted survival, such as those used in the US KAS, are likely to be required to achieve maximum utility of deceased donor kidneys.

The use of administrative datasets to analyse clinical behaviour produces limitations in our analysis. We have determined offer declines based on allocation ranking, however, it is not clear if each potential recipient was actively considered before the organ was declined or if in some circumstances clinicians may have declined organs for all potential recipients at their centre, skipping large portions of the allocation list. Exclusion of CDC positive T cell crossmatches also required some assumptions that may not reflect the nuances of histocompatibility testing where B cell and flow crossmatches may be used to aid interpretation of equivocal results. Organ acceptance behaviours vary significantly across transplanting regions in Australia, we have attempted to account for this clustering by using multilevel modelling in our analysis, however this may incompletely capture this variation in practice.

Australia's decision to report a modification of the US's KDPI with all kidney offers has provided a unique opportunity to explore the potential labelling effect of this index. We conclude that whilst KDPI reporting has been associated with an increased number of offer declines for higher risk and, to lesser extent, standard risk kidneys, this has not resulted in increased non-utilisation of kidneys and may have contributed to a small improvement in donor/recipient age matching and KDPI/EPTS matching for higher risk kidneys. Optimising

the utility of lower risk kidneys is likely to require changes in allocation policies in addition to reporting of survival indices.

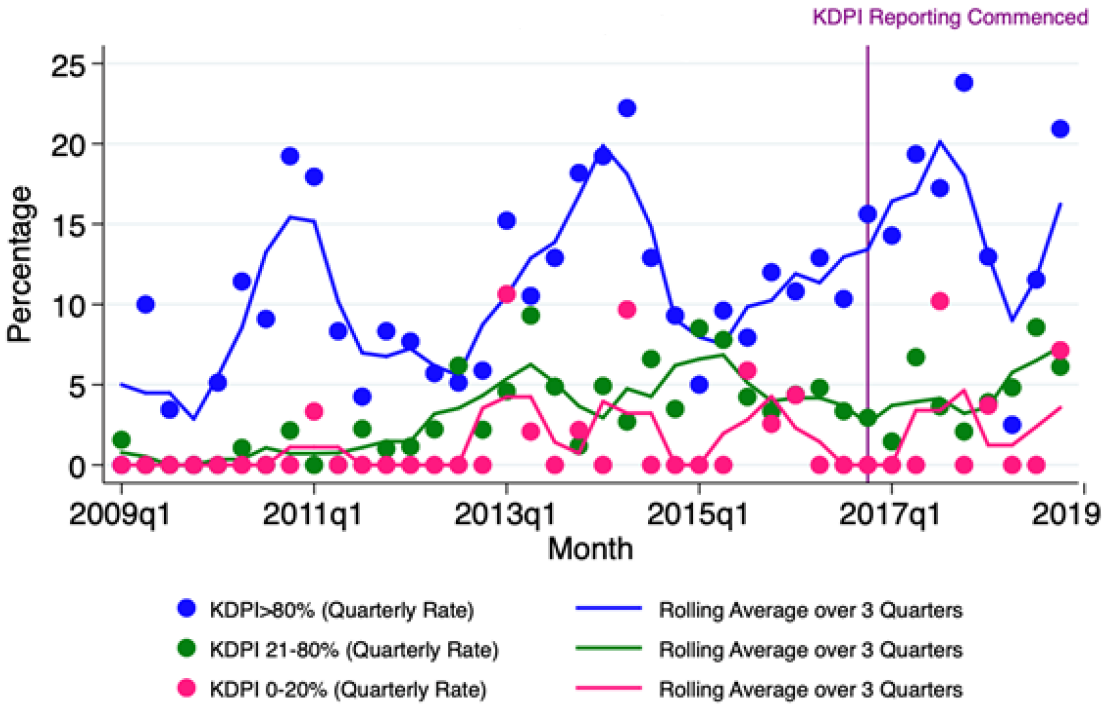

Figure 1.5 Long term trend in kidney non-utilisation by KDPI group, Australia 2009-2018 (supplementary figure)

Long term trend in the percentage of kidneys retrieved for transplantation but not utilised stratified by graft failure risk. Quarterly rates and three quarterly rolling averages are shown. The purple line signifies when kidney donor performance index (KDPI) reporting with organ offers commenced.

Chapter 6 The introduction of cPRA and its impact on access to deceased donor kidney transplantation for highly sensitized patients in Australia

6.1 Preface

The content of this chapter has been accepted for publication in the *Transplantation* (in press). The text is identical to the accepted manuscript apart from minor stylistic changes to figure and table titles and legends.

Authors

Matthew P Sypek, Joshua Y Kausman, Narelle Watson, Kate Wyburn, Stephen G Holt, Peter Hughes, Philip D Clayton

Author contributions are described in the thesis preface.

6.2 Abstract

Background: In March 2016, Australia's deceased donor kidney allocation program introduced calculated panel reactive antibody (cPRA) based on antibody exclusions using multiplex assays to define sensitization for waitlisted candidates. We aimed to assess the impact of this change and review access to transplantation for highly sensitized patients under the current allocation rules. Methods: Registry data was used to reconstruct changes in PRA/cPRA for all patients active on the waiting list between 2013-2018. A multilevel, mixed-effect negative binomial regression model was used to determine the association between sensitization and transplantation rate in the cPRA era. Results: Following the introduction of cPRA there was an increase in the percentage of the waiting list classified as highly sensitized (PRA/cPRA ≥80%) from 7.2% to 27.8% and very highly sensitized (PRA/cPRA ≥99%) from 2.7% to 15.3%. Any degree of sensitization was associated with a decreased rate of transplantation with a marked reduction for those with cPRA 95-98% (adjusted incidence rate ratio (aIRR) 0.36, 95%CI 0.28-0.47, p<0.001) and cPRA ≥99% (aIRR 0.09, 95%CI 0.07-0.12, p<0.001). Conclusions: The proportion of the waiting list classified as highly sensitized increased substantially following the introduction of cPRA and despite current prioritisation, very highly sensitized patients have markedly reduced access to deceased donor transplantation.

6.3 Introduction

Pre-existing antibodies to human leukocyte antigens (HLA) are a major barrier to successful kidney transplantation. Transplant candidates with antibodies to a high percentage of the donor pool can have difficulty accessing transplantation and have increased mortality on the transplant waiting list [47,48]. Australia, like many other transplanting jurisdictions, gives priority to highly sensitized patients within its deceased donor kidney allocation algorithm. The effectiveness of this prioritization in improving access to transplantation for this population has not previously been assessed.

It has long been recognized that kidney transplantation in the presence of a positive T-cell complement dependent cytotoxicity (CDC) crossmatch presents a high risk for hyperacute rejection[250]. Historically, sensitization has been determined by assessing the reactivity of a potential recipient's serum with a panel of T-cell lymphocytes representing the donor population using a CDC assay to determine the percentage of the donor pool to which the transplant candidate was expected to be CDC crossmatch incompatible. This percentage is known as the panel reactive antibody (PRA). Prioritization for transplant candidates with high PRA has been incorporated into many kidney transplant allocation systems, including Australia's, in an attempt to balance the reduced number of transplant opportunities for these patients.

With advances in solid phase assays, particularly bead based flow-cytometric multiplex assays, it has become possible to define the allele specificities of anti-HLA antibodies in a recipient's serum sample[105]. The percentage of potential donors towards whom an

individual has pre-formed antibodies can be estimated by comparing the antibodies detected by this method to the population frequencies of HLA alleles within the relevant population donor pool. This is commonly known as the calculated Panel Reactive Antibody (cPRA). While PRA and cPRA are typically correlated, differences in the reference population and test sensitivity can result in substantial differences in PRA and cPRA for some individuals[251].

As the sensitivity of crossmatching techniques increased over time, in the United States it was noted that organs allocated to highly sensitized patients based on PRA bonuses were often found to be crossmatch incompatible after shipping, resulting in delays in organ placement[251]. Beginning in December 2007 with implementation in October 2009, the United Network of Organ Sharing (UNOS) replaced PRA with cPRA that was calculated based on the list of antibody exclusions entered by transplanting centres with the goal that kidneys allocated based on bonus points for highly sensitized patients would have a high probability of being crossmatch negative[251]. An 83% reduction in the number of kidneys declined due to positive crossmatch was seen in the 6 months following the implementation of this change[252]. cPRA has replaced PRA as the measure of sensitization in many international transplant programs over time, for example France replaced PRA with cPRA in their national allocation program in July 2009[50] and while Eurotransplant planned to introduced cPRA into their 'mismatch probability' calculation in January 2016[253] this was not implemented until February 2020[51].

Late offer declines for highly sensitized patients have not been an issue in Australia as prospective CDC crossmatches are performed for all blood group compatible potential

recipients prior to organ allocation and recipients with positive CDC crossmatch are excluded from allocation. In addition, HLA exclusions have been used since 2000 to prohibit allocation of organs to which a candidate has clinically significant pre-formed anti-HLA antibodies. These have historically been based on individual laboratory definitions, however, in more recent years there has been a coordinated effort to standardize both methods for anti-HLA antibody detection and the definition of an unacceptable antigen, although some variation still exists across the country particularly around mean fluorescence intensity (MFI) thresholds that define routine antibody exclusions.

Deceased donor kidney allocation and matching in Australia is coordinated through a national system called OrganMatch (known as the National Organ Matching System (NOMS) prior to April 2019) based on algorithms developed by the Transplantation Society of Australia and New Zealand (TSANZ)[34]. All kidneys retrieved from deceased donors are initially allocated based on a national formula that prioritizes sensitized patients, well matched kidneys, paediatric patients and addresses inter-regional sharing imbalances (Table 6.1). If the kidney is not transplanted through the national formula it is then allocated locally based on jurisdiction specific rules which take into account both HLA matching and waiting time as well as paediatric and other bonuses, but not the degree of recipient sensitization. Kidneys not allocated locally are once again offered nationally to avoid organ wastage based on a third scoring system that includes sensitization and waiting time to avoid organ wastage. Overall, it is intended that approximately 20% of kidneys are allocated nationally and 80% locally[34].

In March 2016, the Australian deceased donor kidney allocation system changed from using PRA determined from CDC assays that detected only HLA class I antibodies to cPRA calculated based on both class I and class II antibody detection[34]. Although the impacts of this change were modelled prior to implementation, the effect on the distribution of sensitization in patients on the deceased donor waiting list and transplantation rates have not been reported. In addition, the effectiveness of Australia's current system for prioritizing highly sensitized patients has not previously been studied and it is unclear if the current threshold for defining highly sensitized patients (PRA >80%) is appropriate in light of the changed methodology.

In this study we describe how the distribution of PRA has changed for patients active on the deceased donor kidney transplant waiting list in Australia with the introduction of cPRA and assess whether the current allocation rules adequately address the disadvantage in access to kidney transplantation experienced by highly sensitized patients.

Table 6.1 Australia's deceased donor kidney national allocation algorithm

Base Score	Level	Score
0 HLA mismatches, Peak PRA not <50%	Level 1	60 000 000
1 HLA mismatch, Peak PRA >80%	Level 2	59 000 000
2 HLA mismatches, Peak PRA >80%	Level 3	58 000 000
0 HLA mismatches, Peak PRA <50%	Level 4	57 000 000
0 HLA mismatches at HLA-DR, 1 mismatch at HLA-A or HLA-B Peak PRA not >80%, and Centre credit difference <=-3	Level 5	56 000 000
0 HLA mismatches at HLA-DR, 2 mismatches at HLA-A or HLA-B Peak PRA not >80%, and Centre credit difference ≤-6	Level 6	55 000 000
When base score is null and centre credit difference ≤-20	Level 7	54 000 000
Bonuses		
Paediatric bonus		+ 30 000
Recipient at same centre as donor		+ 50 000
Centre Credit Balance		1000 + patient centre credit
Patient waiting period		+ wait months * 1
If score < 54 000 000 go to relevant regional algorithm		

A peak PRA >80% is used to define highly sensitized patients and national bonuses for this group are linked to HLA matching. Australia's regional allocation algorithms do not include sensitization as a factor in determining organ allocation. Centre Credit difference is the difference between the number of kidneys shipped out of a transplanting jurisdiction and the number of kidneys received by that jurisdiction from other regions. Blood group compatible transplants are permitted for kidneys from A, B and AB donors in national allocation. For kidneys from O donors, blood group compatible are permitted at levels 1-4 and blood identical at levels 5-7. HLA -human leukocyte antigen; PRA – panel reactive antibody.

6.4 Materials and Methods

Inclusion criteria

All patients listed as 'active' on the Australian deceased donor kidney transplant waiting list between 01/01/2013 and 12/31/2018 were included in the analysis of the impact of changes in PRA testing methodology. Patients waiting for multiorgan transplant were excluded. Analysis of transplantation rates and characteristics was further restricted to the period in which cPRA has been used (ie 03/01/2016 to 12/31/2018).

Data sources

A de-identified linked data extract from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry and NOMS was used in this analysis.

Unlike the in United States[254], there is no dataset available in Australia that tracks the PRA/cPRA of patients wait listed for kidney transplantation historically over time. It was therefore necessary to construct this dataset from available sources:

1) The NOMS "Waitlist" dataset tracks the status (active, on hold etc) of all patients listed for deceased donor kidney transplant over time.
2) The NOMS "Organ Matches" dataset contains the allocation list for all deceased kidney donors, including the potential recipient PRA/cPRA at the time of matching (the median number of matched recipients per donor in the dataset is 60 [IQR 50-62, range 1-105]). Since March 2016, cPRA has been calculated using a standardised national calculator based on antibody exclusions as defined by local tissue typing laboratories. Most laboratories have used a standard MFI threshold of 4,000 for

defining antibody exclusions (8,000 in some laboratories) with additional curation based on antibody characteristics and clinical circumstances.

3) The NOMS "Antibody List" dataset contain lists of anti-HLA antibodies detected over time for patients registered on the transplant waiting list. The methodology for antibody detection has changed over time and serum treatment and MFI cut off used for antibody exclusions have historically varied across transplant laboratories. Antibody lists in this dataset are separated by HLA class and are accompanied by the "population frequency" or estimated percentage of the donor population excluded by that list of antibodies as entered by the testing laboratory. Prior to 03/01/2016 the "population frequency" for lists of Class I anti-HLA antibodies was equivalent to the PRA. This dataset is a record of all antibody testing by tissue typing laboratories and it cannot be determined from this which antibodies were actually used for exclusions at specific historical time points.

As the "Organ Matches" dataset contains the actual PRA/cPRA used in allocation at the time of organ offer this was the primary dataset used to re-construct a historical record of changes in PRA/cPRA. The following assumptions were used: living donor matches were excluded; if there were multiple matches on the same day the highest PRA/cPRA was used; PRA/cPRA was assumed to be constant between matches with the most recent PRA/cPRA carried backwards to the date of previous match; the last recorded PRA/cPRA was carried forward until the end of the follow up period; PRA/cPRAs were not extended across the date in which methodology of testing changed (03/01/2016).

Eleven percent of the cohort did not have any PRA/cPRA data in the "Organ Match" dataset (12% before 03/01/2016, 11% after this date). For these patients, PRA/cPRA histories were reconstructed from the "Antibody List" dataset. The following assumptions were used: class I antibody frequencies were used to define PRA prior to 03/01/2016; the highest antibody frequency to date was used; for tests performed after 03/01/2016 cPRA was calculated using class I and class II antibody specificities using the current OrganMatch cPRA calculator (antibodies to HLA -A, -B, -C, -DRB1, -DRB3/4/5, -DQA1 and -DQB1 with MFI≥4000 were included in calculations which were based on HLA frequencies in a panel of 2,115 previous Australian kidney donors); PRA/cPRA was assumed to remain constant until a higher PRA/cPRA was recorded; the last PRA/cPRA recorded was carried forward until the end of the follow up period; PRA/cPRAs were not extended across the date in which methodology of testing changed (03/01/2016).

The longitudinal "Waitlist" dataset was combined with the reconstructed longitudinal PRA/cPRA dataset to create a record of PRA/cPRA for all active patients over the study period.

PRA/cPRA was categorised into the following groups for further analysis: 0, 1-49, 50-79, 80-94, 95-98 and ≥99. PRA/cPRA was recorded in the dataset as integers and therefore further subcategorization of PRA/cPRA 99-100 into deciles was not possible.

To assess the accuracy of methods for imputing cPRA history, a deidentified extract of patients active on the deceased donor kidney transplant waiting list on 09/04/2019 was

obtained. cPRA group in this population was compared to a cross-section of patients active on 31/12/2018 in the study population using Chi Squared test.

Statistical methods

Changes in the distribution of PRA/cPRA over time for actively waitlisted patients are presented graphically. Differences in number of patients in each PRA/cPRA category immediately prior to and following the change in methodology were compared using Chi Squared test. Annual transplantation rate per 100 active patient years by PRA/cPRA group is presented graphically with 95% confidence intervals shown.

More detailed analysis of transplantation was restricted to the cPRA era (03/01/2016-12/31/2018). Patient characteristics for cPRA groups are reported according to highest cPRA recorded for each patient during this period. The association between cPRA and transplant rate was assessed using a multilevel mixed effects negative binomial regression model with exposure defined as days active on the deceased donor kidney transplant waiting list and a random intercept for patient ID as individual patients may have changes in cPRA over time. The following characteristics were considered for adjusted analysis and included in the multivariate model if statistically significant on univariate analysis at a p value of <0.2: ABO blood group, gender, ethnicity, age, waiting list region. The linear assumption for continuous variables was assessed by comparing the fit of alternative fractional polynomial models and graphically. Due to a violation in this assumption, paediatric status was considered as a separate confounder with an additional continuous term for every 10 years above the age of 18 years included in the final model. Results for transplanting regions are presented as differences from the observation weighted grand mean. The categorisation of

ethnicity was according to the Australian Standard Classification of Culture and Ethnics Groups (ASCCEG), 2019[255] with a historical ANZDATA code "Caucasoid" mapped to ASCCEG code 1101 "Oceanic – Australian" to align with contemporary data collection – this category is reported as "Australian – non-indigenous".

This research was conducted in line with approval obtained from the Central Adelaide Local Health Network Human Research Ethics Committee (Reference Number HREC/17/RAH/408).

6.5 Results

6.5.1 Impact of changes in testing methodology

A total of 6,217 patients were active on the Australian deceased donor kidney only transplant waiting list at some point during the study period. Of these, 8 (0.1%) had no PRA or antibody data available at all and were excluded from the analysis. Following reconstruction of a longitudinal PRA/cPRA history for all patients active during the study period there was no significant difference in proportion of patients in each cPRA category when comparing a cross section of patients active on 31/12/2018 to an actual waiting list extract from OrganMatch on 09/04/2019 (p= 0.60) supporting the accuracy of these methods.

Following the change from CDC based PRA testing to cPRA in March 2016 there was a substantial change in how waiting list patients were classified in terms of sensitization

(Figure 1.1). The percentage of the waiting list classified as highly sensitized (PRA/cPRA ≥80%) increased from 7.2% to 27.8%. The most dramatic change was seen in the number of patients with PRA/cPRA of ≥99% which increased over 7 fold from accounting for a monthly average of 18 patients in the PRA era to 141 patients in the cPRA era, or an increase from an average of 1.7% of the waiting list each month to 15.3%. The percentage of the waiting list with PRA/cPRA 80-94% increased from 4.0% to 6.6% and PRA/cPRA 95-98% from 1.5% to 5.9%. The large decrease in patients with PRA/cPRA 1-49% across eras suggests that many of these patients were reclassified under new testing methods as either unsensitized (PRA/cPRA=0%) or with higher degrees of sensitization.

Figure 1.2 shows how annual transplantation rates changed over the study period by sensitization group. The overall transplantation rate increased across the study period from 57 to 85 transplants per 100 active waiting years. Throughout the study period, unsensitized patients (PRA/cPRA 0%) had a higher transplant rate compared to all other groups with patients with PRA/cPRA ≥99% having the lowest rates of transplantation.

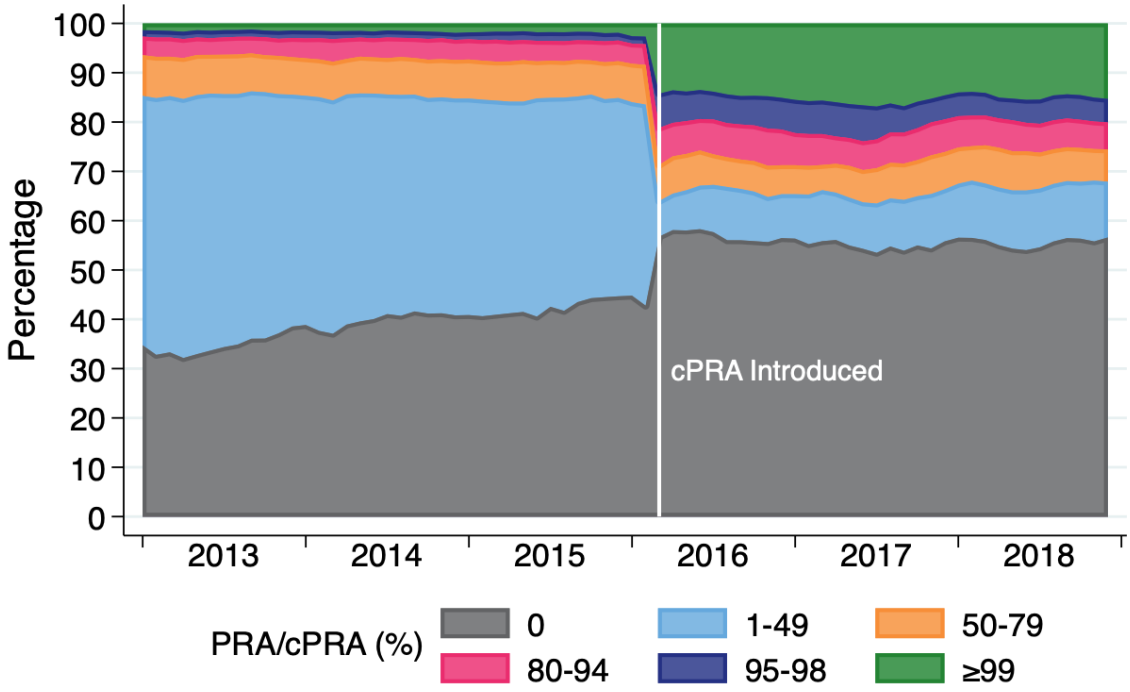

Figure 1.1 Panel reactive antibody of active wait listed patients, kidney only waiting list, Australia 2013-2018

Panel reactive antibody (PRA) of patients active on the kidney only deceased donor waiting list the first of each month. The white line shows the date when calculated PRA based on antibody exclusions was introduced.

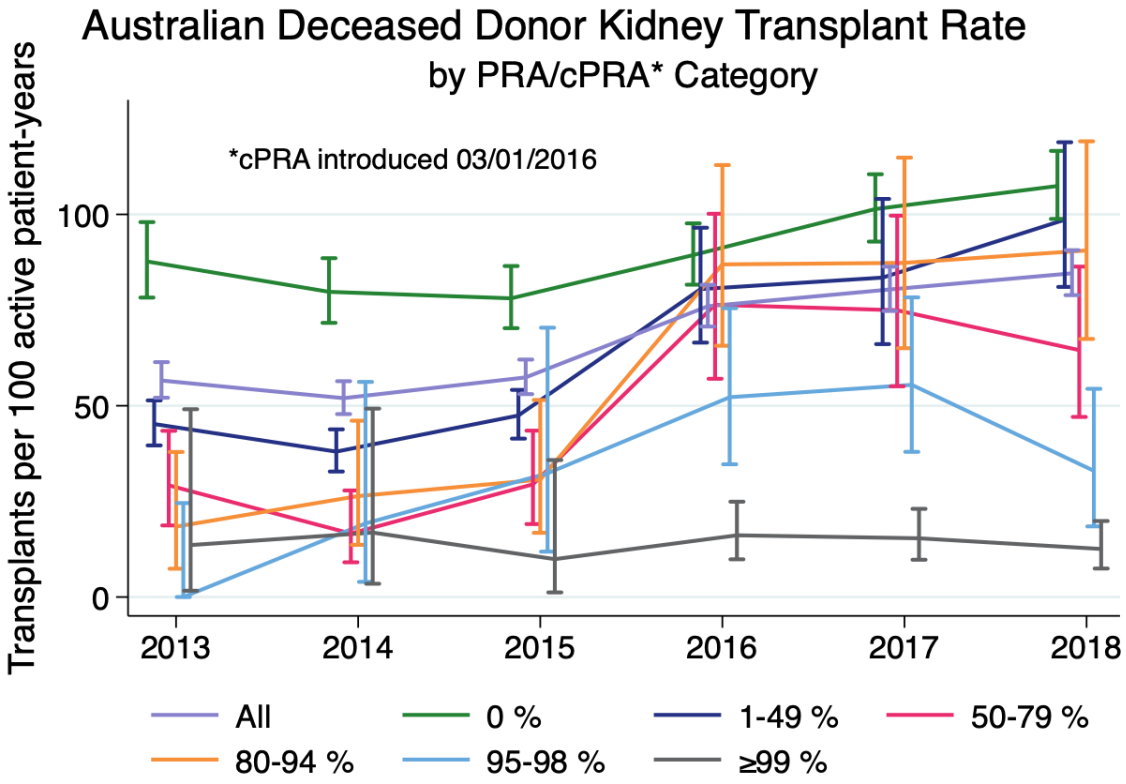

Figure 1.2 Australian deceased donor kidney transplant rate by PRA/cPRA category

Yearly transplantation rate for patients active on the kidney only deceased donor kidney transplant waiting list by panel reactive antibody (PRA). Note that calculated PRA was introduced on 03/01/2016. Bars show 95% confidence intervals.

6.5.2 Transplantation Rates in the cPRA Era

Overall there were 3,794 patients who were active on the deceased donor kidney only transplant waiting list at some point in the cPRA era. Patient characteristics are described in Table 1.2 according to the highest cPRA documented for each patient during this period. Women were overrepresented in the sensitized populations compared to the unsensitized population, making up 51% of patients with cPRA 99% compared to only 29% of unsensitized patients. Significant differences in sensitization of waitlisted patients are noted across Australia's transplanting regions.

Table 1.2 Patients characteristics on the Australian deceased donor kidney waiting list between March 2016-December 2018 by cPRA

		cPRA Group							
Characterister	Level	0 %	1-49 %	50-79 %	80-94 %	95-98 %	≥99 %	All	p- value
Total		2397	471	250	238	155	283	3794	
Gender, n(%)	Female	682 (28.5%)	201 (42.7%)	150 (60.0%)	142 (59.7%)	75 (48.4%)	145 (51.2%)	1395 (36.8%)	<0.001
	Male	1715 (71.5%)	270 (57.3%)	100 (40.0%)	96 (40.3%)	80 (51.6%)	138 (48.8%)	2399 (63.2%)	
Age, median (IQR)		54 (43, 62)	54 (42, 63)	53 (42, 63)	47 (37, 57)	49 (39, 59)	47 (37, 57)	53 (42, 62)	<0.001
Blood group, n(%)	A	803 (33.5%)	145 (30.8%)	73 (29.2%)	73 (30.7%)	65 (41.9%)	91 (32.2%)	1250 (32.9%)	0.21
	AB	87 (3.6%)	16 (3.4%)	13 (5.2%)	10 (4.2%)	4 (2.6%)	16 (5.7%)	146 (3.8%)	
	B	372 (15.5%)	72 (15.3%)	38 (15.2%)	33 (13.9%)	17 (11.0%)	58 (20.5%)	590 (15.6%)	
	O	1135 (47.4%)	238 (50.5%)	126 (50.4%)	122 (51.3%)	69 (44.5%)	118 (41.7%)	1808 (47.7%)	
Region, n(%)	NSW/ACT	858 (35.8%)	143 (30.4%)	84 (33.6%)	64 (26.9%)	47 (30.3%)	69 (24.4%)	1265 (33.3%)	<0.001
	VIC/TAS	727 (30.3%)	203 (43.1%)	79 (31.6%)	82 (34.5%)	67 (43.2%)	147 (51.9%)	1305 (34.4%)	
	QLD	503 (21.0%)	24 (5.1%)	37 (14.8%)	42 (17.6%)	19 (12.3%)	20 (7.1%)	645 (17.0%)	
	SA/NT	167 (7.0%)	53 (11.3%)	33 (13.2%)	33 (13.9%)	10 (6.5%)	16 (5.7%)	312 (8.2%)	
	WA	142 (5.9%)	48 (10.2%)	17 (6.8%)	17 (7.1%)	12 (7.7%)	31 (11.0%)	267 (7.0%)	
Ethnicity, n(%)	Australian - Indigenous	115 (4.8%)	21 (4.5%)	11 (4.4%)	14 (5.9%)	7 (4.5%)	6 (2.1%)	174 (4.6%)	<0.001
	Australian - non-indigenous	1357 (56.6%)	288 (61.1%)	152 (60.8%)	173 (72.7%)	116 (74.8%)	190 (67.1%)	2276 (60.0%)	
	Other	925 (38.6%)	162 (34.4%)	87 (34.8%)	51 (21.4%)	32 (20.6%)	87 (30.7%)	1344 (35.4%)	

Patients are classified according to their highest cPRA recorded during the period. cPRA – calculated panel reactive antibody; IQR – interquartile range, NSW – New South Wales; ACT – Australian Capital Territory; VIC – Victoria; TAS – Tasmania; QLD – Queensland; SA – South Australia; NT – Northern Territory; WA – Western Australia.

Analysis of the association between cPRA and deceased donor transplantation rate showed that any degree of sensitization was associated with a reduced transplant rate compared to non-sensitized (cPRA=0%) patients (Table 1.3, Figure 1.3). A cPRA of ≥99% was associated with the most marked reduction (adjusted incidence rate ratio (aIRR) 0.09 [95%CI 0.07-0.12], p<0.001) followed by cPRA 95-98% (aIRR 0.36 [95%CI 0.28-0.47], p<0.001). Under the current allocation system that gives national priority for patients with cPRA >80%, a cPRA of 80-94% was associated with a more modest reduction in transplant rate (aIRR 0.76 [95%CI 0.62-0.92], p<0.01) than a cPRA of 50-79% (aIRR 0.62 [95%CI 0.51-0.76, p<0.001). The model was adjusted for recipient ABO blood group, gender, transplanting region, ethnicity and age (with paediatric recipients considered separately and age above 18 years as a continuous variable). Of note, whilst female gender was associated with decreased transplantation rate on univariate analysis (IRR 0.87 [95%CI 0.77-0.98), p=0.025), there was no significant association in the model adjusted for sensitization (aIRR 1.05, p=0.389) (Table 1.3).

While the majority of transplants to patients with cPRA <80% were allocated through regional systems, most patients with cPRA ≥80% who were transplanted received kidneys that were allocated through the national system. Overall 19.4% of kidneys were transplanted through the national allocation algorithm, increasing to 77.7% for recipients with cPRA 80-94% and 93.3% for recipients with cPRA ≥99% (Figure 1.4, supplementary figure).

Table 1.3 Predictors of transplantation for candidates on the deceased donor kidney only waiting list, Australia (March 2016-December 2018)

		Univariate Models			Multivariate Model		
Characteristic	Level	IRR	95% CI		aIRR	95% CI	
cPRA (%)	0			Reference			
	1-49	0.85	0.71,1.01	0.066	0.86	0.74,1.00	0.049
	50-79	0.63	0.51,0.79	<0.001	0.62	0.51,0.76	<0.001
	80-94	0.85	0.69,1.06	0.146	0.76	0.62,0.92	0.006
	95-98	0.40	0.30,0.54	<0.001	0.36	0.28,0.47	<0.001
	≥99	0.11	0.08,0.15	<0.001	0.09	0.07,0.12	<0.001
Blood group	A	2.22	1.95,2.52	<0.001	2.2	1.98,2.45	<0.001
	AB	3.66	2.78,4.83	<0.001	3.97	3.15,5.00	<0.001
	B	0.78	0.66,0.93	0.005	0.89	0.76,1.03	0.118
	O			Reference			
Gender	Male			Reference			
	Female	0.87	0.77,0.98	0.028	1.05	0.94,1.16	0.389
Ethnicity	Australian-Indigenous	1.15	0.87,1.53	0.309	1.00	0.79,1.28	0.92
	Australian- non-indigenous			Reference			
	Other	0.60	0.53,0.68	<0.001	0.66	0.59,0.73	<0.001
Age	Age<18 Years	2.02	1.42,2.88	<0.001	2.62	1.90,3.60	<0.001
	Age (per 10 yrs ≥18)	1.11	1.07,1.16	<0.001	1.16	1.12,1.21	<0.001
Region	NSW/ACT	0.69	0.63,0.75	<0.001	0.67	0.62,0.72	<0.001
	VIC/TAS	0.79	0.73,0.85	<0.001	0.91	0.85,0.97	0.003
	QLD	2.00	1.76,2.27	<0.001	1.64	1.47,1.82	<0.001
	SA/NT	0.93	0.77,1.13	0.476	0.85	0.72,1.01	0.059
	WA	4.95	3.98,6.15	<0.001	4.88	4.10,5.81	<0.001

*Multilevel mixed effect negative binomial regression models for transplants per days active on the Australian deceased donor kidney transplant waiting list. All models include a random intercept for patient ID. Results for transplanting regions are shown as differences from the observation weighted grand mean. IRR incident rate ratio; aIRR – adjusted incidence rate ratio; cPRA – calculated panel reactive antibody; NSW – New South Wales; ACT – Australian Capital Territory; VIC – Victoria; TAS – Tasmania; QLD – Queensland; SA – South Australia; NT – Northern Territory; WA – Western Australia. * p<0.05 ** p<0.01 ***p<0.001*

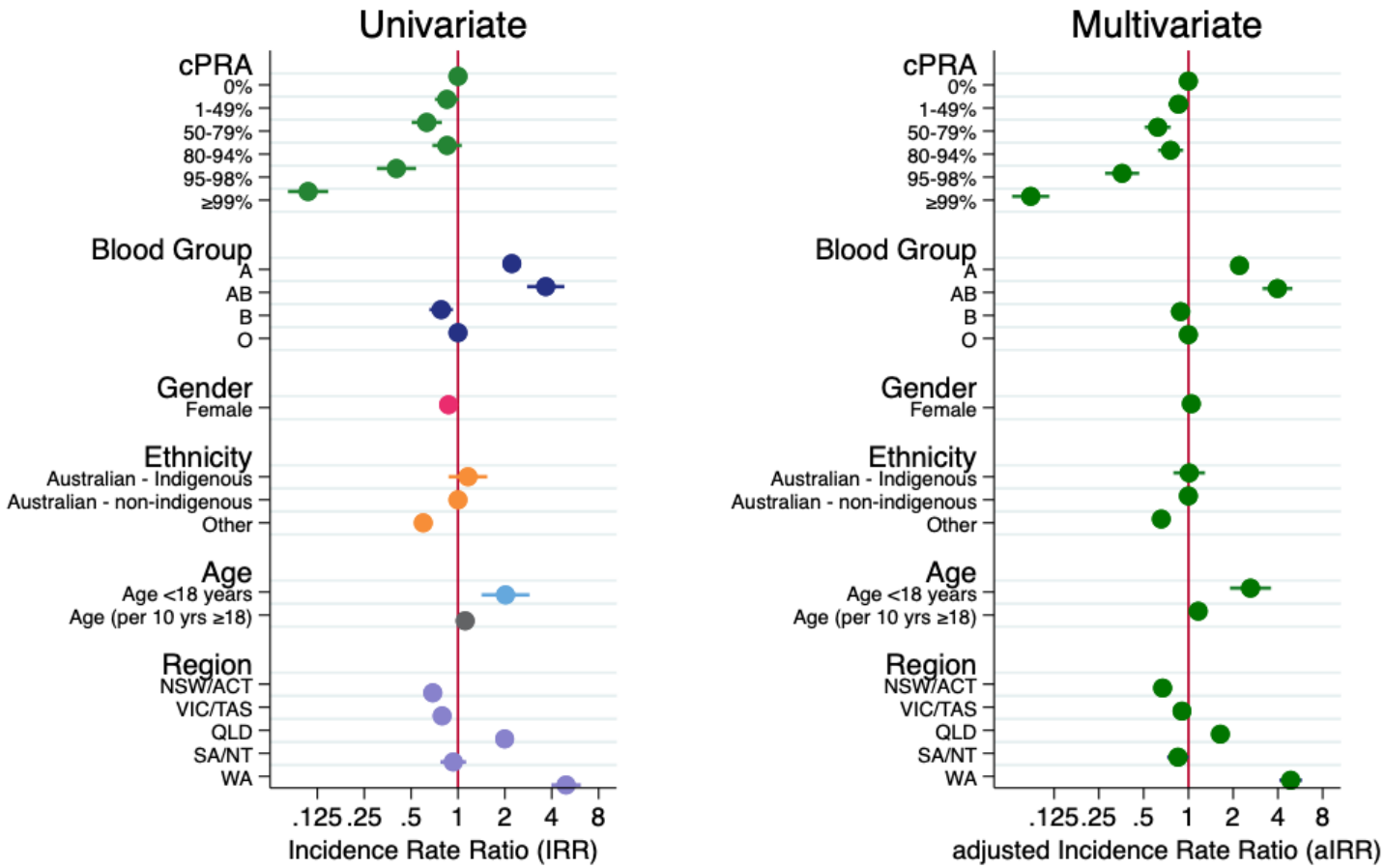

Figure 1.3 Predictors of transplantation for candidates on the deceased donor kidney only waiting list, Australia March 2016-December 2018

Multilevel mixed effect negative binomial regression models for transplants per days active on the Australian deceased donor kidney transplant waiting list. All models include a random intercept for patient ID. Results for transplanting regions are shown as differences from the observation weighted grand mean. IRR incident rate ratio; aIRR – adjusted incidence rate ratio; cPRA – calculated panel reactive antibody; NSW – New South Wales; ACT – Australian Capital Territory; VIC – Victoria; TAS – Tasmania; QLD – Queensland; SA – South Australia; NT – Northern Territory; WA – Western Australia.

6.6 Discussion

Our findings demonstrate that the change from PRA to cPRA to define sensitization in the Australian deceased donor kidney transplant program has resulted in a substantial increase in the percentage of the waiting list classified as highly sensitized (cPRA≥80%) and unmasked a number of very highly sensitized patients (cPRA≥99%) that were not previously identified by PRA testing. We show that under the current allocation system that gives priority in national allocation to candidates with cPRA>80%, patients with cPRA ≥95% - and particularly those with cPRA ≥99% - continue to have markedly reduced transplantation rates compared to less sensitized patients. This raises the question of whether the current prioritization for sensitized candidates is adequate or if this needs to be revised to more accurately target the disadvantage experienced by this population.

As expected, our analysis shows a reclassification of sensitization status for many patients on the waiting list following the introduction of cPRA, which is consistent with previous studies that have shown the correlation between PRA and cPRA was as low as 50% for patients with a PRA of 1-20% and 68% for those with PRA 21-80%[251]. In reporting the magnitude of this change, our results highlight the implications for allocation policy in Australia. Prior to March 2016 patients with a PRA ≥99% made up only 1.7% of the Australia waiting list, however when using cPRA to define sensitization this increases dramatically to over 15%. Similar patterns seen in the US following the introduction of cPRA with the percentage of patients with a PRA/cPRA >95% increased from 5.4% to 8.6% with the change in methodology[252]. However, even prior to the introduction of the 2014 US Kidney Allocation (KAS) patients with cPRA ≥99% made up only 7.9% of the US kidney transplant

waiting list[256], around half of the percentage on Australia's waiting list. Reasons for this disparity may include variations in testing methodologies, differing thresholds for defining unacceptable antigens or differences in historical transplantation rates for this population across the two countries based on either allocation policies or the size of the donor pool that have resulted in the accumulation of highly sensitized patients on the Australian waiting list.

Coinciding with introduction of cPRA we see improvements in transplantation rates for all groups of sensitized patients except of those with PRA/cPRA ≥99% which in part reflects the increase in overall transplantation rate in Australia due to increases in donor numbers. It is also likely that patients with broad sensitization that was resulting in extremely limited opportunities for transplantation were assigned a relatively lower PRA than reflected their actual likelihood of transplantation using CDC methods, and cPRA is a more accurate reflection of their transplant opportunities. In particular, PRA did not detect antibodies against HLA Class II antigens which are now included in the calculation of cPRA.

Our study demonstrates that under the current allocations rules, very highly sensitized patients have a markedly reduced transplantation rate compared to unsensitized patients. Without mechanisms to prioritize sensitized patients in kidney allocation it is a mathematical inevitably that these patients will have fewer transplant opportunities as their likelihood of a positive crossmatch and subsequent exclusion from the allocation list is directly related to their cPRA[47]. Hence, like Australia, most national and trans-national transplant programs give bonus points or priority allocation to highly sensitized patients[52]. Cut-offs for defining a highly sensitized candidate varying across jurisdictions, but most

(including Australia, Eurotransplant, Scanditransplant, France, Spain) use a threshold of 80-85%[52]. In Israel, bonus points increase incrementally for every 25% increase in PRA[40] and in the US, bonus points are awarded incrementally on an exponential scale[53]. Outside of the United States, few countries have reported on the effectiveness of these bonus systems in addressing the disadvantage experienced by highly sensitized patients or the justification for these cuff-offs.

While any degree of sensitization is associated with a reduced kidney transplant rate in Australia, this is most dramatic for patients with cPRA ≥99% and to a lesser extent, those with cPRA 95-99%. Our findings indicate that in order to achieve improved equity in access to transplantation across degrees of sensitization, more priority needs to be given to those patients with cPRA 95% and above. While the reduction in transplant rate for patients with cPRA 80-95% is relatively modest in our study, it is important to note that over three quarters of these patients received their transplant based on existing bonuses in the national allocation formula and this should also be considered in any revision of Australia's allocation algorithms.

Exposure to foreign HLA through pregnancy results in an over-representation of women in the highly sensitized population. While female gender is associated with decreased transplant rate in univariate analysis, on adjusted analysis this association is no longer significant, indicating that improving transplantation rates for highly sensitized patients may also help to address some of the gender inequality seen in access to transplantation in Australia. Australia is an ethnicity diverse society and we found that patients from ethnic minorities (excluding Indigenous Australians) had a lower transplantation rate compared to

the majority population. Indigenous Australians with end stage kidney disease do have reduced access to transplantation compared to non-indigenous Australians, however, this relates primarily to differences in living donor transplantation and access to waiting list rather than a reduced in transplantation rate once activated on the list[257,258]. Detailed analysis of the complex interaction of HLA genetics and ethnic identity were beyond the scope of this registry-based study but these finding highlight the importance of considering how allocation policies based on HLA matching and antibody exclusions may inadvertently impact ethnic minorities.

While our study is the first to report on the effectiveness of current allocation policies on access to transplantation for highly sensitized patients in Australia, limitations in the available data highlight the need for improved data collection. A complete historical record of changes in PRA/cPRA of waitlisted patients in Australia does not exist and the assumptions used in our methods of data reconstruction are subject to error. For example, for the 11% of patients for whom cPRA was calculated from raw antibody data we chose to use an MFI of ≥4000 to define antibody exclusions as this is the threshold used by most laboratories in Australia, however, some laboratories have used a threshold of ≥8000 and in many cases exclusions will be adjusted for individual patients based on antibody characteristics and clinical circumstances. Despite these assumptions, the comparison to an extract from the current waiting list supported the accuracy of our methods.

The choice of categorisation of PRA/cPRA grouping was based on both the current Australian allocation policy cut offs and transplantation rates from previous US studies, however relatively small numbers of patients limited more granular analysis. cPRA was only

available in integer values and we were unable to examine deciles above 99% which have been shown to be important in previous studies[254]. While the calculation of cPRA leans heavily on a somewhat arbitrary MFI cut off from solid phase assays, immunological risk assessment should also include factors such as the history of sensitizing events, other characteristics of the antibodies and functional assays[259].

Due to limitations in available outcome data for our cohort this study focuses primarily on equity in access to transplantation for sensitized patients and does not address the issue of graft survival according to PRA/cPRA or whether increasing transplantation rates for highly sensitized patients will impact the overall utility of deceased donor transplantation in Australia. Historically, highly sensitized patients (PRA >80%) in Australia have be shown to have greater risk of rejection, graft failure, cancer and death post transplant[260]. While the introduction of additional priority for very highly sensitized patients in the United States did not result in worsening of outcomes for patients with cPRA-100%[261], concerns have been raised about the increase in the proportion of high quality kidneys going to highly sensitized recipients and the impact this may have on overall utility[262].

The widespread adoption of molecular techniques for HLA typing and sensitive, highly specific methods for anti-HLA antibody detection have enabled more nuanced assessment of immunological risk in transplantation. These tools can also be used to highlight inequities in access to kidney transplantation under current policies. Our study demonstrates the disadvantage experienced by highly sensitized patients awaiting kidney transplantation and how the change in methodology for defining sensitization has unmasked the scale of this issue in Australia. The United States has taken the lead in implementing a bonus points

system in their Kidney Allocation System that more accurately addresses the relationship between sensitization and reduced transplant opportunities. The Australian Renal Transplant Allocation Committee is currently revising Australia's organ allocation algorithms and our findings strongly support the need to review the thresholds used to define highly sensitized transplant candidates and whether increased priority for the very highly sensitized can help improve transplantation opportunities for this population.

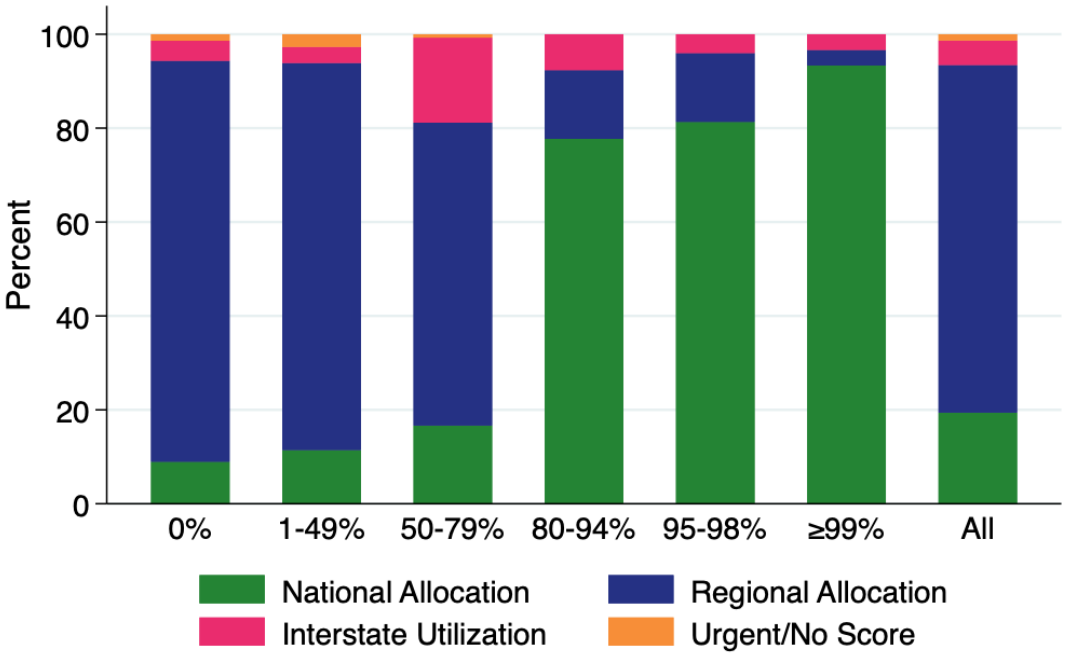

Figure 1.4 Kidney transplant allocation algorithm by recipient cPRA, Australia March 2016-December 2018 (supplementary figure)

Overall around 20% of deceased donor kidneys transplanted in Australia and allocated through the national algorithm that includes priority for highly sensitized patients. The vast majority of patients with cPRA ≥80% receive their transplants through the 'National allocation' system which is a national program prioritizes sensitized patients, well matched kidneys, paediatric patients and addresses inter-regional sharing imbalances. 'Regional Allocation' refers to transplants where the donor and recipient are located within the same jurisdiction and are allocated based on local jurisdictional rules that included bonus points for HLA matching and waiting time but not cPRA. 'Interstate Utilization' refers to national sharing of kidneys not transplanted locally that aims to avoid organ wastage.

Chapter 7 Paediatric Deceased Donor Kidney Transplant in Australia a 30 Year Review: What have Paediatric Bonuses Achieved and Where to From Here?

7.1 Preface

The content of this chapter has been submitted for publication in the journal Pediatric Transplantation. The text is identical to the manuscript submitted for publication.

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Author contributions are described in the thesis preface.

7.2 Abstract

Background: In this 30-year national review, we describe trends in deceased donor (DD) transplantation for paediatric recipients, assess the impact of paediatric allocation bonuses and identify outstanding areas of need for this population. Methods: A retrospective review of all DD kidney only transplants to paediatric recipients (<18-years-old) in Australia between 1989 and 2018 was conducted using de-identified extracts from the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry. Results: Of the 1011 kidney only transplants performed in paediatric recipients during the study period, 426 (42%) were from deceased donors. Paediatric candidates on the DD waiting list had consistently higher rates of transplantation and shorter time from dialysis initiation to transplantation compared to adult candidates (median 372 vs 832 days in 2018, for example). Donor characteristics remained more favourable for paediatric recipients, despite a decline in the overall quality of the donor pool. The mean number of HLA antigen mismatches for paediatric recipients of DD transplants increased each decade (2.86 (1989-1998), 3.85 (1999-2008), 4.01 (2009-2018)). Both patient and graft survival have improved for paediatric DD transplant recipients in the most recent era (5-year graft and patient survival 85% vs 65% and 99% vs 94%, respectively, for 2009-2018 vs 1999-2008). Conclusions: The current DD kidney allocation system in Australia provides rapid access to high quality organs for paediatric recipients and early graft loss has decreased significantly in recent years, however, additional targeted interventions to address HLA matching may improve long term outcomes in this population

7.3 Background

End stage kidney disease (ESKD) is a rare diagnosis in the paediatric population but has profound consequences for the child and their family[263]. For most children with ESKD, kidney transplantation not only offers a survival benefit when compared with dialysis[66], but also provides improved opportunities for growth[12], development[13], education and social interaction[14], and a superior quality of life[15]. Recognising the unique needs and potential benefits of transplantation for this population, many transplant programs worldwide have specific deceased donor organ allocation rules aimed at prioritising access to transplantation for children with ESKD[43,45].

Allocation of deceased donor kidneys in Australia is performed according to a national protocol developed by the Transplantation Society of Australia and New Zealand (TSANZ) and implemented by the OrganMatch system that includes both national sharing and local allocation among the five transplanting regions[34]. In brief, all kidneys are first allocated through a national program that prioritizes highly sensitized patients and well-matched kidneys and addresses sharing imbalances between regions. Organs are then allocated within transplanting regions based on local algorithms that consider both human leukocyte antigen (HLA) matching and recipient waiting time. If no suitable recipient is identified locally, the kidney is once again offered nationally to avoid organ wastage. Around 20% of kidneys are allocated through the national sharing program and 80% through regional algorithms.

Over the past two decades, Australia has introduced a series of bonuses for paediatric transplant candidates in both the national and regional kidney allocation algorithms as outlined in Table 7.1. These bonuses range between 30,000 to 100,000 points. To put this in context, scores in the national allocation system range from 54,000,000 to over 60,000,000 and scores in the jurisdictional systems range from 0 to over 50,000,000[34]. Therefore, the paediatric bonuses do not give absolute priority to children, but rather give them a priority over adults with similar rankings based on HLA matching, sensitization and other bonuses, but who have a longer waiting time. These bonuses are not contingent on donor quality or human leukocyte antigen (HLA) matching. It is also important to note that whilst the two largest transplant regions have formal bonus point systems for paediatric patients, the three smaller regions have informal local priorities for children (such as routine listing with 'urgent' status) that are not documented in the national guidelines but have been verbally communicated to the authors.

There are ethical arguments based on principles of both equity and utility for introducing positive discrimination for children in accessing deceased donor organs[67]. However, it is also important to consider potential unintended consequences of this prioritization in a system dependent on the availability of scarce organs[264,265]. Expedited access to deceased donor transplantation may negatively impact living donor transplant rates, affect donor selection or have detrimental effects for other populations on the waiting list.

We aimed to review trends in deceased donor renal transplantation for paediatric recipients in Australia over the last three decades to identify changes in transplant activity, patient and donor characteristics and graft survival. With incremental changes in the paediatric bonus

over time, it is difficult to ascribe causation to any specific policy changes, however, we aimed to identify issues that may require further targeted policy interventions.

This work was commissioned by TSANZ's National Review of Paediatric Kidney Transplant Recipients.

Table 7.1 Timeline of paediatric bonuses introduced to Australia's national and regional deceased donor kidney allocation algorithms

Date of Implementation	Jurisdiction	Description	Bonus Points
07/04/2000	National	Age < 18 years. First dialysis before 15th birthday. Duration of dialysis ≥1 year.	30 000
04/08/2000	NSW/ACT	Age < 18 years. First dialysis before 15th birthday. Duration of dialysis ≥1 year.	100 000
22/11/2011	National	Age <18 years. Duration of dialysis ≥ 1 year	30 000
10/12/2013	VIC/TAS	Age <18 years. Duration of dialysis ≥ 1 year.	100 000
14/02/2018	National NSW/ACT VIC/TAS	Removal of requirement to have been on dialysis ≥ 1 year to be eligible for paediatric bonus.	30 000 (National) 100 000 (NSW/ACT & VIC/TAS)

Timeline of paediatric bonuses introduced to Australia's national and regional deceased donor kidney allocation algorithms. NSW – New South Wales; ACT – Australian Capital Territory; VIC – Victoria; Tas – Tasmania

7.4 Methods

A deidentified data extract from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) linked to data from the National Organ Matching Service (now OrganMatch) was used in this analysis. ANZDATA is a binational registry of all patients receiving renal replacement therapy (RRT) for the treatment of ESKD in Australia and New Zealand. The registry aims to include 100% of patients across both countries and is linked to the Australia and New Zealand Organ Donor Registry (ANZOD) to ensure complete capture of transplant activity. Participation in the registry is via a process of opt out consent.

Inclusion/Exclusion Criteria

All patients who commenced renal replacement therapy in Australia under the age of 18 years between 01/01/1989 and 31/12/2018 were included in the study. This period was chosen to give a long-term trend and to roughly coincide with the era of calcineurin use in kidney transplantation which were introduced into routine practice in the mid 1980s. For analysis relating to transplant activity, only patients aged under the age of 18 at the time of transplant were included. Patients waitlisted for multiorgan transplantation (n=9) were excluded from the analysis. Patients receiving renal replacement therapy in New Zealand were not included. Selective comparisons are made with the non-paediatric population, aged 18 years and older.

Scope and definitions:

We report on six areas including: incidence and prevalence of RRT, transplant activity, access to deceased donor transplantation, donor characteristics, HLA matching, and patient and graft survival.

HLA mismatches were defined at the antigen level and considered at the -A, -B and -DRB1 loci, giving a potential of up to six mismatches between donor and recipient. Although the number of HLA mismatches is a discrete variable, as well as the percentage in each discrete mismatch category, the mean number of mismatches is also presented to give a representation of overall trend in the population. Kidney Donor Performance Index (KDPI) was determined by calculating the Kidney Donor Risk Index (KDRI) based on the US Organ Procurement and Transplant Network's (OPTN) donor only formula[59] and scaling this from 1-100 based on a reference population of all utilised donors in Australia during the preceding three years[65]. Donor race was assumed to be non-African American and if hepatitis C status was missing this was presumed to be negative. As a consequence of changes in data collection over time, some results are only reported for more recent years for which the relevant data field were available, this includes: some donor characteristics only reported from 1993, KDPI data only able to be calculated from 1996, allocation algorithm data only available from 2001 and waiting list data only reported from 2006.

Statistical methods:

Due to the small number of deceased donor paediatric kidney transplants performed in Australia annually this report is predominantly descriptive with information presented as summary statistics and in graphical form. Formal hypothesis testing has not been performed

apart from in comparison of donor characteristics and the analysis of patient and graft survival.

Donor characteristics for adult and paediatric recipients were compared using ANOVA for normally distributed continuous variables, the Wilcoxon rank-sum test for non-normally distributed continuous variables and the Pearson's chi-squared test for categorical variables.

For survival analysis, exposure was defined as decade of transplantation (1989-1998, 1999-2008, 2009-2018). The survival function was calculated using the Kaplan-Meier method. Differences were tested using the Log-rank test. Graft survival was not censored for death and survival statistics were unadjusted.

7.5 Results

7.5.1 Incidence and prevalence of RRT

Over the three decades, a total of 1,157 patients under the age of 18 years commenced RRT in Australia. Figure 7.1 shows the change in annual incidence over time which increased by around 23% in the study period, from an average of 37 patients annually in the 1990s-2000s to an average of 45 patients annually in the last decade. Although there is considerable year on year variability, there was little difference in the trend in incident patients by age group. In contrast, the number of prevalent paediatric RRT recipients almost doubled over the study period, from 156 in 1989 to 309 in 2017 (Figure 7.2). While the prevalent haemodialysis and peritoneal dialysis populations have remained static for many years

(average 20 patients and 35 patients respectively), the number of prevalent transplant patients has shown a 2.4-fold increase over the last 30 years, from 107 in 1989 to 264 in 2018.

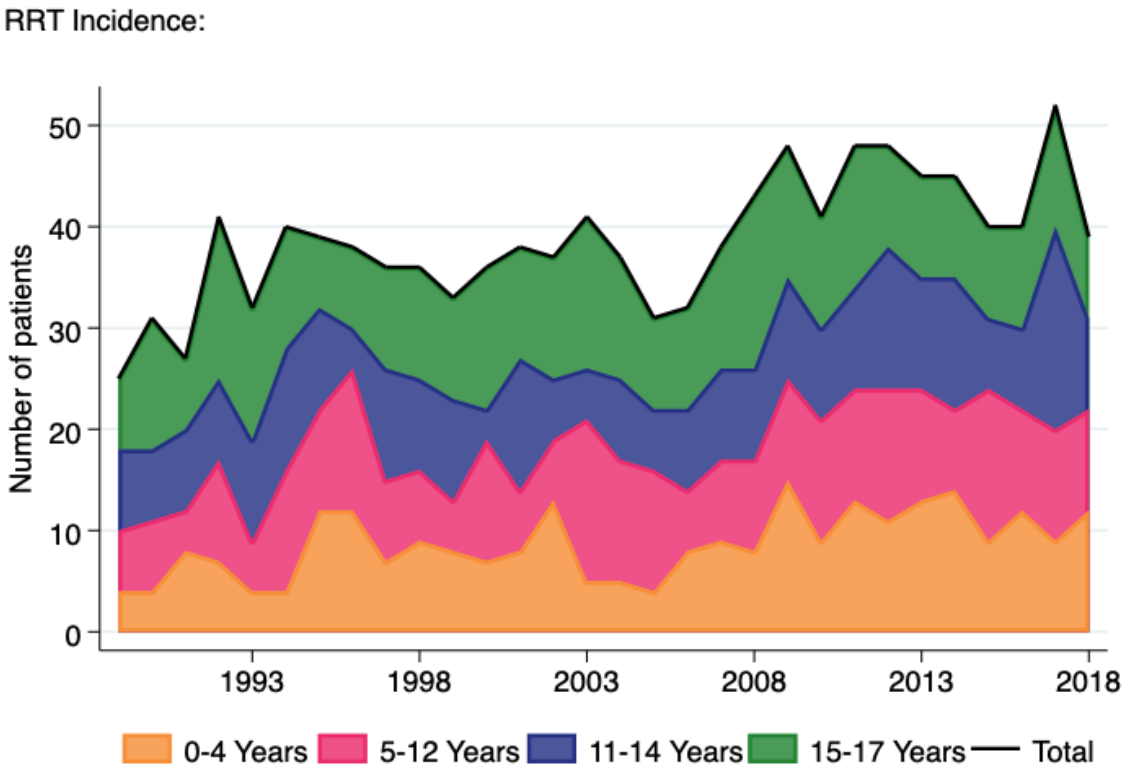

Figure 7.1 Total number of patients aged less than 18 commencing renal replacement therapy annually, Australia 1989-2018

Age categories stacked. Includes peritoneal dialysis, haemodialysis and pre-emptive transplantation.

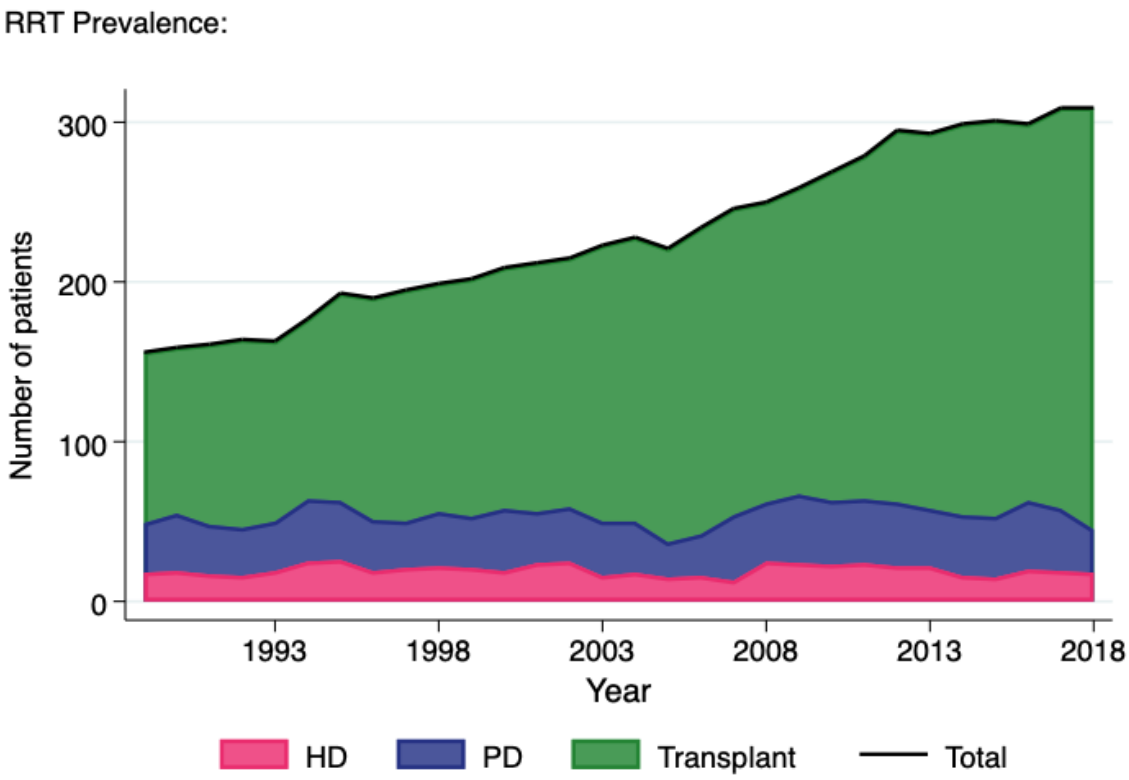

Figure 7.2 Total number of prevalent patients less than 18 receiving renal replacement therapy annually, Australia 1989-2018

Treatment modalities stacked.

7.5.2 Transplant activity

A total of 1011 kidney only transplants were performed in paediatric recipients in Australia during the 30-year study period, 585 (58%) from living donors and 426 (42%) from deceased donors. This accounts for 9.8% of all living donor kidney transplants and 3.2% of all deceased donor kidney only transplants performed in Australia during this period. There was an average of 20 deceased donor transplants to paediatric recipients annually that gradually increased over the last decade from a nadir of 6 in 2009 to a peak of 28 in 2017 (Figure 7.3). No clear trend was observed in the number of deceased donor kidney transplant by age group (Figure 7.11, supplementary figure). Across the last two decades there was a reduction in percentage of transplants from living donors for this population, from a peak of 77% 1999 to 47% in 2018 (Figure 7.12, supplementary figure). This mirrored the trend seen in the adult transplant recipient population over the last decade, although the proportion remained significantly higher in the paediatric group (47% vs 21% in 2018). Of the living donor transplants performed in paediatric recipients, 12 (2%) were performed through the Australian Paired Kidney Exchange (AKX) program and 16 (3%) were ABO blood group incompatible.

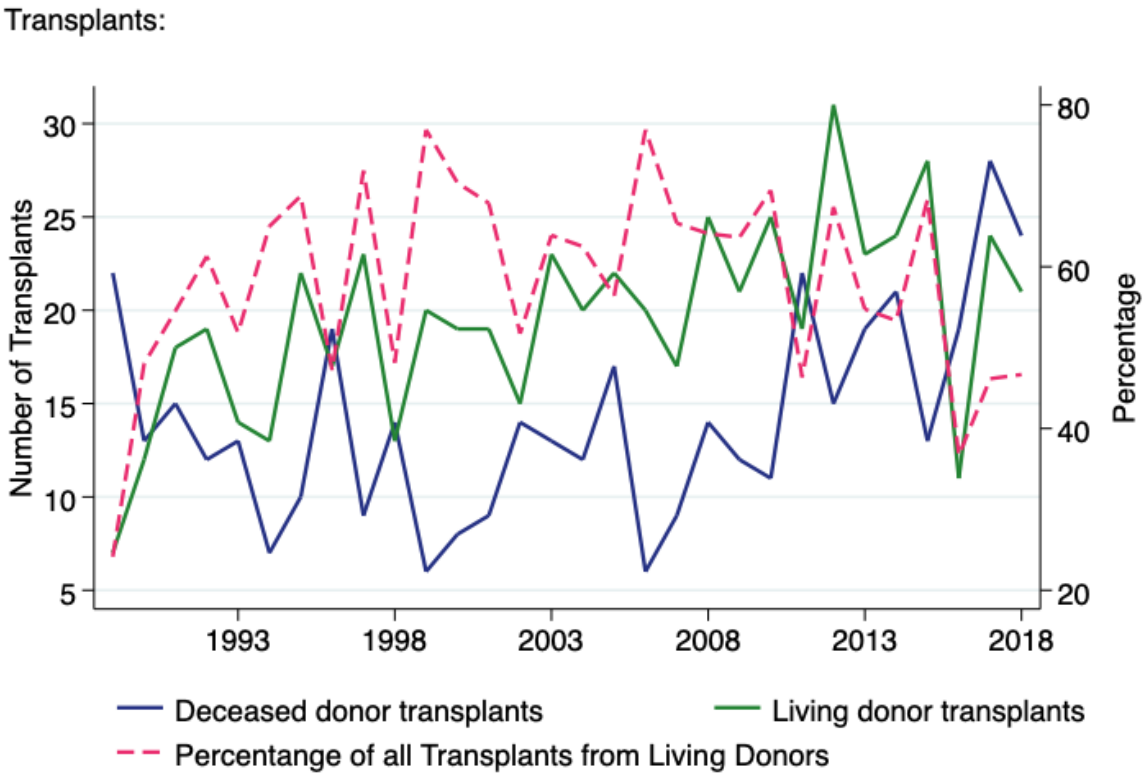

Figure 7.3 Number of kidney only transplants performed in recipients less than 18 annually, Australia 1989-2018, by donor type

The dotted line shows the annual percentage of all kidney only transplants from living donors.

7.5.3 Access to Deceased Donor Transplantation

Paediatric patients on the deceased donor waiting list had a higher rate of transplantation compared to other age groups (averaging 103 transplants per 100 patient years active on the deceased donor waiting list over the 13 years for which waitlist data was available) (Figure 7.4). All other age groups showed an increasing rate over time, such that in 2015/2016 the paediatric rate approximated that of patients aged over 60 years. However, in 2017/2018 there was a marked increase in the transplantation rate for paediatric patients reaching a peak of 214 transplants per 100 active years in 2018, more than double that of any other age group.

The median time since commencing RRT for paediatric recipients receiving a primary deceased donor renal transplant reached a peak of 2.46 years in 2000 which approximated the adult median at the time (Figure 7.5). Following the introduction of the initial paediatric bonus in 2000 this gradually declined and remained at an average of 1.25 years over the last decade of the study period with some fluctuation. In contrast the adult median continued to increase to reach almost 4 years in 2005 and gradually reduced to 2.7 years in the most recent study year. When children under the age of 5 at the time of transplant were excluded to account for the period of dialysis required for many infants prior to achieving a transplantable weight, the average time spent on dialysis prior to deceased donor transplant for paediatric recipients in the last decade dropped slightly to 1.21 years.

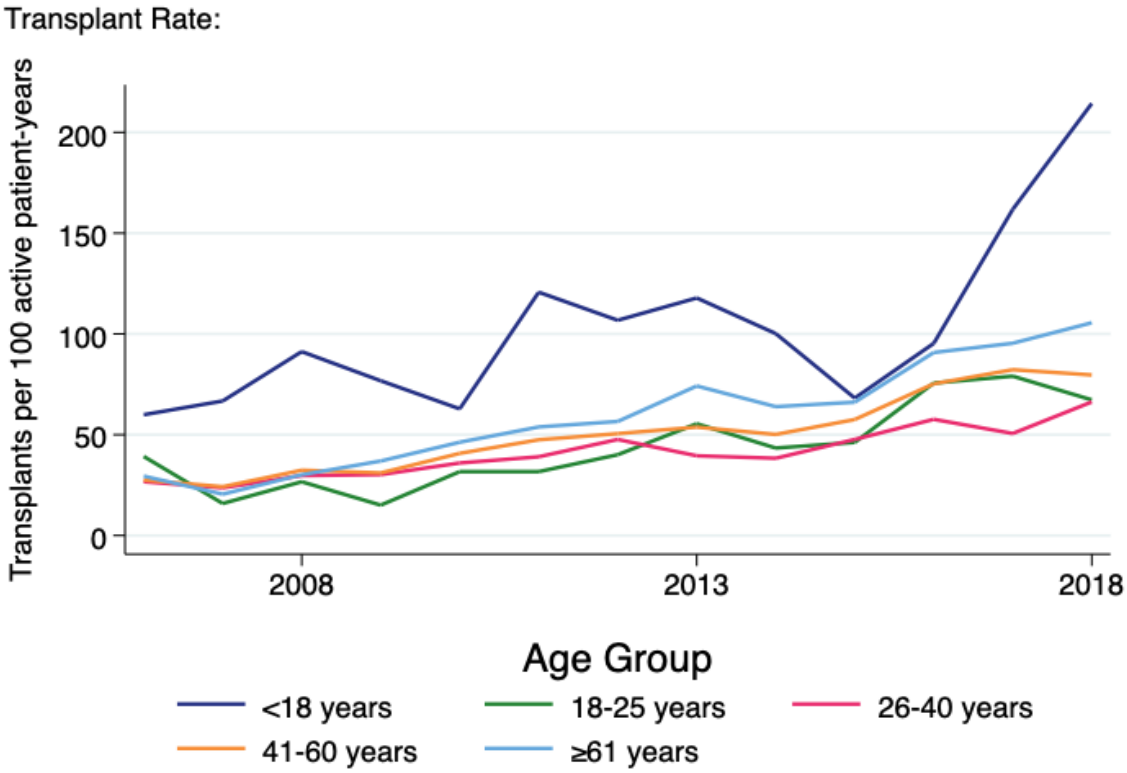

Figure 7.4 Annual transplant rate per 100 active patient years for patients on the deceased donor kidney transplant waiting list, Australia 2006-2018, by age group

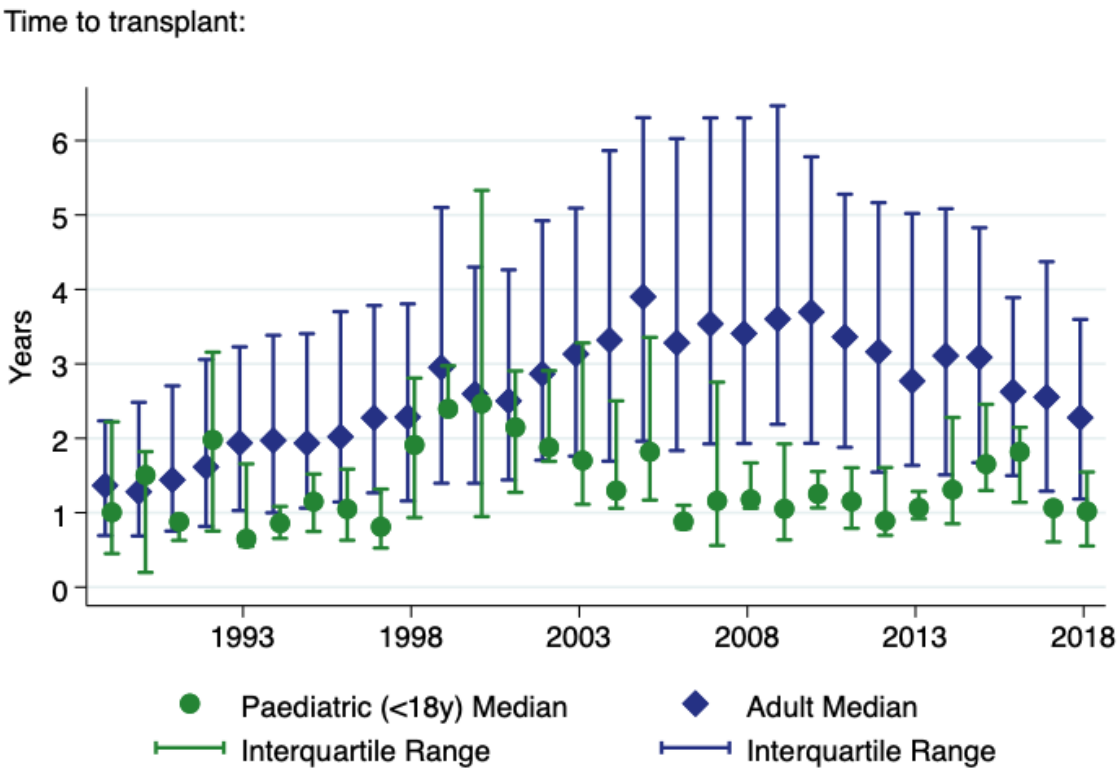

Figure 7.5 Time from initial renal replacement therapy to deceased donor transplantation for paediatric and adult patients receiving their primary deceased donor transplant, Australia 1989-2018

7.5.4 Deceased Donor Characteristics

Donor characteristics for all recipients of deceased donor kidney transplants during the study period are shown in Table 7.2. Compared to the donors of adult recipients, donors of paediatric recipients were younger (median age 34 vs 46 years) and were less likely to have hypertension (6.8% vs 19.3%), diabetes (2.3% vs 4.8%) or to have donated via the donation after circulatory death (DCD) pathway (8.9% vs 13.7%). There was a higher percentage of donors to paediatric recipients donating after traumatic brain injury (32.9% vs 23.9%) and they were less likely to be overweight or obese.

While there was a gradual increase in donor age for adult recipients up until the last 3 years of the study period, the trend in donor age for paediatric recipients appeared to diverge from the late 1990s onwards (Figure 7.6). This divergence was mirrored in the trends in the composite Kidney Donor Risk Index (KDRI) over time, potentially amplified by differences in donor hypertension and donation pathway over time, which are two of the donor characteristics used to calculate KDRI.

The Kidney Donor Performance Index (KDPI) is a scaling of the KDRI based on the population of deceased donors from whom at least one kidney was transplanted in the preceding 3 years. Figure 7.7shows the KDPI quintile for paediatric deceased donor transplants over time. In the most recent year for which data is available (2018), over 90% of paediatric recipients received a kidney from a donor with KDPI <40% and no child in Australia had received a kidney from a donor with KDPI ≥80% since 2012. (Note that sufficient donor data required to determine this score is only available from 1996).

Table 7.2 Comparison of donor characteristics for paediatric and adult recipients of deceased donor kidney only transplants in Australia 1989-2018

Donor Characteristic	Paediatric Recipients	Adult Recipients	p-value
N	426	12793	
Donor age, median (IQR)	34 (20, 46)	46 (29, 57)	<0.001
KDRI, raw score, median (IQR)	1.02 (0.86, 1.25)	1.23 (0.98, 1.60)	<0.001
KDPI %, median (IQR)	34.00 (17.50, 57.00)	56.00 (30.00, 79.00)	<0.001
Donor cause of death category, n (%)			<0.001
Intracranial Haemorrhage	140 (32.9%)	5582 (43.6%)	
Traumatic Brain Injury	140 (32.9%)	3058 (23.9%)	
Cerebral Infarct	10 (2.3%)	654 (5.1%)	
Cerebral Hypoxia / Ischaemia	76 (17.8%)	2134 (16.7%)	
Other Neurological Condition	1 (0.2%)	68 (0.5%)	
Non-Neurological Condition	21 (4.9%)	512 (4.0%)	
Missing	38 (8.9%)	785 (6.1%)	
Donation Pathway, n (%)			0.004
DBD	388 (91.1%)	10996 (86.0%)	
DCD	38 (8.9%)	1753 (13.7%)	
Missing	0 (0.0%)	44 (0.3%)	
Hypertension, n (%)			<0.001
No	327 (76.8%)	8539 (66.7%)	
Yes	29 (6.8%)	2469 (19.3%)	
Missing	70 (16.4%)	1785 (14.0%)	
Diabetes, n (%)			0.022
No	354 (83.1%)	10608 (82.9%)	
Yes	10 (2.3%)	619 (4.8%)	
Missing	62 (14.6%)	1566 (12.2%)	
Smoker, n (%)			0.36
No	157 (36.9%)	4580 (35.8%)	
Yes	200 (46.9%)	6436 (50.3%)	
Missing	69 (16.2%)	1777 (13.9%)	
BMI (kg/m^2) , n (%)			0.003
Underweight (<18.5)	20 (4.7%)	350 (2.7%)	
Normal (18.5-<25)	202 (47.4%)	5408 (42.3%)	
Overweight(25-<30)	131 (30.8%)	4360 (34.1%)	
Obese(≥30)	59 (13.8%)	2308 (18.0%)	
Missing	14 (3.3%)	367 (2.9%)	
Hepatitis C Positive, n (%)			0.11
No	364 (85.4%)	11144 (87.1%)	
Yes	0 (0.0%)	77 (0.6%)	
Missing	62 (14.6%)	1572 (12.3%)	
Creatinine - terminal, mean (SD)	89.72 (69.69)	93.51 (67.61)	0.26

Comparison of donor characteristics for paediatric and adult recipients of deceased donor kidney only transplants in Australia 1989-2018. IQR – interquartile range; SD – standard deviation; KDRI - Kidney Donor Risk Index; KDPI – Kidney Donor Performance Index; DBD – donation after brain death; DCD – donation after circulatory death; BMI – body mass index

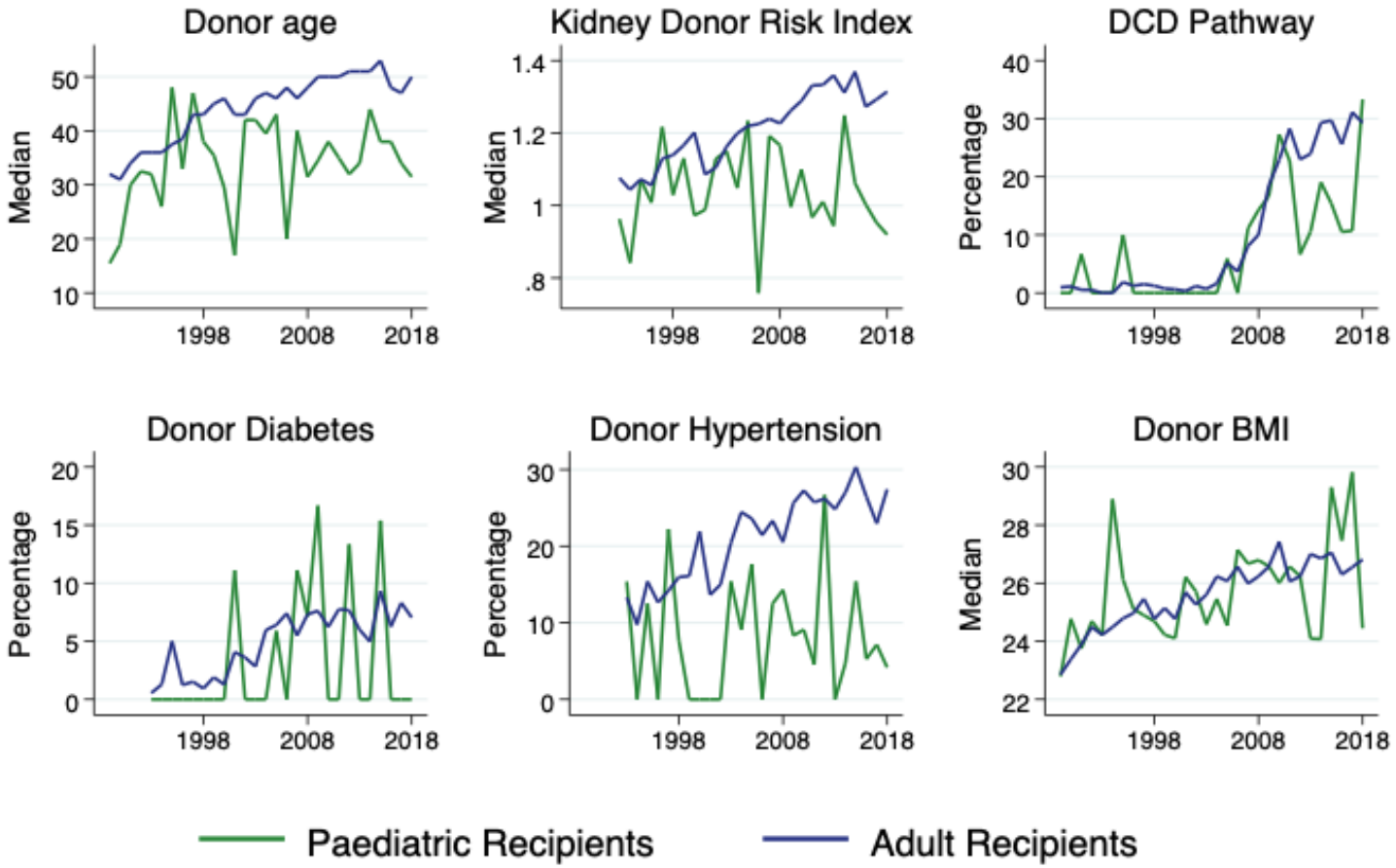

Figure 7.6 Trends in donor characteristics for paediatric and adult recipients of deceased donor kidney only transplants, Australia 1989-2018

Note that due to changes in data collection over time, some donor characteristics are only available for earlier years.

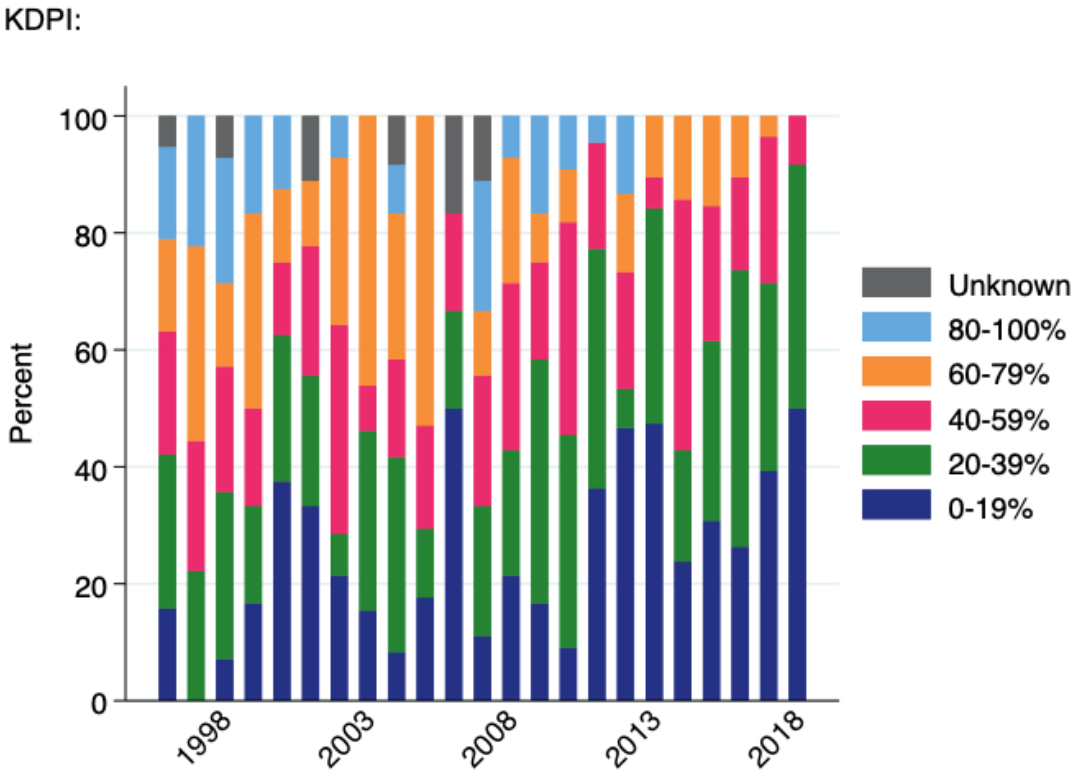

Figure 7.7 Kidney Donor Performance Index (KDPI) for deceased donor kidney only transplants performed in recipients aged less than 18 years of age, Australia 1996-2018

7.5.5 HLA Matching in Deceased Donor Transplants

The average number of HLA antigen mismatches for paediatric patients receiving deceased donor grafts across the study period was 3.61. This increased each decade: 2.86 (1989-1998), 3.85 (1999-2008), 4.01 (2009-2018), mirroring a similar trend in the adult population (Figure 7.8). Over the last 2 decades of the study period the mean number of HLA mismatches was higher for paediatric recipients of deceased donor transplants compared to adult recipients in all but 1 year, although the differences were relatively small (3.83 vs 3.70 mismatches in 2018, for example). Figure 7.9 shows the breakdown of HLA antigen mismatches for paediatric recipients of deceased donor transplants by year.

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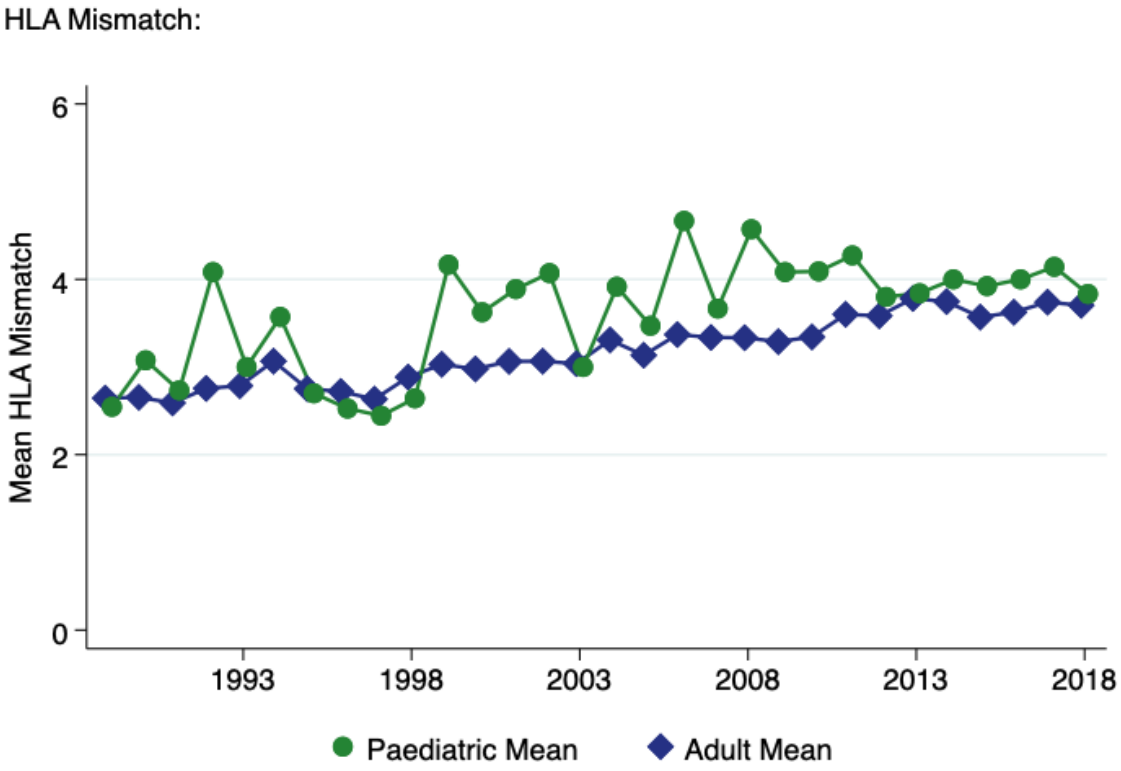

Figure 7.8 Mean human leukocyte antigen (HLA) mismatch (-A, -B and -DR) for deceased donor kidney only transplants performed in paediatric and adult recipients, Australia 1989-2018

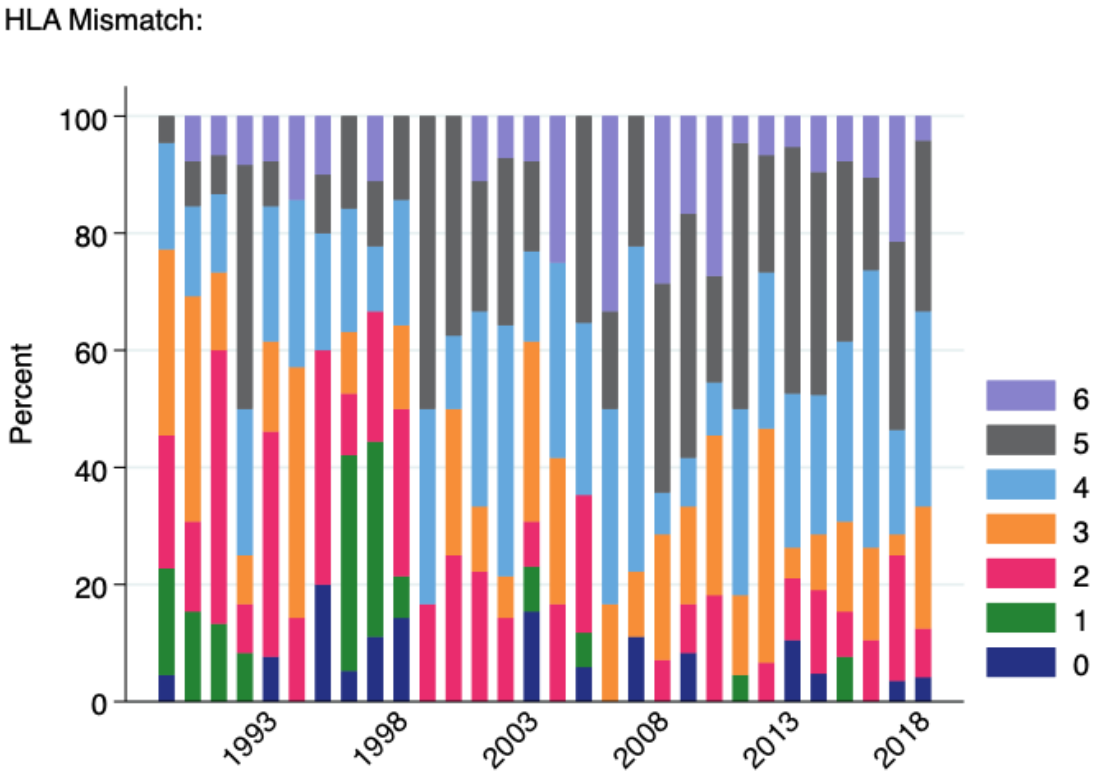

Figure 7.9 Human leukocyte antigen (HLA) mismatches (-A, -B and -DR) for deceased donor kidney only transplant in recipients ages less than 18 years of age, Australia 1989-2018

7.5.1 Patient and Graft Survival

There was a significant improvement in both patient and graft survival in the most recent decade (2009-2018) for paediatric recipients of deceased donor kidney transplants (Figure 7.10). Five-year patient survival in the most recent era (2009-2018) was 99% [95%CI 95-100] compared to 94% [95%CI 88-97] in the decade prior (1999-2018). Similarly, there has been a dramatic improvement in 5-year graft survival over the same period from 65% [95%CI 55-73] to 85% [95%CI 77-90], mainly driven by reductions in early graft loss.

Outcomes:

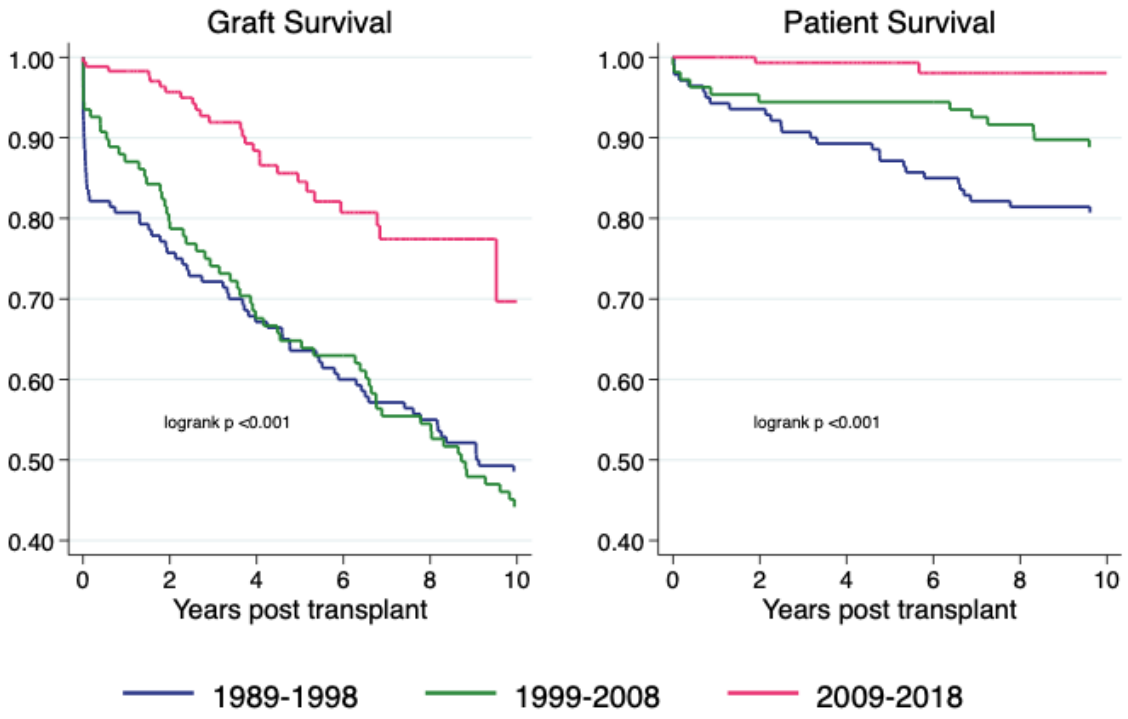

Figure 7.10 Kaplan Meier survival curves of graft survival and patient survival for recipients of deceased donor kidney only transplants aged less that 18 years by decade of transplantation, Australia 1989-2018

7.6 Discussion

The optimal deceased donor kidney for a child with ESKD is one that can be accessed quickly to avoid the morbidity associated with dialysis, has the best possible long-term graft survival and reduces the risk of sensitization to preserve future transplant opportunities. Our analysis demonstrates that under Australia's current paediatric bonus system, children with ESKD received more timely access to higher quality kidneys from deceased donors compared with adult recipients, however, we highlight the need for better strategies to improve donor-recipient HLA matching for paediatric recipients.

Paediatric bonuses in deceased donor kidney allocation are common across organ allocation algorithms globally[43,45]. In the US this has evolved from the allocation of bonus points for children who had not received a kidney within time goals in the waiting list (1998)[58], to introduction of the Share35 program that prioritized young donors to paediatric candidates (2004)[58], to the current Kidney Allocation System (2014) which gives priority to paediatric candidates for kidney with 0 HLA mismatches or from donors with a KDPI <35%[266]. Practice varies widely across Europe with many jurisdictions linking paediatric bonuses to donor age or HLA matching, and others giving relative bonuses or absolute priority[45]. A novel approach has been taken in the UK, where paediatric bonuses per se have been removed from the allocation algorithm (except in the case of clinically urgent paediatric listings) and replaced with a combined HLA match and age score that is calculated for all patients[38]. This functions to give paediatric candidates high priority only for well-matched transplants and does not have a specific age cut off, but gradually reduces with increasing age.

Widespread adoption of paediatric bonuses implies a broad international consensus on the value of positive discrimination in organ allocation of this population. A white paper produced by the OPTN/UNOS Paediatric Transplantation and Ethics Committees set out several philosophical justifications for paediatric priority including the prudential lifespan account, the principles of 'fair innings' and maximising the minimum benefit to the least advantaged, and utility considerations[67]. Children also have unique growth and neurodevelopmental needs that can be optimised through earlier access to transplantation[12,13] and studies into community preferences in the allocation or deceased donor organs have consistently shown support for prioritizing younger recipients[32,267,268] However, others have challenged the legitimacy of these arguments[265]. The impacts of the US Share35 program also serve as an example of the potential for unintended consequences when implementing a priority allocation system. Whilst this program achieved its goal of improving access to deceased donor transplantation for paediatric candidates, the expedited access was associated with a decline in living donor transplant rates and increase in HLA mismatches for this population[70].

Due to the incremental implementation of paediatric bonuses across national and regional allocation systems in Australia, and in light of informal priorities given to the population in some jurisdictions, it is challenging to determine the impacts of, or attribute causation for the observed trends to specific policy changes. However, since the introduction of Australia's first national priority for paediatric patients in 2000, this population have consistently maintained transplantation rates that are higher than the adult population, resulting in substantially less time spent on dialysis prior to deceased donor transplantation.

The most recent two years saw a spike in transplantation rate for paediatric candidates, this pre-dated a major policy change with the removal of the requirement for paediatric patients to spend 12 months on dialysis prior to becoming eligible for paediatric bonuses, however, this may have contributed to record high rates in 2018. Despite rapid access to transplantation, paediatric recipients are still spending on average over a year on dialysis prior to receiving a deceased donor graft. In the setting of a relatively small donor pool, this time may reflect a period of time waiting for a suitable organ offer.

Since the late 2000s both the transplantation rate per waiting time and the time spent on dialysis prior to transplant have shown ongoing improvements for the adult population as well as the paediatric population. This is likely due in part to the formation of the Organ and Tissue Donation and Transplantation Authority in 2009 which implemented a nationally coordinated approach to improving deceased donor rates across Australia which has been associated in a 124% increase in deceased donor numbers between 2009-2018[269]. In the setting of small absolute numbers, the expedited access to deceased donor transplants for paediatric recipients does not appear to have a discernible negative impact on transplantation rates for adult recipients.

In the context of increased access to deceased donor transplantation for both adult and paediatric recipients, a fall in the percentage of all transplants coming from living donors has emerged in both populations. For the paediatric population this does not appear to be a result of reduced absolute numbers of living donor transplants. With historically high rates of living donor transplantation in this population, the decrease in the proportion in recent years may represent an exhaustion of suitable living donors and appropriate use of the

deceased donation pathway for children who do not have access to an appropriate donor. Two large population studies in 2014 demonstrated small but significant increased long term risks for living kidney donors[270,271] which may potentially have impacted clinical practice in the approach to accepting living donors, including for younger parents wishing to donate to children with ESKD[272].

Although paediatric bonuses are not linked to donor age or organ quality in Australia, our results indicate that paediatric recipients are receiving higher quality kidneys in more recent years, despite changes in the overall donor pool. While the donor age has remained relatively static for this population in the context of increasing overall donor age, we demonstrate a trend towards lower KDRI over time. The differences in donor characteristics between paediatric and adult recipients suggest that clinicians are using the priority access to organs to be more discerning about the quality of organs accepted for these patients. KDPI is not used in the organ allocation algorithm in Australia, however from March 2016 this score has been reported to clinicians with all organ offers[65]. Despite no specific policy on the allocation of lower KDPI kidneys, in the most recent year over 90% of paediatric recipients received a kidney from a donor with KDPI <40%. This finding is similar to data from the US where in 2018, 95.2% of paediatric recipients of deceased donor kidneys received an organ from a donor with KDPI <35%[18] as a result of specific allocation rules prioritising patients with low EPTS for low KDPI kidneys .

While it can be argued that the current system is achieving timely access to deceased donor transplantation and favourable donor characteristics for paediatric recipients, we have demonstrated that it is not resulting in superior donor-recipient HLA matching, compared

with adult recipients. HLA mismatches are not only associated with poorer long term graft survival but also increased sensitization and decreased future transplant opportunities following graft failure[141,273,274]. These issues are of particular importance for paediatric recipients who, as a result of excellent long-term patient survival, require both extended primary graft survival and likely subsequent transplantation. A recent study by Ruck et al[275] in the United States, showed that children with 3-6 HLA mismatches had a 43% increased risk of graft failure compared to those with 0-2 mismatches. Despite the introduction of progressive paediatric bonuses in Australia there has been a gradual increase in mean HLA mismatches for paediatric recipients of deceased donor kidney transplants over the past three decades. Similar trends have been seen in the United States where median HLA mismatch has increased from 4 in 1995-2004 to 5 in 2005-2014 for this population[276] and a study reporting the impact of new KAS introduced in 2014, did not show an improvement in the percentage of transplants with ≤3 HLA mismatches for paediatric recipients[275]. In stark contrast, a recent report on paediatric kidney transplantation in the UK where age based allocation points are linked to HLA matching, showed that in 2016 84% of children transplanted through the deceased donor program received a well matched graft (either 0 mismatches, or 0 -DR and 0/1 -B mismatches, this compared to only 27% in 1992[277]. Although we show significant improvements in graft survival in the most recent decade, this is mainly driven by decreases in early graft loss and optimising HLA matching may offer an opportunity to further decrease late graft loss.

Our analysis of immunological matching in paediatric recipients of deceased donor kidney transplants is limited by the resolution of HLA typing data available from the ANZDATA registry. An increasing body of evidence suggests that considering HLA matching based on

serological epitopes, rather than at the antigen level, may provide a more granular tool for assessing immunological risk in kidney transplantation[6,97,101], however, the high resolution molecular typing required to assess epitope matching was not available for this analysis. At least one paediatric transplant unit in Australia is using a novel HLA epitope based approach to improving immunological matching where HLA antigens carrying a high number of epitope mismatches with the potential recipient are prospectively entered into the allocation system as unacceptable antigens and therefore organs from donors with unfavourable HLA profiles will not be allocated to these patients[4]. Informal HLA epitope based immunological assessment of deceased donor kidney offers in a number of other Australian paediatric transplanting centres has also been reported to the authors. With the widespread availability of HLA molecular typing, epitope based organ allocation offers the potential for a more granular method of immunologic risk assessment in transplantation however, more clinical outcome data and feasibility studies are required before this can be implemented at a system wide level[6,278,279].

Deceased donation is an important pathway for children with ESKD to access kidney transplantation in Australia, however, the absolute numbers remain low and make up a small proportion of overall deceased donor transplant activity. Current paediatric bonuses have facilitated rapid access to deceased donor kidneys and enabled selection of high-quality organs for these recipients, however, immunological matching, considered at the HLA antigen level, has not improved with the introduction of these bonuses and could be optimised to improve long term outcomes for this population. In the setting of a relatively small donor pool, increased priority linked to HLA matching coupled with novel approaches

such as HLA epitope-based matching may assist in optimising long-term graft survival and re-transplantation opportunities for children receiving deceased donor grafts.

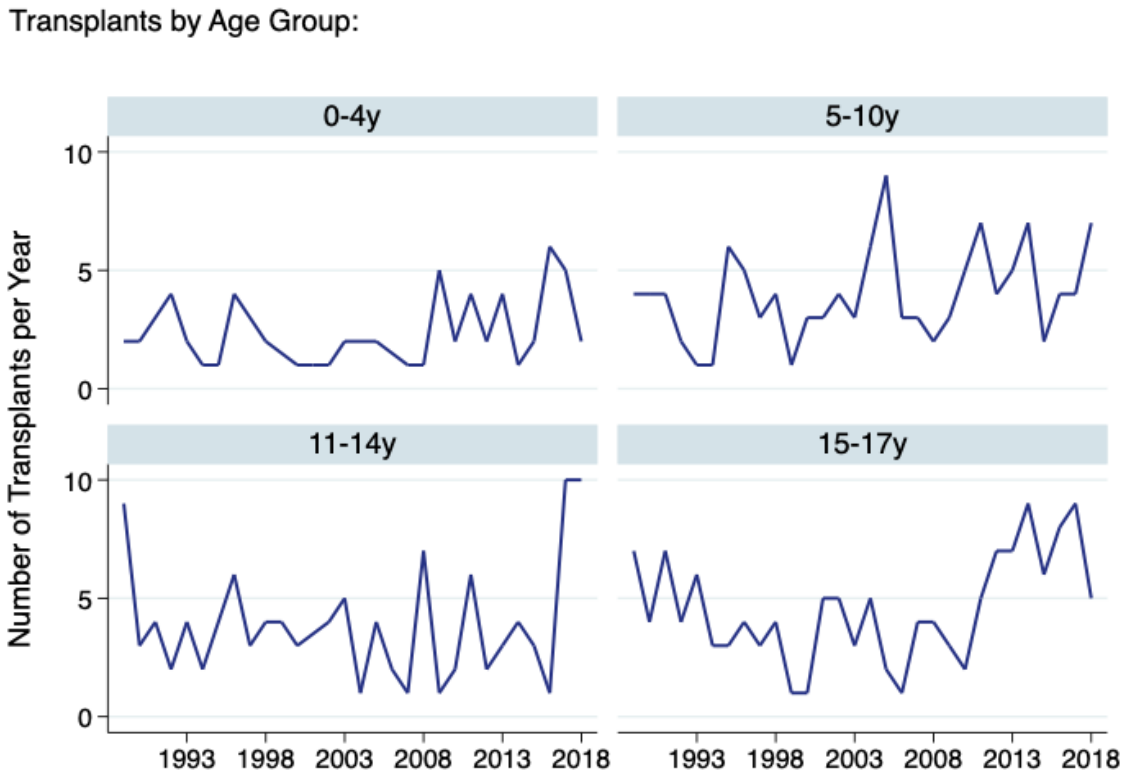

Figure 7.11 Number of deceased donor kidney only transplants performed annually in patients less than 18 years of age, by age group, Australia 1989-2018 (supplementary figure)

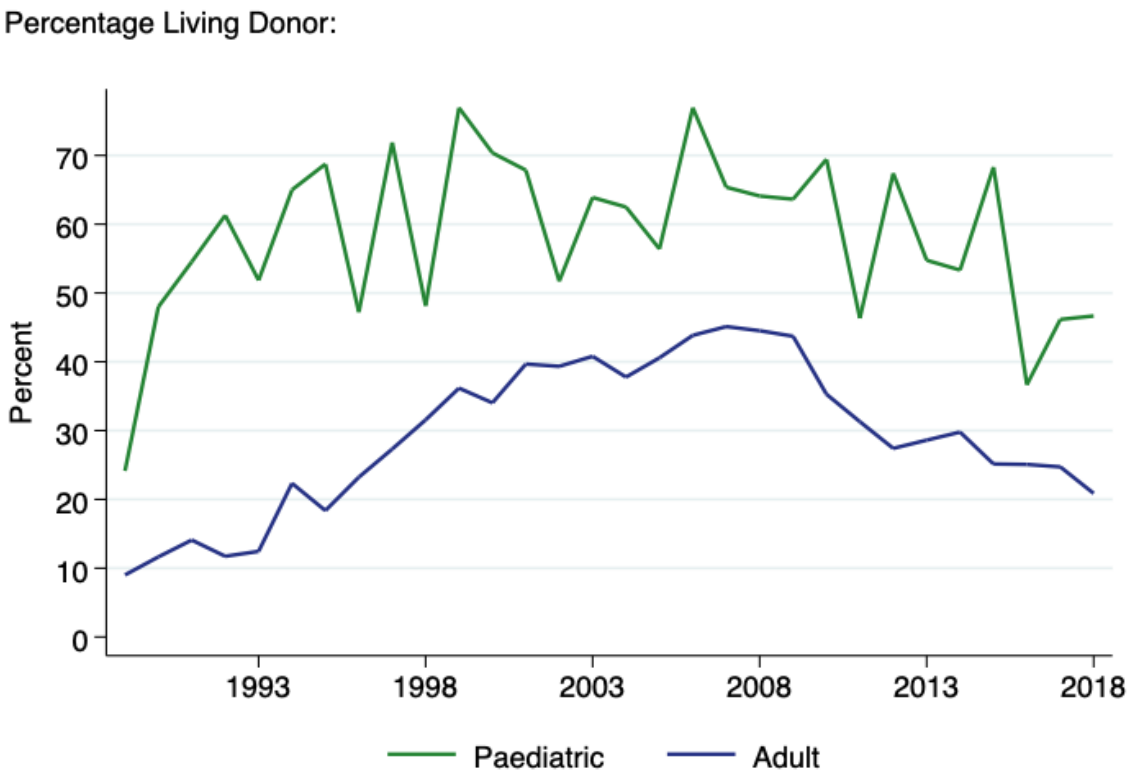

Figure 7.12 Percentage of all kidney only transplants from living donors performed in paediatric and adult recipients, Australia 1989-2018 (supplementary figure)

Chapter 8 Human leukocyte antigen eplet mismatches and long-term clinical outcomes in paediatric renal transplantation: a pragmatic, registry based study

8.1 Preface

The content of this chapter has been published in the journal *Pediatric Transplantation* (2020 Jun;24(4)e13705). The text is identical to the published manuscript apart from minor stylistic changes to figure and table titles and legends.

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Author contributions are described in thesis preface.

8.2 Abstract

Background: HLA epitope based matching offers the potential to improve immunological risk prediction and management in children receiving renal allografts, however, studies demonstrating the association between systems for defining epitope mismatches and clinical endpoints are lacking in this population. Methods: We conducted a pragmatic, retrospective, registry-based study of paediatric recipients of primary renal allografts in Victoria, Australia between 1990-2014 to determine the association between HLA eplet mismatches (EpMM) and clinical outcomes including graft failure, re-transplantation and de novo donor specific antibody (dnDSA) formation. Results: A total of 196 patients were included in the analysis with a median age of 11 years. Median follow up period was 15 years during which time 108 (55%) primary grafts failed and 72 patients were re-transplanted. HLA class I but not class II EpMM was a significant predictor of graft failure on univariate analysis but not in adjusted models. EpMM was associated with reduced likelihood of re-transplantation in univariate but not adjusted analysis. Within the limitations of the study, class specific EpMM was a strong predictor of dnDSA formation. Associations were stronger when considering only the subset of antibody verified EpMM. Conclusion: Associations between HLA EpMM and clinical outcomes in paediatric renal allograft recipients seen on univariate analysis were attenuated following adjustment for confounders. These findings are inconclusive but suggest that HLA EpMM may provide one tool for assessing long term risk in this population whilst highlighting the need for further clinical studies.

8.3 Background

With increased recognition of the dominant role of humoral immunity in long term renal allograft outcomes and advances in our understanding of human leukocyte antigen (HLA) structure, many have argued that HLA matching should be considered at the epitope level[97,98,100,102,191]. Various systems have been proposed to define HLA epitopes including based on antibody adsorption/elution studies[280] and in silico methods analysing the sequence and structure of HLA molecules[167,281]. Duquesnoy's system of defining HLA *functional* epitopes using *eplet* designations has gained popularity due to its comprehensive inclusion of all theoretical epitopes, the ease of calculating eplet mismatches (EpMM) using freely available software[282] and a growing body of evidence regarding its clinical application[5,283]. This system has demonstrated value in assisting with epitope specific anti-HLA antibody analysis and acceptable mismatching for sensitized patients[57,284]. However, Duquesnoy himself, and others stress the importance of the need for further clinical validation of the eplet system for defining HLA epitopes and its role in predicting alloimmune risk post-transplant[259,278,285].

A number of studies have demonstrated the association between EpMM and primary alloimmune responses in renal transplant recipients, including; donor specific antibody formation[180–183,286], transplant glomerulopathy[185] and sensitization following graft failure[184]. However, studies examining hard clinical endpoints including graft survival and re-transplantation are limited and have shown conflicting findings [182,287–289]. Studies in this area are challenging due to the requirement of a long follow up period to observe clinical outcomes and the limited availability of high-resolution typing on historical cohorts.

It is well recognised that transplantation is the best treatment for most children with end-stage kidney disease[290,291] and that long term patient survival is excellent[292,293]. As a result, many children will require multiple transplants throughout their lives and therefore the proposed benefits of improved epitope matching are of particular importance in this patient population. These potential benefits have already prompted us, and other paediatric transplantation units, to integrate eplet matching into clinical practice[4,188,189]. However, additional evidence is required to support the ongoing role of eplet matching in improving long term outcomes particularly when the potential benefits of improved immunological matching must be weighed against other factors in donor choice including donor age and organ quality.

We aimed to use a pragmatic study design to conduct a retrospective, registry-based study of paediatric renal transplant recipients over the last 25 years in Victoria, Australia to explore the relationship between epitope matching, as defined by Duquesnoy's eplets, and clinical outcomes.

8.4 Methods

Cohort

Patients were eligible for the study if they received a primary, kidney only transplant in Victoria, Australia, between 1990-2014, and were aged less than 18 years of age at the time of transplantation. Patients were excluded from the primary analysis if they had primary non-function of their graft or failure within the first 2 weeks following transplantation. Follow up data was available to 31st December 2017.

Clinical outcome data was obtained from the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA), a binational database that collects information on all patients with end-stage kidney disease receiving renal replacement therapy in Australia and New Zealand. HLA typing information and anti-HLA antibody testing was obtained from the Australian Red Cross Blood Service, Victoria Transplantation and Immunogenetics Service (VTIS), which is responsible for all transplant immunological testing in the state of Victoria.

Outcome, exposure and confounders:

The primary outcome was time to graft failure (including death with a functioning graft). Secondary outcomes included time to re-transplantation in patients who experienced graft loss during the study period and development of de novo donor specific antibodies (dnDSA) in a subset of patients with testing available. Post-transplant DSA monitoring was performed at the discretion of treating units, and included screening, testing for clinical indications and testing prior to relisting for subsequent transplantation after primary graft failure. Recipient

serum samples (pre and post-transplant) were screened for anti-HLA antibodies by either mixed bead or single antigen bead (SAB) assays (One Lamda Inc.) as per standard protocol and assessed for presence of DSA with median fluorescence intensity (MFI) cut-off >1000 being used. Surveillance biopsies were not routinely performed in this cohort.

The exposures of interest were class specific HLA EpMM, with a secondary analysis examining only antibody verified HLA EpMM. Effect was estimated per EpMM. Potential confounders included in multivariate modelling were: recipient age at transplant, gender, primary renal disease (categorised as congenital abnormalities of the kidney and urinary tract (CAKUT), glomerulonephritis and other) and sensitization status at primary transplant (detection of any anti-HLA antibody vs non-sensitized); and donor age and source (living donor vs deceased donor). Note that prior to February 2016 sensitization status was based on HLA class I cytotoxic antibody detection only and after this date was based on detection of class I or class II antibodies on SAB assay according to methods outlined above.

HLA typing and Calculation of Eplet Mismatches

Due to the retrospective nature of our study design, the technology used for HLA typing evolved over the years and a variety of these technologies are reflective in this cohort, however, 4 digit molecular typing is required to calculate EpMM. Serological complement dependent cytotoxicity (CDC) HLA typing only, was used in a proportion of patient and donors, with 4-digit HLA alleles assigned using local haplotype and allele frequencies gathered from over 5000 local donors typed by next generation sequencing (NGS) methods. These same assigned alleles were used for any low resolution (ie. 2-digit) molecular typing that was performed. Low resolution typing was determined by Luminex sequence specific

oligonucleotide (SSO) (One Lambda Inc.) or sequence specific primers (SSP). All high resolution results reported are from either Sanger sequencing or next generation sequencing (NGS) methods. For a proportion of typing at HLA-DRB3/4/5 and HLA-DQA/DQB no typing information was available and high resolution typing was assumed based on population linkages only. Table 8.1 shows the proportion of patients assigned 4 digit typing using each method.

Table 8.1 Methods for human leukocyte antigen typing in the study cohort

	Recipient Typing					Donor Typing				
	Serological Typing Only	Low/Intermediate Resolution Molecular Typing	High Resolution Molecular Typing	Assumed based on population based linkages	Total	Serological Typing Only	Low/Intermediate Resolution Molecular Typing	High Resolution Molecular Typing	Assumed based on population based linkages	Total
HLA-A/B	62 (31%)	49 (25%)	87 (44%)	-	198 (100%)	99 (50%)	-	99 (50%)	-	198 (100%)
HLA-DRB1	27 (14%)	55 (28%)	116 (59%)	-	198 (100%)	52 (26%)	61 (31%)	85 (43%)	-	198 (100%)
HLA-DRB3/4/5	24 (12%)	-	61 (31%)	113 (57%)	198 (100%)	43 (22%)	-	43 (22%)	112 (57%)	198 (100%)
HLA-DQB1/A1	52 (26%)	-	124 (63%)	22 (11%)	198 (100%)	81 (41%)	-	97 (49%)	20 (10%)	198 (100%)

The methods of human leukocyte antigen (HLA) typing for recipients and donors in the cohort at each loci. For non high-resolution testing, 4-digit HLA alleles assigned using local haplotype and allele frequencies gathered from over 5000 local donors typed by next generation sequencing methods.

Eplet mismatches were determined using HLAMatchmaker v02, released June 2016, available from www.epitopes.net. Class I EpMM included the A and B loci only, class II EpMM considered DRB1, DRB3/4/5, DQA1 and DQB1 loci. The *eplet* repertoire is designed to include all potential HLA epitopes, however, not all of these have been confirmed to be targets of clinically observed antibodies and remain descriptors of potential epitopes. In addition to examining total EpMM for each HLA class, we also assessed the association of the subset of antibody verified eplet mismatches which are also reported by the HLAMatchmaker application.

Statistical methods

Cox proportional hazards regression models were used to determine the association between EpMM and clinical outcomes including graft survival and re-transplantation. Due to the ad hoc nature of dnDSA detection, logistic regression models were used to determine predictors of dnDSA formation at any point during the follow up period. Confounders were considered for inclusion in multivariate adjustment if statistically significant at a p value of <0.2 on univariate analysis. Linearity of continuous predictors was tested by plotting Martingale residuals and comparing the fit of alternative fractional polynomial models; linear splines or categorisation were introduced where non-linearity was detected. The Cox proportional hazards assumption was tested using scaled Schoenfeld residual and a piecewise model was created to deal with significant violations.

The final models were adjusted for the following confounders: graft survival model – recipient age (age under 12 years vs age 12 years and over, with a piece wise model

estimating separate effects for 0-10 years post-transplant and >10 years post-transplant), primary renal disease, donor age (with a linear spline knotted at age 30 years), and donor type; re-transplantation model – age at primary transplant (continuous), primary renal disease and sensitization status; dnDSA model – age at primary transplant (continuous). Eight patients were missing data on pre-transplant sensitization, sensitivity analyses imputing these as either sensitized or non-sensitized did not alter results and hence these patients were excluded from the re-transplantation adjusted model (n=3).

Additional sensitivity analyses were conducted for the dnDSA models excluding zero HLA class I and class II serological mismatch transplants at traditional A/B and DR loci and including HLA class specific serological mismatches in the adjusted model.

Results were considered statistically significant at a p value of <0.05. All analysis were conducted using STATA 15.1, Statacorp, TX, US.

8.5 Results

8.5.1 Cohort description

A total of 198 patients were identified within the ANZDATA database according to the inclusion criteria. Two patients were unable to be matched in the VTIS database and were excluded.

Table 8.2 shows the patient characteristics of the entire cohort. Fifty five percent were male and the median age was 11 years old (IQR 5-15). The most common cause of renal failure was congenital abnormalities of the kidney and urinary tract (CAKUT) (57%). A large majority of transplants were from living donors (79%) with a median donor age of 42.5 years (IQR 37-50). The median overall follow-up time was 15 years during which time 108 (55%) primary grafts failed and 72 patients received a re-transplantation.

Table 8.3 summarizes the HLA matching between donors and recipients using both HLA antigens (serological equivalents) and EpMM. Overall, the cohort was reasonably well matched, particularly at class II with 27% have zero HLA DR antigen mismatches. The median total EpMM was 10 (IQR 5-14) for class I (A and B loci) and 21 (IQR 2.5-33) for class II (DRB1, DRB345, DQA1, DQB1). This compares to a median of 5 (IQR 3-8) for class I and 8 (IQR 0-13) for class II when only antibody verified EpMM are considered. Figure 8.1 shows the distribution of HLA Class I and Class II total EpMM and antibody verified EpMM. Figure 8.2 shows the total class specific EpMM by HLA antigen mismatch, demonstrating significant overlap in EpMM across difference degrees of antigen mismatch.

Table 8.2 Characteristics of the study cohort

Factor	Level	n (%)
		196 (100%)
Gender	Male	108 (55.1%)
	Female	88 (44.9%)
Age at transplant, median (IQR)		11 (5, 15)
Primary Renal Disease	CAKUT	111 (56.9%)
	GN	43 (22.1%)
	Other	41 (21.0%)
Sensitization	Non-sensitized	120 (63.8%)
	Sensitized	68 (36.2%)
Donor Type	Living Donor	155 (79.1%)
	Deceased Donor	41 (20.9%)
Donor age, median (IQR)		42.5 (37, 50)
Transplant Failure	No	88 (44.9%)
	Yes	108 (55.1%)
Re-transplantation Outcome	Functioning Primary Graft	88 (44.9%)
	Death with Functioning Graft	9 (4.6%)
	Re-transplanted	72 (36.7%)
	Not re-transplanted	27 (13.8%)

Note sensitization refers to the detection of any anti-HLA antibody pre transplant. IQR – interquartile range; CAKUT – congenital abnormalities of the kidney and urinary tract; GN – glomerulonephritis.

Table 8.3 Human leukocyte antigen and eplet mismatches for transplants performed in the study cohort

HLA Class I		
HLA-A/B Serological Equivalent Mismatches, n (%)	0	14 (7.1%)
	1	59 (30.1%)
	2	87 (44.4%)
	3	27 (13.8%)
	4	9 (4.6%)
Class I EpMM - Total, median (IQR)		10 (5, 14)
Class I EpMM - Ab Verified, median (IQR)		5 (3, 8)
HLA Class II		
HLA-DR Serological Equivalent Mismatches, n (%)	0	53 (27.0%)
	1	112 (57.1%)
	2	31 (15.8%)
Class II EpMM - Total, median (IQR)		21 (2.5, 33)
Class II EpMM - Ab Verified, median (IQR)		8 (0, 13)

The number of patients at each level of HLA antigen mismatches is shown as well as the median HLA eplet mismatches for the entire cohort. HLA – human leukocyte antigen; IQR – interquartile range; EpMM – eplet mismatch.

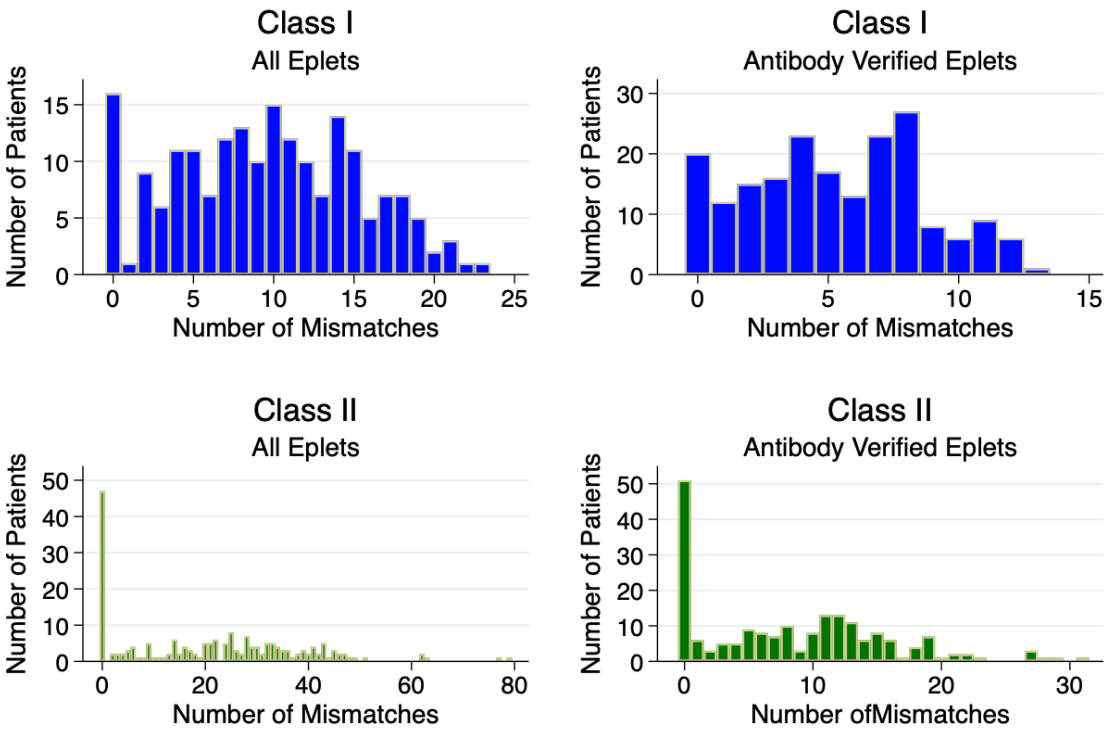

Figure 8.1 Distribution of HLA eplet mismatches for transplants performed in the study cohort

The distribution of eplet mismatches in the entire cohort (n=196) for both total eplet mismatches and mismatches in the subset of antibody verified eplets by HLA class. HLA – human leukocyte antigen.

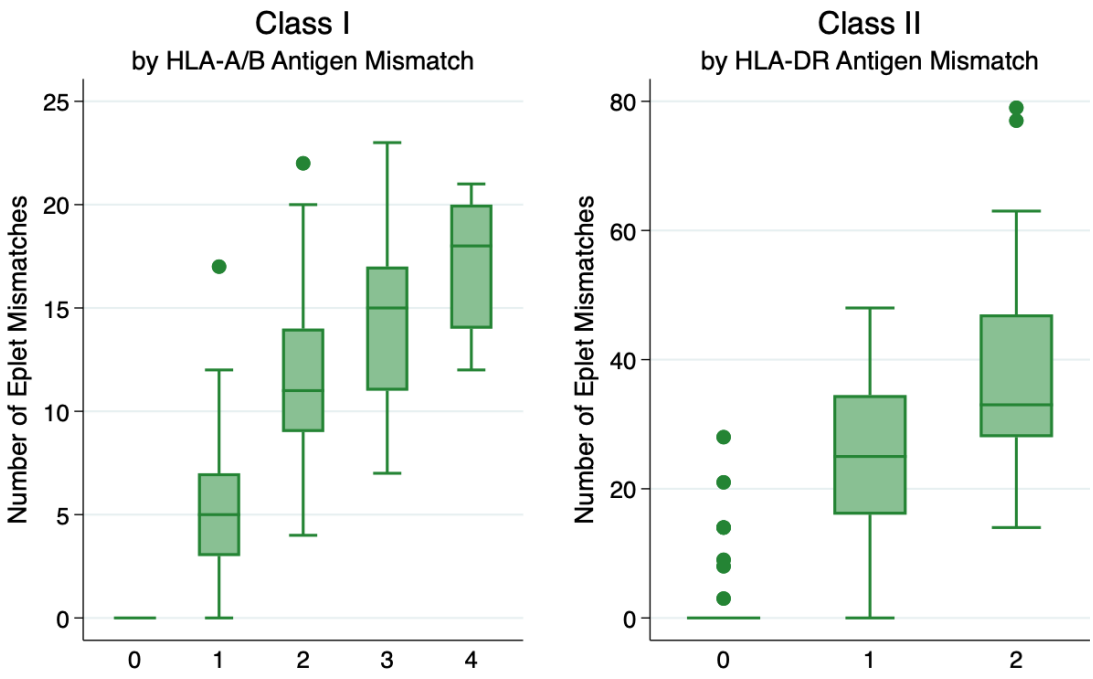

Figure 8.2 HLA eplet mismatches by HLA antigen mismatch, all eplets

Box plots of total class specific eplet mismatches by HLA antigen (serological equivalent) mismatches at the three loci traditionally considered in renal transplant HLA matching. Not the considerable overlap of eplet mismatches across levels of antigen mismatch. HLA – human leukocyte antigen.

8.5.2 Association between eplet mismatches and clinical outcomes

The associations between class specific EpMM and clinical outcomes in both univariate and adjusted models are shown in Table 8.4.

8.5.3 Graft Survival

Twelve patients were excluded due to primary non-function of their graft or graft failure within the first 14 days. Of the 184 patients included in the primary analysis, 96 (52%) experienced graft failure during the follow up period, including 9 patients who died with a functioning graft.

HLA Class I EpMM was associated with a 5% increase in hazards for graft failure for each eplet mismatch on univariate analysis (HR 1.05 per MM, 95%CI 1.01-1.09, p=0.022) however this association was not significant after adjustment for confounders (recipient age group and primary renal disease, and donor age and source) (adjusted HR 1.03 per MM, 95%CI 0.98-1.07, p=0.220). The effect size was greater when considering only antibody verified class I EpMM (HR 1.08 per MM, 95%CI 1.01-1.15, p=0.023) however, was also not significant after adjustment for confounders. There was no significant association between class II EpMM and graft failure on either univariate or adjusted analysis, either when considering all EpMM or only the subset of antibody verified mismatches (Table 8.4).

Table 8.4 Associations between HLA eplet mismatches and clinical outcomes in paediatric kidney transplant recipients

	Univariate Models		Adjusted Models	
Model 1: Graft Survival				
	n=184		n=184	
	Hazard Ratio	95% CI	Adjusted Hazard Ratio	95% CI
Class I EpMM - Total	1.05*	1.01,1.09	1.03	0.98,1.07
Class II EpMM - Total	1.01	1.00,1.02	1.00	0.99,1.02
Class I EpMM – Ab Verified	1.08*	1.01,1.15	1.05	0.98,1.12
Class II EpMM – Ab Verified	1.02	0.99,1.05	1.00	0.96,1.03
Model 2: Re-transplantation				
	n=99		n=94	
	Hazard Ratio	95% CI	Adjusted Hazard Ratio	95% CI
Class I EpMM - Total	0.96	0.93,1.00	0.98	0.94,1.02
Class II EpMM - Total	0.98*	0.97,1.00	0.99	0.97,1.00
Class I EpMM – Ab Verified	0.93*	0.87,1.00	0.94	0.88,1.01
Class II EpMM – Ab Verified	0.95**	0.92,0.98	0.96	0.93,1.00
Model 3: Class I dnDSA				
	n=118		n=118	
	Odds Ratio	95% CI	Adjusted Odds Ratio	95% CI
Class I EpMM - Total	1.09*	1.02,1.17	1.11**	1.03,1.19
Class II EpMM - Total	1.00	0.98,1.02	0.98	0.96,1.01
Class I EpMM – Ab Verified	1.18**	1.05,1.32	1.22**	1.08,1.38
Class II EpMM – Ab Verified	0.98	0.93,1.02	0.94*	0.90,1.00
Model 4: Class II dnDSA				
	n=118		n=118	
	Odds Ratio	95% CI	Adjusted Odds Ratio	95% CI
Class I EpMM - Total	1.05	0.99,1.12	1.02	0.95,1.09
Class II EpMM - Total	1.05***	1.03,1.08	1.05***	1.02,1.08
Class I EpMM – Ab Verified	1.09	0.98,1.22	1.04	0.92,1.17
Class II EpMM – Ab Verified	1.12***	1.05,1.18	1.11**	1.04,1.18

The associations between eplet mismatches and post-transplant outcomes. Hazard ratios and odds ratios are reported per eplet mismatch. Model are adjusted for the following confounders: model 1 - recipient age (age under 12 years vs age 12 years and over, with a piecewise model estimating separate effects for 0-10 years post-transplant and >10 years post-transplant), primary renal disease, donor age (with a linear spline knotted at age 30 years), and donor type; model 2 - age at primary transplant (continuous), primary renal disease and sensitization status; models 3 and 4 - age at primary transplant (continuous). CI – confidence interval; EpMM – eplet mismatch; Ab – antibody; dnDSA – de novo donor specific antibody.

8.5.4 Re-Transplantation

Of the 99 patients who experienced graft failure and remained alive, 72 (73%%) went on to have a second transplant during the study follow up period, 50% of these were from living donors.

HLA Class II, but not class I, total EpMM was associated with a reduced likelihood of re-transplantation on univariate analysis (HR 0.98 per MM, 95%CI 0.97-1.00, p=0.012). After adjustment for significant confounders (age and sensitization at time of first transplant and primary renal disease) neither class I nor class II EpMM with the first kidney donor was associated with re-transplantation in this cohort (Table 8.4). When only considering antibody verified EpMM, there were significant associations between both class I and class II and re-transplantation on univariate analysis (HR 0.93 per MM, 95%CI 0.87-1.00, p=0.036 and HR 0.95, 95%CI 0.92-0.98, p=0.004, respectively), however, after adjustment for confounders these associations were no longer statistically significant.

8.5.5 De Novo Donor Specific Antibodies

A total of 127 patients (65%) were tested for DSA at some point following their primary transplant. Patients with DSAs tested were slightly younger that those without testing (median age 10 vs 13 years, p = 0.010) but other baseline characteristics were similar (Table 8.5). Nine patients with pre-transplant DSA were excluded from this analysis. Of these 118 patients, 16 (14%) developed isolated class I dnDSA and 19 (16%) developed isolated class II dnDSA, with 51 patients (43%) developing both class I and class II dnDSA.

Table 8.5 Demographics and baseline characteristics comparing patients who had post-transplant donor specific antibodies (DSAs) tested and those who did not

Factor	Level	DSA Not Tested	DSA Tested	p-value
		n=69	n=127	
Gender	Male	41 (59.4%)	67 (52.8%)	0.37
	Female	28 (40.6%)	60 (47.2%)	
Age at transplant, median (IQR)		13 (9, 16)	10 (4, 14)	0.010
Primary Renal Disease	CAKUT	41 (60.3%)	70 (55.1%)	0.78
	GN	14 (20.6%)	29 (22.8%)	
	Other	13 (19.1%)	28 (22.0%)	
Sensitization	Non-sensitized	48 (71.6%)	72 (59.5%)	0.097
	Sensitized	19 (28.4%)	49 (40.5%)	
Donor Source	Living Donor	57 (82.6%)	98 (77.2%)	0.37
	Deceased Donor	12 (17.4%)	29 (22.8%)	
Donor age, median (IQR)		43 (37, 47)	42 (36, 53)	0.57

. IQR – interquartile range; CAKUT – congenital anomalies of the kidney and urinary tract; GN – glomerulonephritis.

There was a strong association between class specific EpMM and dnDSA formation both on univariate analysis and when adjusting for the recipient age at time of transplantation (adjusted OR 1.11 per EpMM, 95%CI 1.03-1.19, p 0.006 for class I and adjusted OR 1.05 per EpMM, 95%CI 1.02-1.08, p<0.001 for class II). The associations were stronger when considering only antibody verified eplets (adjusted OR 1.21 per EpMM, 95%CI 1.06-1.36, p= 0.003 for class I and adjusted OR 1.21 per EpMM, 95%CI 1.13-1.33, p = 0.001 for class II). As expected, class I EpMM was not associated with class II dnDSA formation and vice versa. On sensitivity analysis that excluded HLA A/B or HLA DR zero antigen mismatch transplants, the above associations were no longer observed. Similarly, no associations between EpMM and dnDSA formation were seen when HLA A/B and HLA DR antigen mismatches were included in the models.

8.6 Discussion

We present the first retrospective, registry-based study of the association between EpMM and long term clinical outcomes in a paediatric renal transplant population. Within the limitations of available data, we have demonstrated an association between HLA class I, but not class II, EpMM and graft survival in this population that is attenuated after adjustment for confounders. Similarly, associations between HLA class II EpMM and class I antibody verified EpMM and reduced likelihood of re-transplantation were seen on univariate analysis but not after model adjustment. Despite the ad hoc and incomplete data available

on post-transplant dnDSA, class specific EpMM was strongly associated with this surrogate endpoint, supporting previous studies.

Our study represents a pragmatic attempt to investigate if the theoretical benefits of improved epitope matching, as defined by the eplet repertoire, are supported by long term clinical outcomes. We chose a retrospective, registry-based approach as the key clinical outcomes of interest (graft survival and re-transplantation) occur on the scale of decades in this population making a prospective study infeasible. A major weakness of this study is the limited high-resolution, extended HLA typing available on this historical cohort which necessitated a number of assumptions in assigning this for the purposes of EpMM calculations. We used the available HLA typing in combination with information on local haplotype frequencies and extended class II linkage associations to determine the most likely complete, high resolution typing. There is limited evidence that using haplotype based assumed high resolution typing to determine quantitative EpMM may be sufficiently accurate for the purpose of epidemiological studies[294,295], however, due to this major limitation, our findings should be viewed as hypothesis generating only.

While there is a growing body of evidence linking EpMM and dnDSA formation, studies examining graft survival are limited and have shown conflicting results. Haririan et al conducted a retrospective study of 101 predominantly African American renal allograft recipients with a mean follow up of 18 months[289]. They found that the number of triplet (an earlier iteration of eplets) mismatches did not have a significant association with the risk of graft loss, however, in an exploratory analysis a threshold of 10 class I triplet mismatches was predictive of graft survival (no predictive class II threshold was identified) and a

subgroup analysis of 76 patients with data on HLA DQ matching did show some significant associations between triplet mismatch and graft survival. In a study of 62 adult renal allograft recipients, Silva et al found no differences in 10 year graft survival between patients with more or less than 10 HLA class I EpMM[288]. Both of these studies used methods that presumed high resolution typing based on serological equivalents. In a more recent analysis, Wiebe et al examined the synergistic association of class II EpMM and non-adherence with graft failure[182]. They dichotomised EpMM into high and low risk categories based on a previous study exploring associations been EpMM threshold and risk of dnDSA and reported that these risk categories interacted with adherence, with high risk, non-adherent patients more likely to experience graft failure than low risk adherent patients.

Our analysis showed a significant association with HLA class I antibody verified EpMM and graft failure, but not class II. There are several reasons why this finding may differ from previously published reports on a stronger association between class II antigen mismatches and graft failure, compared to class I antigen mismatches. Firstly, our cohort of predominantly living donor transplant recipients had around a quarter of patients with zero HLA DR antigen mismatches compared to only 6% with zero HLA A and B antigen mismatches, potentially reducing the power of the study to detect class II effects. In addition, due to the lack of historical HLA DQA, DQB and DRB3/4/5 typing, more assumptions were required to assign extended high-resolution class II typing potentially obfuscating class II EpMM associations. Information about medication adherence was not available and we were therefore unable to assess any synergistic effects of EpMM and non-adherence on graft survival.

We elected to report our results per EpMM rather than per 10 EpMM or by quantiles, or explore statistically significant EpMM cutoffs, as others have chosen to do[185,186,281,296]. One of the potential benefits of an epitope based approached to HLA matching is in increased granularity of risk prediction and after testing the assumption of a linear relationship between eplet mismatches and the linear predictor in our models, we feel that reporting hazard and odds ratios per eplet allows the reader to better understand incremental risk. The clinical relevance of significant associations becomes more apparent by considering the effect per 10 eplet mismatches (HR 1.56 per 10 eplets [95% CI 1.06-2.29, p=0.02], compared to HR 1.05 per eplet [95% CI 1.01-1.09, p=0.02] for the unadjusted association between class I EpMM and graft failure, for example), however, without a clinical or biological justification for defining these cut offs the magnitude of the effect size reported seems arbitrary.

Preservation of re-transplantation opportunities is of paramount importance when considering allograft selection of paediatric renal transplant recipients. Based on studies demonstrating associations between EpMM and degree of post-transplant sensitization[183,184] we hoped to demonstrate that EpMM was a predictor of this important clinical endpoint in a real world paediatric cohort. While we saw a signal for this on univariate analysis, particularly for HLA class II EpMM, this association did not persist in our multivariate modelling. The two most significant predictors of re-transplantation in our cohort were sensitization prior to primary graft and primary renal disease. In light of these, our study may have been underpowered to detect a true association between EpMM and re-transplantation. Alternatively, this finding may suggest that children who are demonstrated to have formed anti-HLA antibody prior to their first transplant may have an

increased risk of subsequent sensitization that overwhelms any risk associated with increased EpMM, although this hypothesis remains to be tested.

There are significant limitations in the data that was available to us on post-transplant dnDSA formation, and caution should be taken when extrapolating from the results reported here. Due to the changes in technology over our study period, lack of standardized protocols across units, and cost and lack of proven benefit of post-transplant dnDSA surveillance testing, this was performed on an ad hoc and inconsistent basis across our cohort. Many samples may have been tested after primary graft failure at time of relisting and the relationship to graft nephrectomies is unknown. Testing protocols were not standardized across time and detailed antibody specificity data was not available for analysis. The use of a logistic regression model here is dubious as duration of follow up varies amongst patients and this analysis does not account for censoring, however, it was not possible to perform survival analysis with the available data. Despite these limitations, our findings in this real world study add weight to the growing body of evidence that HLA EpMM are an important predictor of dnDSA formation, which is itself strongly associated with antibody mediated rejection and poor graft outcomes[153,297]. However, caution should be exercised when examining association with surrogate outcomes and further clinical evidence is required before practice change can be recommended.

To our knowledge, this is the first study to examine the associations with the subset of antibody verified EpMM and clinical outcomes. Our models demonstrated stronger and more consistent associations between antibody verified EpMM when compared to all EpMM. The eplet system for defining HLA epitopes remains a theoretical description of

functional epitopes, some of which may not be biologically relevant. Our findings suggest that considering whether or not eplets have been shown to be associated with antibody formation may be an important consideration when assessing risk based on this system of defining HLA matching. This highlights the ongoing need to standardize systems of defining HLA serological epitopes, an ongoing goal of the International HLA and Immunogenetics Workshop.

While the use of registry-based data for this analysis allowed us to capture a broad population with very long term follow-up, it presents additional limitations to our analysis. Our study population was limited to available data and as such the analysis may have been underpowered to detect all significant associations. Due to incomplete collection of rejection data by the registry over our study period, we were unable to analyse this important outcome. Information relating to specific causes of graft failure was limited and could not be meaningfully reported.

Overall, the findings of this pragmatic, registry-based study are inconclusive, however, within its many limitations, our study does suggest a signal for an association between EpMM and the important long term outcomes of graft survival and re-transplantation in this population. The lack of significant associations in our key adjusted analyses may reflect that our study was underpowered to detect a true difference in this well-matched cohort. Or alternatively, this may reflect an important reality, that immunological matching is only one factor that determines long term outcomes for children receiving renal transplants and must be weighed against a number of other factors including organ quality and expediting access

to transplantation when making decisions about the best transplant option for each individual child.

Chapter 9 Healthcare professional and community preferences in deceased donor kidney allocation

9.1 Preface

The content of this chapter is under preparation for submission for in The American Journal of Transplantation.

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Author contributions are described in the thesis preface.

9.2 Abstract

Deceased donor kidneys are a scarce community resource, therefore the principles underpinning organ allocation should reflect societal values. This study aimed to elicit community and healthcare professional preferences for principles guiding the allocation of kidneys from deceased donors and compare how these differed across the two populations. A best-worst scaling survey including 29 principles in a balanced incomplete block design was conducted among a representative sample of the general community (n=1237) and healthcare professionals working in kidney transplantation (n=206). Sequential best-worst multinomial logistic regression was used to derive scaled preference scores (PS) (range 0-100). Thematic analysis of free text responses was performed. Five of the six most valued principles among members of the community related to equity, including priority for the longest waiting (PS 100), difficult to transplant (PS 94.5) and sickest (PS 93.9), and equality between genders (PS 94.0) whereas the top four principles for healthcare professional focused on maximising utility (PS 89.9-100). Latent class analysis identified unmeasured class membership among community members. Qualitative analysis revealed themes related to considering recipient behaviour and lifestyle in allocation in both study populations. Discordant views between community members and healthcare professionals should be considered in the design of deceased donor kidney allocation protocols.

9.3 Background

Deceased donor kidney transplantation relies on the altruism of donors and their families in providing an organ that will ultimately benefit an individual with whom they have no personal connection. As such, the general community who make up the potential pool of organ donors should be considered a key stakeholder in organ allocation policy. The need for kidneys far exceeds the current supply, therefore deceased donor organs are a scarce resource and the ethical principles that underpin their utilisation should reflect the values of all stakeholders. The algorithms that determine how this resource is allocated are typically designed by healthcare professionals with expertise in the clinical and technical aspects of transplantation. It is not clear that the principles valued by this group necessarily reflect the priorities of the broader community.

Scarcity produces a situation in which competing ethical principles that underpin decision making must be balanced[23]. As the world faces an unprecedented crisis due to the global COVID-19 pandemic, the difficult decisions about the rationing of essential resources have been brought sharply into focus[22]. On one hand, principles of equity and justice should be considered to ensure that those most in need or most deserving have access to the resource, and that access is not arbitrarily contingent on an individual's characteristics such as gender, ethnicity, socioeconomic situation or age. It can also be argued that the overall benefit derived from the resource should be maximised or perhaps that allocation should be designed to reward and promote socially beneficial behaviours. These principles are often in conflict and the effect of prioritising one may inadvertently result in compromising another.

While technical expertise is an essential pre-requisite for those designing the allocation system, the experience and knowledge of experts may result in views and priorities that are distinct from the population who are providing the resource. In recent years, an increased focus on ensuring that researchers and health care professionals partner with patients and community members in protocol design and funding applications has aimed to ensure that the allocation of resources aligns with a broad range of priorities[298,299]. Transplantation relies on a uniquely personal act of generosity in providing a precious resource and it is vital that we respect the views of the community in determining how that gift should be used.

We undertook a two-part online study examining the preferences of the community and of healthcare professional for the allocation of kidneys from deceased donors to determine how these overlapped and differed.

9.4 Methods

Study population and recruitment

Community: Adult participants were recruited from the community using an Australia wide online research panel administered by an external organization (Survey Sampling International, Shelton, CT, USA). Quota sampling on age, sex, ethnic background and State/Territory of residence was used to obtain a respondent population that was broadly representative of Australian adults with a target sample size of 1,000. Data was collected during March 2018.

Healthcare professionals: Healthcare professionals working in Australia in organ donation or kidney transplantation were recruited through email invitation and advertising in professional society newsletters. Email invitations were sent to all registered contributors to the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), all members of the Renal Society of Australia (RSA) and Transplant Nurses Association (TNA). An invitation was sent to all renal unit department heads with the request it be circulated amongst unit staff. Advertisements were placed in the newsletters of the Australian and New Zealand Society of Nephrology (ANZSN), the Transplant Society of Australia and New Zealand (TSANZ), RSA and TNA. Data was collected between October 2018 and January 2019.

Best-Worst Scaling

An object case (Case 1) best-worst scaling survey, a type of discrete choice experiment, was conducted[300]. Participants were shown a list of possible allocation principles and asked to choose the best (most important) and worst (the least important) to them. The participants were shown multiple questions, each presenting a subset of the allocation principles, and preferences estimated from the choices using multinomial logit regression[301,302]. Survey design and analysis is underpinned by random utility theory[303,304].

Allocation Principles:

Based on the findings of qualitative and quantitative studies in the Australian community, literature review and expert panel, a total of 29 principles for allocation were identified[267,268,305]. To assist with interpretation of results, principles were grouped into four broad themes as proposed by Persad, Wertheimer and Emanuel(2009)[22,23]: 1) treating

people equally - including principles focussing on equity in access across different patients groups and queuing justice, 2) favouring the worst-off/most likely to benefit - including principles focussing on priority for patients with greater need or potential to benefit, 3) maximizing total benefit - principles that maximised the overall efficiency of resource use, and 4) promoting and rewarding usefulness – principles that encouraged socially positive behaviour or rewarded previous actions. The theme of maximising total benefit was further divided into principles in which utility maximization was either explicitly stated or implied, to account for differences in underlying knowledge between the two study populations. Theme groupings were used for reporting only and were not indicated to respondents within the survey. The full list of principles is provided in Table 9.6 (supplementary table).

Survey design:

A partially balanced incomplete block design was used. Both designs used the same 29 principles. However, due to differences in technical knowledge between the study populations and to increase the statistical power of the healthcare professional survey with a smaller target population, the number of principles included in each choice set varied between the two surveys. The community survey consisted of 8 blocks of 10 choice sets, each containing 4 choice options with each participant randomly assigned to complete one block. The healthcare professional survey consisted of 5 blocks of 15 choice sets with 6 choice options in each set. Both designs used the same 29 principles. The survey was programmed using Qualtrics *(Qualtrics Software, Provo, UT, United States)*. An example of a single best-worst task from the community study is shown in Figure 9.1. The best-worst tasks were preceded by background information on deceased donor organ allocation and instructions on how to complete the tasks. The principles were displayed in simple

language; no additional information was provided as to meaning or implications. A free-text response question offering the opportunity to nominate additional principles was included at the end of the surveys. Self-reported demographic details were collected. For the community study these included: State/Territory of residence, rural or metropolitan location, gender, age, education, marital status, ethnicity, first language spoken at home and knowledge/experience of end stage kidney disease and kidney transplants. For the healthcare professional study these included: State/Territory of practice, rural or metropolitan location, gender, age, professional role, years practicing and whether or not the respondent had practiced overseas.

Figure 9.1 Example of a best worst choice set from the community study

Participants are requested to select what they view as the most important principle related to deceased donor kidney allocation followed by the least important principle.

9.4.1 Analysis

Quantitative analysis

The relative importance of the 29 allocation principles was determined using a sequential best worst multinomial logit (SBWMNL) regression model[301] by applying a conditional logistic regression model to an expanded choice set in order to capture information on sequential choice behaviour. Each choice set consisting of J alternatives was duplicated to create a second choice set including J-1 alternatives by excluding the option chosen as 'best'. Principles in the 'worst' choice set were recoded as -1 to give a negative utility for the principle selected as least important. Regression coefficients were then estimated conditioned on the choice sets with standard errors clustered around respondent ID to allow for intragroup correlation. Following this approach, the regression coefficients of this function provided the relative importance scores for each outcome [306]. As the regression coefficients have the same underlying scale, preference scores were able to be adjusted to any scale, in this case we use a scale of 0-100 (least important-most important).

Heterogeneity of preferences was evaluated using a panel specification of a latent class BWMNL regression model. A latent class model can be used to identify segments or classes of differing preference structures across unobserved subgroups[307]. Membership within a class is a latent property and it is only possible to estimate the likelihood that a respondent may be a member of a latent class. Linking probability of class membership to respondent covariates provides an understanding of the composition of the classes and the characteristics of individuals with differing preference profiles. An iterative process based on model fit criteria and the ability to predict composition of individual classes was used to

define the optimal number of latent classes included in the model (for the community study, 3 classes were specified; for the healthcare professional study, latent class analysis did not yield meaningful insights and is not reported).

The partially balanced incomplete block design block design was undertaken using SAS version 9.4, SBWMNL analysis was conducted using Stata version 15.0 (*Stata Corp, Texas, USA*) and latent class analysis using NLOGIT V6 *(Econometric Software Inc.)*.

Qualitative analysis

Thematic analysis of the free-text responses was undertaken. Themes were identified by authors ED and MS, deductively through application of pre-defined principles covered in the survey as well as inductively, to capture additional relevant concepts. Initial codes and themes were reviewed by the investigator group and refined to reach agreement.

The study was approved by the University of Sydney Human Research Ethics Committee (HREC:2017/869).

9.5 Results

9.5.1 Participants

A total of 1,237 people were recruited to participate in the community survey. Of these, 115 (9%) did not consent to proceed with the survey, 40 (3%) started but did not complete the survey and 1,082 (87%) completed the survey. The characteristics of those completing the survey are shown in Table 9.1. In general, the proportion of participants in the key demographic groupings were similar to the Australian adult population as estimated from the 2016 Australian population census from the Australian Bureau of Statistics (ABS)[308]. Key differences included an underrepresentation of younger people in the study population and a higher proportion with a tertiary education compared to the general population. A small number of respondents had end stage kidney disease (32 (3%) on dialysis and 16(1%) with a transplants). Almost half (48%) of participants of all respondents were registered as organ donors. The majority reported to be 'slightly' or 'not at all' knowledgeable about chronic kidney disease (68%), transplant (70%) and organ donation (50%).

A total of 206 healthcare professionals consented to the study, completed at least one question and were included in the analysis (169 (82%) completed all questions), demographics of this population are also shown in Table 9.1. Almost half (48%) were doctors. Women were over-represented in the healthcare professional survey (68%) compared to both the general population (51%) and the community survey (50%). The majority of respondents were aged 41-60 years old (51%) and had been practicing for over 10 years (58%).

Table 9.1 Demographics of survey respondents compared with the Australian population from the Australian Bureau of Statistics Census, 2016

		Community Study	Healthcare Study	Australian Population
Characteristic	Levels	n(%)	n(%)	%
N		1082	206	
Age group:	18-30	146 (14)	12 (6)	22
	31-40	158 (15)	30 (15)	18
	41-50	168 (16)	51 (25)	17
	51-60	240 (22)	53 (26)	16
	61-70	212 (20)	11 (5)	13
	>70	95 (9)	4 (2)	12
	Missing	63 (6)	45 (22)	-
Gender:	Female	540 (50)	141 (68)	51
	Male	542 (50)	64 (31)	49
	Non-Binary	n/a	1 (1)	n/a
State/Territory:	Australian Capital Territory	11 (1)	7 (3)	2
	New South Wales	322 (30)	52 (25)	32
	Northern Territory	7 (1)	2 (1)	2
	Queensland	218 (20)	40 (19)	20
	South Australia	115 (11)	8 (4)	7
	Tasmania	33 (3)	8 (4)	1
	Victoria	265 (25)	71 (35)	26
	Western Australia	111 (10)	18 (9)	10
Location:	Metropolitan	812 (75)	165 (80)	71
	Regional/Rural	270 (25)	41 (20)	29
Ethnicity:	Australian (Indigenous)	18 (2)		3
	Australian (non-indigenous)	789 (73)		67
	Other Ethnicity	275 (25)		30
Main language:	English	1004 (93)		90
	Other	78 (7)		10
Relationship status:	Married /defactor	647 (60)		58
	Single	250 (23)		18
	Separated/Divorced	142 (13)		9
	Widowed	36 (3)		5
	Other	7 (1)		10
Highest education:	University/Technical College	732 (68)		55
	High School	191 (18)		47
	Primary School	158 (15)		6
	Non Stated	-		9
Annual household income (pre-tax):	Not Stated	126 (12)		10
	Up to $35,000	224 (21)		18
	$35,000- $65,000	255 (24)		29
	$65,001- $95,000	169 (16)		11
	$95,001 - $125,000	131 (12)		10

	$125,001 - $150,000	84 (8)		6
	>$150,000	93 (9)		15
End Stage Kidney Disease	Dialysis	32 (3)		
	Transplantation	16 (2)		
Registered Donor	Yes	498 (46)		
CKD Knowledge:	Not knowledgeable at all	276 (26)		
	Slightly knowledgeable	457 (42)		
	Moderately knowledgeable	246 (23)		
	Very knowledgeable	78 (7)		
	Extremely knowledgeable	25 (2)		
Transplant Knowledge	Not knowledgeable at all	323 (30)		
	Slightly knowledgeable	430 (40)		
	Moderately knowledgeable	241 (22)		
	Very knowledgeable	69 (6)		
	Extremely knowledgeable	19 (2		
Organ Donation Knowledge	Not knowledgeable at all	156 (14)		
	Slightly knowledgeable	386 (36)		
	Moderately knowledgeable	371 (34)		
	Very knowledgeable	118 (11)		
	Extremely knowledgeable	51 (5)		
Healthcare professional role:	Nephrologist		87 (42)	
	Transplant Surgeon		6 (3)	
	Doctor in Training		7 (3)	
	Nurse/Transplant Coordinator		73 (35)	
	Donation Coordinator		12 (6)	
	Allied Health		6 (3)	
	Other		15 (7)	
Practice years:	Less than 2 years		27 (13)	
	2 to 5 years		26 (13)	
	5 to 10 years		33 (16)	
	More than 10 years		119 (58)	
Previously worked overseas:	Yes		47 (23)	
	No		158 (77)	

9.5.2 Preferences for allocation principles:

The regression coefficients and 95% confidence intervals for the sequential best worst MNL model are presented in Table 9.2. Scaled preference scores represent the relative importance of each principle for each study population and are also shown in Table 9.2 and Figure 9.2.

Of the 6 principles with a preference score (PS) of greater than 90 in the community survey, 5 of these related to equity within allocation. These included principles related to treating people equally, for example prioritizing those who had been waiting the longest (PS 100.0) and equality in access regardless of gender (PS 94.0) or socioeconomic circumstances (PS 91.9). Principles of needs-based equity were also rank highly, with priority for those who are difficult to transplant (PS 94.5) and for the sickest patients (PS 94.0) both being highly preferred. Of the principles related to maximizing total benefit, maximizing quality of life (PS 93.2) was a key priority in the community study, followed by maximizing survival (PS 89.3) and the overall number of transplants (PS 85.6).

In contrast, 5 of the 6 top priorities for healthcare professionals related to maximizing the overall benefit of the system. Allocating kidneys with the best predicted survival to either the recipients with the best predicted survival (PS 100.0) or to the young (PS 90.1) were key priorities, as were maximising overall survival (PS 93.0) and quality of life (PS 87.0) and minimizing the total waiting time across the waiting list (PS 89.9). The highest ranked equity principle was ensuring equality of access for Indigenous candidates (PS 87.0).

Table 9.2 Relative preferences for principles guiding deceased donor kidney allocation among community members and healthcare professionals

	Community				Healthcare Professionals			
Summary of Principle	Coefficient	95% CI		Preference Score	Coefficient	95% CI		Preference Score
Priority for Longest Waiting	1.58	1.45	1.72	100.0	2.62	2.26	2.99	81.4
Priority for Difficult to Transplant	1.49	1.36	1.63	94.5	2.63	2.30	2.97	81.7
Gender Equality	1.49	1.35	1.63	94.0	2.42	2.05	2.78	75.0
Priority for Sickest	1.48	1.34	1.63	93.9	1.42	1.12	1.72	44.1
Maximise QoL	1.47	1.34	1.60	93.2	2.74	2.43	3.05	85.2
Socioeconomic Equality	1.45	1.30	1.60	91.9	2.66	2.25	3.07	82.7
Maximise Survival	1.41	1.28	1.54	89.3	3.00	2.68	3.31	93.0
Maximise Transplants	1.35	1.21	1.49	85.6	1.92	1.51	2.34	59.7
Priority for Greatest Improvement in QoL	1.33	1.20	1.47	84.4	2.24	1.90	2.58	69.5
Minimize Waiting Time	1.29	1.15	1.42	81.6	2.89	2.54	3.25	89.9
Priority for Children	1.26	1.12	1.40	79.9	2.60	2.23	2.97	80.8
Equality for Indigenous Persons	1.25	1.11	1.40	79.7	2.80	2.44	3.17	87.0
Priority for Poorest QoL	1.19	1.06	1.31	75.6	1.32	1.03	1.61	41.0
Best Kidney to Best Survival	1.18	1.04	1.31	74.9	3.22	2.86	3.58	100.0
Best Kidneys to Young	1.12	0.98	1.25	71.1	2.90	2.56	3.25	90.1
Priority for First Transplant	0.92	0.79	1.04	58.9	0.94	0.66	1.22	29.2
Priority to Prior Donors	0.87	0.73	1.01	56.0	1.62	1.22	2.02	50.3
Young Donors to Young Recipients	0.78	0.65	0.91	50.4	2.47	2.10	2.83	76.6
Priority for Young Adults	0.78	0.65	0.91	50.1	1.93	1.60	2.26	59.9
Age Equality	0.77	0.65	0.90	49.9	0.89	0.64	1.14	27.7
Consider Future Transplant Opportunities	0.49	0.37	0.60	32.1	1.78	1.42	2.14	55.3
Equality Regardless of Adherence	0.39	0.26	0.52	26.0	0.61	0.31	0.91	18.9
Choice to Accept Poorer Kidney	0.38	0.26	0.50	25.5	1.57	1.27	1.87	48.8
Equality Regardless of Past Lifestyle	0.38	0.25	0.51	25.5	1.37	1.05	1.68	42.4
Poorer Kidneys to Older Patients	0.30	0.19	0.42	20.7	1.30	1.01	1.59	40.5
Poorer Kidneys to Poorer Survival	0.26	0.15	0.38	18.3	1.71	1.37	2.05	53.1
Priority to Registered Donors	0.17	0.04	0.29	12.4	0.01	-0.29	0.31	0.2
Priority for Older Adults	Reference			2.0	Reference			0.0
Priority to Same State	-0.03	-0.17	0.10	0.0	0.69	0.36	1.03	21.5

Caption for Table 9.2 *Regression coefficients and 95 % confidence intervals for the sequential best worst conditional logistic regression model are shown. These have been scaled to preference scores that represent the relative importance of each principle for each study population ranging from 0 to 100 where 0 is the lowest preference and 100 is the top preference. QoL – quality of Life*

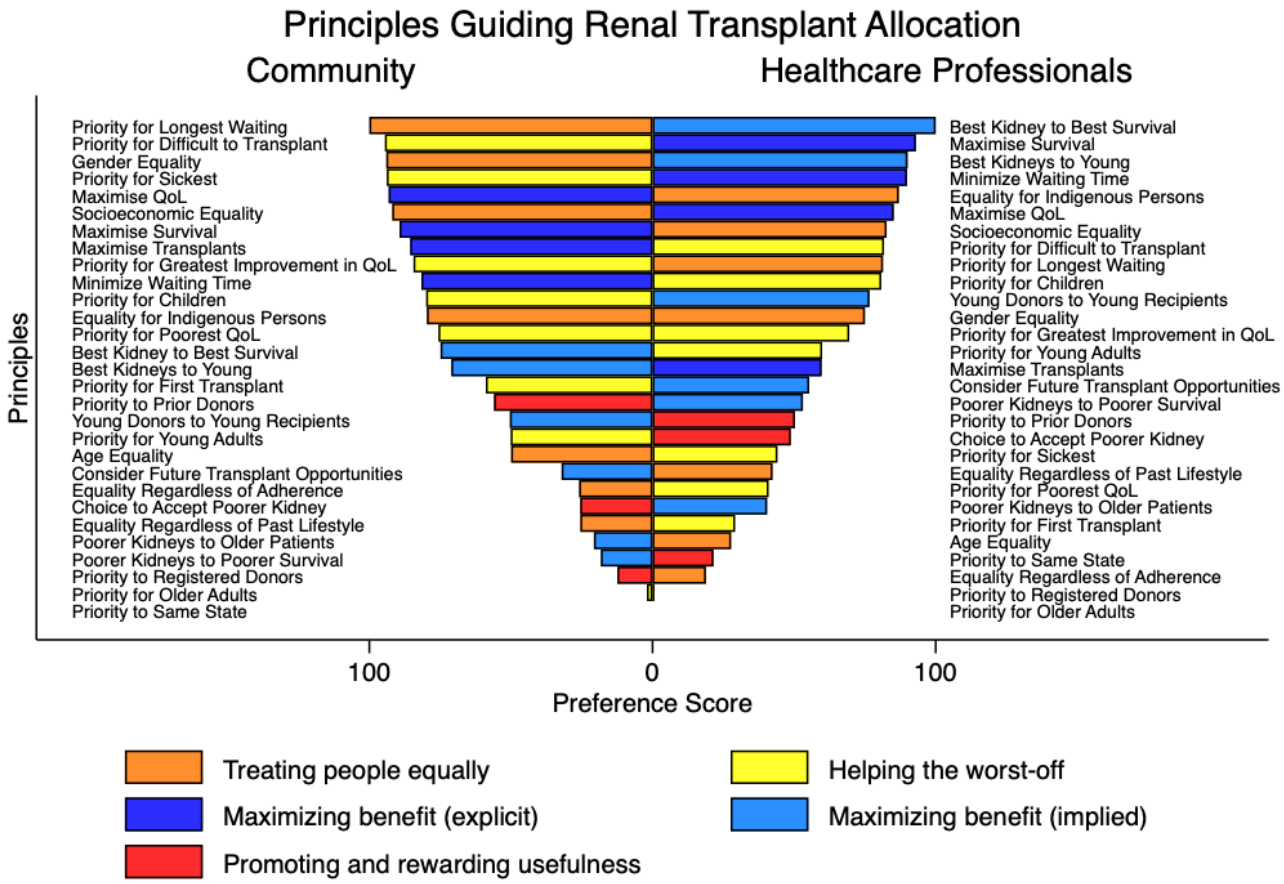

Figure 9.2 Relative preferences for principles guiding deceased donor kidney allocation among community members and healthcare professionals

Preference scores are scaled coefficients from the sequential best worst conditional logistic regression model and represent the relative importance of each principle for each study population ranging from 0 to 100 where 0 is the lowest preference and 100 is the top preference. QoL – quality of Life

Principles that promoted or rewarded social usefulness were of lower priority for both study populations. For example, priority for prior kidney donors or for those who were registered as organ donors had preference scores ≤50 for both community members and healthcare professionals. Other principles that were not highly prioritised by either cohort included priority for older recipients or for allocation of local donor organs to local recipients.

9.5.3 Latent Class Analysis:

The latent class analysis of the community study identified 3 distinct classes with average class probabilities of 0.29, 0.42, 0.30, respectively. Coefficients of principles for each latent class in the 3 class model are shown in Table 9.5 (supplementary table). The class 1 preference profile is dominated by the principles reflecting treating people equitably with the most valued principle being equity for socially disadvantaged groups followed by priority to the longest waiting, equity between genders and for Indigenous Australians, maximising transplants and priority to the sickest. The class 2 profile is dominated by principles that reflect a consideration for helping the worst-off with the most highly valued principles being priority to the sickest, longest waiting, more difficult to transplant, first transplant and poorest quality of life. Finally, the class 3 profile is dominated by principles favouring the young and maximising survival particularly for children. This was followed by organs with best predicted survival to the young, greatest improvement in quality of life, organs with best predicted survival going to individuals also with best predicted survival and young donors to young.

Five predictors of membership of latent classes 1 and 2 relative to 3 were identified (Table 9.3). Latent class 1 (*treating people equitably*) can be characterized as being less likely to include men (odds ratio[95%CI]; 0.49 [0.28-0.87]), and registered donors (0.61 [0.35-1.04]) and more likely to be younger than 50 years (2.84 [1.55-5.19]. Class 2 (*helping the worst off*) is less likely to be a registered donor (0.35[0.21-0.55]) or have little or no knowledge of kidney disease (0.59 [0.36-0.95]), and more likely to live in a metropolitan area (2.03 [1.17-3.51]) and to be younger than 50 years (1.68 [1.02-2.74]). Consequently, class 3 (*age and survival*) are more likely to be older than 50 and to be registered donors compared to classes 1 and 2.

Latent class analysis of the healthcare professions study did not yield add to the interpretation of the existing BWSMNL analysis and is not reported.

Table 9.3 Predictors of class membership in the latent class analysis of the sequential best worst MNL model of community preferences in deceased donor kidney allocation

	Latent Class								
	1			2			3		
Predictor	Odds ratio	95% Confidence interval	P	Odds ratio	95% Confidence interval	P	Odds ratio	95% Confidence interval	P
Male	0.49	0.28-0.87	0.01	0.81	0.50-1.30	0.37			
Metropolitan resident	0.87	0.50-1.51	0.62	2.03	1.17-3.51	0.01			
Registered donor	0.61	0.35-1.04	0.07	0.35	0.21-0.55	<0.01		Reference	
Younger than 50 years	2.84	1.55-5.19	<0.01	1.68	1.02-2.74	0.04			
Little or no knowledge of kidney disease	1.02	0.57-1.84	0.94	0.59	0.36-0.95	0.03			

9.5.4 Qualitative analysis:

Free text comments that reiterated or commented on principles contained within the preceding survey items were not included in the qualitative analysis as they did not contribute additional insights beyond the quantitative analysis above. Illustrative comments of themes described are shown in Table 9.4.

Thematic analysis of remaining free text comments from community members revealed three additional key themes: *considering health behaviours, penalising antisocial behaviour* and *decisional burden*. A prominent theme in free text responses was that those with past or current *lifestyle behaviours* deemed to be unhealthy (e.g. alcohol consumption, smoking, "bad lifestyle") should be penalized or given lower priority in organ allocation, particularly if those behaviours contributed to their illness. Conversely, respondents commented that patients who adhered to a healthy lifestyle should be prioritized. Some respondents commented that candidates with *anti-social behaviours* such as criminal activity, illicit drug use or having tattoos, should be given lower priority or even excluded from the allocation of organs. Many described *decisional burden* in completing the survey, reporting they felt poorly equipped to make such decisions and that these should be deferred to doctors with appropriate expertise. Respondents commented on the burden of "playing God" and expressed relief that others were responsible for these decisions.

Analysis of free text responses in the healthcare professional survey again revealed a prominent theme focused on recipient health and *lifestyle behaviours and adherence*. Additional themes identified included considering *contribution to society*, *patient choice* to accept higher risk organs, *simplicity and transparency* and a focus specifically on *highly*

sensitized patients. A broader range of themes in the healthcare professional study and the length of many free text comments likely represents pre-existing opinions on the subject in this population.

Table 9.4 Illustrative quotations from the general community and healthcare professionals

Theme	Quotation
Illustrative Quotations from Community Members	
Considering health behaviours	*"The current system is most ethical, but if you are going to prioritise, preference should be given to those whose organ failure is not their fault e.g. those with self-inflicted liver failure from alcohol, lung failure from smoking and kidney/ pancreas failure from type 2 diabetes from poor diet should be a lesser priority."*
	"People who live a lifestyle that gives them a poorer chance of surviving the transplant should be lower down the list than those who take care of their health."
Anti-social behaviour	*"Those with a criminal history should not be considered for a kidney transplant...eg those in jail or have been released"*
	"Person who has history of using drugs (illegal drugs) should not be given the new kidneys."
Decisional burden	*"Not something I feel qualified to comment on. Medical practitioners are best to decide."*
	"I do not envy the team making these allocation decisions."
	"It is a very difficult area to attempt to bring such black and white decision processes to bear. I certainly don't envy the people who have to do it."
Illustrative Quotations from Health Care Professionals	
Lifestyle behaviours and adherence	*"Behaviour: Potential adult recipients should demonstrate their intention to respect the gift of a transplant by their conduct in their pre-transplant life (keeping appointments, taking medications as prescribed, accepting advice from health professionals)"*
	"I believe there should be emphasise on behaviours epically life style, compliance to medication and diet mental health as the organs are valuable commodity and we don't want them to be wasted."
Contribution of society	*"Single parents whose children's lives will be improved because of a parent who can care for them because of a kidney transplant should be given some priority."*
	"Priority to get workers back to work - supporting families and improving quality of life for their spouses and children. Priority to get children and young adults back to education and life, to improve their long term outcomes in contributing to society"
Patient choice to accept risk	*"Patients should be able to choose if they wish to take donor kidneys at higher risk than average, eg due to infection risk or young age"*
	"Patient choice in receiving kidneys with poorer predicted outcome."
Simplicity and transparency	*"Values and principles vary from person to person and it can make things more complicated than they should be."*
	"The balance between equity and utility should always be a transparent. The process should be inclusive not exclusive,"
Highly sensitized patients	*"In those potential recipients that are highly sensitized - they should preferentially receive a deceased donor kidney if crossmatch negative and minimal or no DSA."*
	"Priority to be given to those that are highly sensitized and to children, after that time wait or best HLA matching."

Illustrative quotations from the general community and healthcare professionals in response to the question "Are there any values or principles that you would like to nominate as being important when considering allocating kidneys from deceased donors?"

9.6 Discussion

This best worst scaling study demonstrates important differences in the priorities held by members of the community compared with healthcare professional working in the transplant field regarding the allocation of the scarce resource of deceased donor kidneys. While principles relating to equity, both in terms of treating people equally and favouring the worst off, are most valued by members of the general community, higher relative priority for the maximisation of utility is seen amongst healthcare professionals. Not only do the specific principles prioritised by each group help to inform the design of allocation protocols, but these differences highlight the need for policy makers and those developing allocation protocols to be aware of their own potential biases and to consider a broad range of stakeholder priorities. Furthermore, using latent class analysis we identified preference heterogeneity among respondents in the community. This highlights the need to consider multiple viewpoints as preferences and values may vary depending on characteristics such as age, gender and personal experience.

Previous studies on community preferences for the allocation of solid organ transplants have highlighted the complexity in balancing competing ethical principles that underpin attitudes to this challenging issue in the broader population. In a systematic review of fifteen qualitative and quantitative studies, Tong et al (2010)[32] identified seven themes describing community preferences including maximum benefit, social valuation, moral deservingness, prejudice, 'fair innings', 'first come, first served' and medical urgency. A more recent systematic review by Oedingen et al (2019)[33] used a framework of principles of distributive justice to examine the same issue. They found that whilst studies showed a

preference for a rational utilitarian ethical model, this was contradicted by a simultaneous priority to treat the most in need and concluded that "data on public preferences regarding clear trade-offs in donor organ allocation are skill lacking". Similarly, in a qualitative study into perspectives of nephrologists on deceased donor kidney wait listing and allocation, Tong et al (2011)[79] explored a key theme of reconciling tensions between achieving equity and maximizing societal benefit. By using a BWS study design, we are able to report on the relative priorities of competing preferences in these two populations, adding additional insights to previous research.

Among the broader community we found that while principles that explicitly described maximizing utility were prioritized (preference score range 82-93) the strongest preference was for principles relating to treating people equally and helping those most in need. This would indicate that whilst there may be general community support for policies designed to maximise utility, when making trade-offs between equity and utility within the organ allocation system, the broader community may favour policies that ensure justice and fairness over those that maximise efficiency at the cost of inequality. This finding is similar to an earlier discrete choice experiment in general solid organ transplantation, in which Howard et al (2015)[305] found that for the general community "lower pre-transplant life expectancy (need) was more important that higher post-transplant life expectancy (utility)". They concluded that movements toward implementing allocation algorithms favouring utility may be misaligned with community preferences. In contrast, there was a clear predominance of principles that maximise the efficiency of the system amongst health care professionals.

Since the introduction of longevity matching in the US Kidney Allocation System (KAS) in 2014, there has been significant interest in the Australian transplant community about the potential role of survival indices in the Australian context[60,61]. Although not yet used in allocation of kidneys, the Kidney Donor Performance Index (KDPI) is now reported with all kidney offers [65,309]. Of the top 3 principles for healthcare professionals, 2 related explicitly to survival-based matching (allocating the organs with best predicted survival to recipients with the best predicted survival or to younger recipients), and the third to overall maximization of patient survival. This finding indicates support for longevity-based matching amongst transplant clinicians in Australia and its prominence may indicate awareness of the current policy debate. In contrast, among the general community, survival base matching had a preference score of 74.9 with 13 of 29 principles rated more highly. This finding highlights the need for healthcare professionals to consider the potential unintended consequences of implementing survival based matching in Australia to ensure that the impacts of any changes in policies also align with priorities of the broader community.

Deceased donor kidney transplantation is a highly specialized field of medicine and despite the provision of uniform background information to both groups, prior knowledge is highly likely to have influenced the participants' responses in this study. For example, we found that community members prioritized principles in which maximizing benefit was explicitly stated (eg "Overall patient survival should be maximised" (preference score 89.3)) higher than principles in which increased utility was implied, but specialized knowledge may have been required to appreciate this (eg "Organs with best predicted survival should be given preferentially to those who have the best predicted survival" (preference score 74.9)). The prominent theme of *decisional burden* in free text comments from community members

affirms the difficultly many had in weighing priorities in this complex and specialised area. The current structure for consumer input into kidney allocation policy in Australia, where 1-2 members of the community participate in the Renal Transplant Advisory Committee (RTAC) comprising up to 22 healthcare professionals[310], may place excessive decisional burden on these individuals and alternative strategies for community consultation should be considered[311]. For healthcare professionals, a high degree of pre-existing knowledge of the current allocation system may result in responses that reflect the specific deficiencies of the current system, such as the need to specifically prioritize highly sensitized transplant candidates. Only a small number of people with personal experience of end stage kidney disease were included in our community study and further studies into the preferences of this population are also needed, as well as into the preferences of family and friends of previous organ donors.

Preference scores in our study indicate the relative priority for principles within each population and those with low scores may still be supported, albeit with lower importance. Despite this, insights can be gained from examining those principles not prioritized strongly by either population. For example, giving priority to registered donors had a preference score of 12.4 among the general community and 0.2 among health care professionals, suggesting that introducing a bonus for this population (as has been implemented in Israel[46]) is not a key priority in Australia. Noting the lower priority seen across both groups for certain principles, such as the allocation of kidneys to a recipient within the same region as the donor or priority for registered donors, may help inform which components of the current or a proposed allocation algorithm could be omitted or given a different weight.

The 29 principles used in our study were based on review of previous literature and refined by iterative expert panel review, however, there may be important principles that were omitted and we can't rule out the presence of framing effects relating to the wording of the principles [312,313]. For example, the principle included in our study related to lifestyle behaviors was phrased *"Access to transplantation should be equal regardless of whether or not past lifestyle behaviours contributed to the cause of their kidney disease"* and received relatively low preference scores among both the community and healthcare professionals (25.5 and 42.4 respectively). In the qualitative analysis, themes relating to penalizing poor health behaviors and rewarding positive lifestyle choices were seen in both groups and healthcare professionals commented specifically on prioritizing patients for whom a transplant would enable them to contribute to society by returning to work or caring for children, for example. A principle framed as *"Priority should be given people for whom past lifestyle behaviours has not contributed to the cause of their kidney disease"* may have received a higher preference score that the framing that was included in the survey. In the particular case, our framing was intended to align with the Australian National Health and Medical Research Council's Ethical Guidelines for Organ Transplantation from Deceased Donors[29] that state "There must be no unlawful or unreasonable discrimination against potential recipients on the basis of … (the) need for a transplant arising from the medical consequences of past lifestyle". The contradiction of some views expressed in free text responses with current ethical guidelines demonstrates that while considering stakeholder preferences is important in developing allocation policy this does not replace the need for a vigorous ethical critique of allocation policy.

As the current global COVID-19 pandemic draws into sharp focus the difficult choices that must be made in allocating scarce resources, our findings highlight the need for policy makers to recognize that the priorities held by healthcare professionals do not necessarily reflect those of the broader community and other stakeholders. Current policy debates among healthcare professionals in deceased donor kidney allocation focused on optimising organ and recipient survival matching and maximising overall utility should remain cognisant of the community preference to ensure equitable access to organs. Further studies that explore acceptable tradeoffs such as discrete choice experiments, focus groups, and consultation with people experiencing kidney disease are important next steps in a comprehensive approach to stakeholder engagement in the redesign of kidney allocation systems.

Table 9.5 Latent class analysis of community preferences study (supplementary table)

Principle	Coefficient	95% Confidence Interval		p value
Class 1				
Socioeconomic Equality	3.48	3.14	3.81	<0.001
Priority for Longest Waiting	3.00	2.69	3.31	<0.001
Gender Equality	2.86	2.54	3.18	<0.001
Equality for Indigenous Persons	2.77	2.44	3.10	<0.001
Maximise Transplants	2.75	2.43	3.08	<0.001
Priority for Sickest	2.71	2.38	3.04	<0.001
Maximise QoL	2.66	2.34	2.98	<0.001
Priority for Difficult to Transplant	2.58	2.27	2.90	<0.001
Minimize Waiting Time	2.57	2.25	2.89	<0.001
Maximise Survival	2.54	2.24	2.84	<0.001
Priority for Poorest QoL	2.43	2.12	2.73	<0.001
Age Equality	2.28	1.93	2.64	<0.001
Priority for Greatest Improvement in QoL	1.86	1.56	2.17	<0.001
Best Kidney to Best Survival	1.49	1.20	1.79	<0.001
Priority for Children	1.26	0.96	1.56	<0.001
Best Kidneys to Young	1.26	0.94	1.57	<0.001
Priority to Prior Donors	1.21	0.91	1.51	<0.001
Priority for First Transplant	1.12	0.84	1.41	<0.001
Choice to Accept Poorer Kidney	0.97	0.68	1.25	<0.001
Equality Regardless of Past Lifestyle	0.91	0.56	1.25	<0.001
Consider Future Transplant Opportunities	0.86	0.58	1.15	<0.001
Equality Regardless of Adherence	0.86	0.50	1.21	<0.001
Priority for Young Adults	0.67	0.37	0.98	<0.001
Young Donors to Young Recipients	0.63	0.33	0.93	<0.001
Poorer Kidneys to Older Patients	0.54	0.26	0.81	<0.001
Priority for Older Adults	0.33	0.06	0.60	0.016
Poorer Kidneys to Poorer Survival	0.26	-0.02	0.54	0.068
Priority to Registered Donors	0.00			
Priority to Same State	-0.24	-0.56	0.09	0.149
Class 2				
Priority for Sickest	0.99	0.74	1.24	<0.001
Priority for Longest Waiting	0.91	0.67	1.15	<0.001
Priority for Difficult to Transplant	0.48	0.25	0.71	<0.001
Priority for First Transplant	0.47	0.25	0.69	<0.001
Priority for Poorest QoL	0.46	0.23	0.70	<0.001
Gender Equality	0.45	0.22	0.67	<0.001
Priority for Children	0.43	0.19	0.66	<0.001
Maximise QoL	0.39	0.17	0.61	0.001
Maximise Survival	0.34	0.11	0.57	0.003
Minimize Waiting Time	0.33	0.10	0.56	0.005
Priority for Greatest Improvement in QoL	0.30	0.07	0.53	0.012
Priority to Prior Donors	0.29	0.06	0.51	0.012
Best Kidney to Best Survival	0.26	0.04	0.49	0.021
Equality Regardless of Adherence	0.22	0.00	0.45	0.055
Maximise Transplants	0.18	-0.05	0.40	0.127
Best Kidneys to Young	0.13	-0.10	0.36	0.273
Equality Regardless of Past Lifestyle	0.12	-0.12	0.36	0.336
Age Equality	0.12	-0.12	0.35	0.340

Poorer Kidneys to Poorer Survival	0.11	-0.11	0.32	0.323
Equality for Indigenous Persons	0.10	-0.15	0.34	0.446
Socioeconomic Equality	0.05	-0.19	0.29	0.683
Young Donors to Young Recipients	0.03	-0.20	0.27	0.797
Priority to Registered Donors	0.00			
Priority to Same State	0.00	-0.23	0.23	0.997
Poorer Kidneys to Older Patients	0.00	-0.22	0.21	0.966
Priority for Young Adults	-0.01	-0.24	0.23	0.962
Consider Future Transplant Opportunities	-0.08	-0.30	0.14	0.492
Choice to Accept Poorer Kidney	-0.13	-0.35	0.10	0.273
Priority for Older Adults	-0.31	-0.52	-0.09	0.005
Class 3				
Priority for Children	2.43	2.05	2.81	<0.001
Best Kidneys to Young	2.36	2.01	2.72	<0.001
Priority for Greatest Improvement in QoL	2.29	1.99	2.60	<0.001
Best Kidney to Best Survival	2.14	1.83	2.45	<0.001
Young Donors to Young Recipients	1.86	1.53	2.20	<0.001
Maximise QoL	1.86	1.57	2.16	<0.001
Maximise Survival	1.86	1.56	2.16	<0.001
Priority for Young Adults	1.84	1.49	2.20	<0.001
Priority for Difficult to Transplant	1.80	1.49	2.10	<0.001
Maximise Transplants	1.69	1.37	2.01	<0.001
Gender Equality	1.63	1.31	1.95	<0.001
Socioeconomic Equality	1.62	1.25	1.99	<0.001
Equality for Indigenous Persons	1.37	1.01	1.72	<0.001
Minimize Waiting Time	1.36	1.06	1.65	<0.001
Priority for Longest Waiting	1.21	0.91	1.50	<0.001
Priority to Prior Donors	1.11	0.78	1.43	<0.001
Priority for First Transplant	1.04	0.74	1.33	<0.001
Priority for Sickest	0.87	0.55	1.19	<0.001
Priority for Poorest QoL	0.83	0.54	1.12	<0.001
Consider Future Transplant Opportunities	0.52	0.23	0.82	0.001
Poorer Kidneys to Older Patients	0.05	-0.24	0.34	0.736
Choice to Accept Poorer Kidney	0.03	-0.25	0.31	0.822
Poorer Kidneys to Poorer Survival	0.00	-0.30	0.31	0.978
Priority to Registered Donors	0.00			
Age Equality	-0.06	-0.36	0.23	0.672
Equality Regardless of Past Lifestyle	-0.31	-0.64	0.02	0.062
Equality Regardless of Adherence	-0.39	-0.73	-0.06	0.020
Priority to Same State	-0.53	-0.84	-0.21	0.001
Priority for Older Adults	-0.56	-0.84	-0.28	<0.001

Three latent classes were identified with class probabilities of 0.29, 0.42 and 0.30 respectively. Coefficients and 95% confidence intervals for principles are shown for each class.

Table 9.6 List of principles guiding the allocation of deceased donor kidneys for transplantation (supplementary table)

Category (Use in reporting only)	Principle and description as included in the best worst scaling survey	Short Description (used in reporting only)
Treating people equally	**Indigenous and non-Indigenous Australians should have equal access** *Allocate kidneys across the wait-list so that access to transplantation is the same for all people regardless of whether or not they are Aboriginal or Torres Strait Islander Australians*	Equality for Indigenous Persons
Treating people equally	**Age should have no influence on allocation** *Allocate kidneys across the wait-list so that all age groups have equal access*	Age Equality
Treating people equally	**Women and men should have equal access** *Allocate kidneys across the wait-list so that access to transplantation is the same regardless of whether or not they are male or female*	Gender Equality
Treating people equally	**People from higher and lower socioeconomic backgrounds should have equal access** *Allocate kidneys across the wait-list so that access to transplantation is the same for all people regardless of social disadvantage*	Socioeconomic Equality
Treating people equally	**Access to transplantation should be equal regardless of whether or not past lifestyle behaviours contributed to the cause of their kidney disease** *Allocate kidneys across the wait-list so that access to transplantation is the same for all people irrespective of whether their life-style contributed to their kidney failure*	Equality Regardless of Adherence
Treating people equally	**Access should be equal regardless of prior problems in sticking to medication schedules and healthy lifestyles** *Allocate kidneys across the wait-list so that access to transplantation is the same for all people irrespective of whether they are known to have difficulties in maintaining the strict medication schedules and a healthy lifestyle*	Equality Regardless of Past Lifestyle
Treating people equally	**Priority should be given to those who have been on the wait-list for the longest time** *Selectively allocate kidneys across the wait-list so that those who have been waiting the longest get preferential access*	Priority for Longest Waiting
Favouring the worst off/most likely to benefit	**Priority should be given to children over adults** *Selectively allocate kidneys across the wait-list so that children are given preferential access*	Priority for Children

Favouring the worst off/most likely to benefit	**Give priority to those for whom it is difficult to find a compatible kidney** *When a suitable kidney is available this should be allocated first to those where a compatible kidney is most difficult to find rather than those where it is less difficult*	Priority for Difficult to Transplant
Favouring the worst off/most likely to benefit	**Priority should be given to those waiting for their first transplant** *Selectively allocate kidneys across the wait-list so that those waiting for their first transplant get preferential access compared to those who have had prior transplants*	Priority for First Transplant
Favouring the worst off/most likely to benefit	**Give priority to those predicted to have the greatest improvement in quality of life** *Selectively allocate kidneys across the wait-list so that those patients who are expected to have the greatest gain in quality of life after transplantation are given preferential access*	Priority for Greatest Improvement in QoL
Favouring the worst off/most likely to benefit	**Give priority to those who have the poorest quality of life on dialysis** *Selectively allocate kidneys across the wait-list so that those with the poorest quality of life are given preferential access*	Priority for Poorest QoL
Favouring the worst off/most likely to benefit	**Priority should be given to older people** *Selectively allocate kidneys across the wait-list so that older patients are given preferential access*	Priority for Older Adults
Favouring the worst off/most likely to benefit	**Priority should be given to those who are sickest** *Selectively allocate kidneys across the wait-list so that the sickest who are most likely to die while waiting for a transplant get greater access*	Priority for Sickest
Favouring the worst off/most likely to benefit	**Priority should be given to younger adults over older adults** *Selectively allocate kidneys across the wait-list so that younger adults are given preferential access over older adults*	Priority for Young Adults
Maximizing total benefit (implied)	**Allocation should consider how the transplant will affect a person's future transplant opportunities (for second or subsequent kidneys)** *Selectively allocate kidneys taking into account how the transplant might limit a person's chance of receiving another transplant in the future*	Consider Future Transplant Opportunities
Maximizing total benefit (explicit)	**Overall the quality of life should be maximised** *Selectively allocate kidneys across all wait-list patients in a way that maximises the overall improvement in quality of life*	Maximise QoL
Maximizing total benefit (explicit)	**Overall patient survival should be maximised** *Selectively allocate kidneys across all wait-list patients in a way that maximises the total years of survival*	Maximise Survival

Maximizing total benefit (explicit)	**The number of transplants should be maximised** *Across all wait-list patients ensure that the number of donated kidneys used is maximised*	Maximise Transplants
Maximizing total benefit (explicit)	**Overall the total number of years waiting on dialysis should be minimised** *Selectively allocate kidneys across all wait-list patients so that the total number of years remaining on dialysis is minimised*	Minimize Waiting Time
Maximizing total benefit (implied)	**Organs with best predicted survival should be given preferentially to those who have the best predicted survival** *Selectively allocate kidneys so that healthier people on the wait list, who are expected to live longer after transplantation, have preferential access to organs donated from healthier donors*	Best Kidney to Best Survival
Maximizing total benefit (implied)	**Organs that have the best predicted survival should be given preferentially to young people** *Selectively allocate kidneys so that children and young adults have preferential access to organs donated from healthier donors*	Best Kidneys to Young
Maximizing total benefit (implied)	**Organs with poorer predicted survival should be preferentially allocated to older wait-list patients** *Selectively allocate kidneys so that older people on the wait list are given preferential access to organs donated from less healthy and older donors*	Poorer Kidneys to Older Patients
Maximizing total benefit (implied)	**Organs with poorer predicted survival should be preferentially allocated to wait-list patients who also have poorer predicted survival after transplantation** *Selectively allocate kidneys so that less healthy people on the wait list, who are expected to live for a shorter time after transplantation, have greater access to organs donated from less healthy and older donors*	Poorer Kidneys to Poorer Survival
Maximizing total benefit (implied)	**Kidneys from young donors should be given preferentially to young people** *Selectively allocate kidneys so that children and young adults have greater access to organs donated from younger donors*	Young Donors to Young Recipients
Promoting and rewarding usefulness	**To minimise time on the wait list, people should be able to choose to accept donated organs that have poorer predicted survival** *Individuals could elect to accept an organ from an older and less healthy donor rather than wait for organs from donors with better predicted outcomes after transplantation (younger and healthier)*	Choice to Accept Poorer Kidney
Promoting and rewarding usefulness	**People who have previously donated a kidney should be given priority** *Allocate kidneys across the wait-list so that people who previously donated one of their kidneys are given preferential access to all donated kidneys*	Priority to Prior Donors

Promoting and rewarding usefulness	**Priority should be given to people who are registered organ donors** *Allocate kidneys across the wait-list so that people who are registered donors are given preferential access to donated kidneys*	Priority to Registered Donors
Promoting and rewarding usefulness	**Organs should be preferentially allocated to wait-list patients located in the same state/territory as the donor** *Donated kidneys should be selectively allocated to people on the wait-list who live in the same State or Territory as the donor over those living a different State or Territory*	Priority to Same State

List of principles included in the best worst scaling choice experience. Note that the category and short description for each principle were used for reporting only and were not included in the survey.

Chapter 10 Simulating a proposed new allocation system to improve priority for highly sensitized kidney transplant candidates in Australia

10.1 Preface

Thus far in this thesis I have presented a number of studies addressing various aspects of the current deceased donor kidney transplantation system in Australia and evidence that can inform the re-design of the system. In this final chapter, I present a framework for simulating proposed changes and assessing their likely impacts and give a real-world example of how this framework has already been used to inform the current process of policy design in Australia. Whereas the preceding 7 chapters have been presented as concise manuscripts that have either been accepted for publication in academic journals or are in the process of submission, a detailed description of the methods for this final study are outlined below as well as a narrative of how this body of work has had a direct impact on allocation policy reform through a process of iterative simulations presented to the committee responsible for kidney transplantation allocation policy in Australia. The methods, results and subsequent impact of the work outlined below serve as a proof of concept for what will hopefully be an ongoing robust and evidence-based approach to the design of organ allocation algorithms in Australia.

Matthew P Sypek is the sole author of this chapter. The contributions of Philip Clayton, Aarti Guylani and Peter Hughes to the work reported in this chapter are described in the preface to the thesis and in relevant sections below.

10.2 Background

As demonstrated in Chapter 6 of this thesis, transplant candidates who are highly sensitized against a broad range of HLA antigens experience a dramatically reduced rate of deceased donor kidney transplantation in Australia compared to candidates with lower degrees of sensitization and internationally it has been shown that these patients experience higher rates of mortality on the waiting list[314]. We have shown that the current priority for highly sensitized patients in Australia's deceased donor kidney allocation system, which is based on a calculated panel reactive antibody (cPRA) of >80% and only applies to well matched kidneys, is outdated and is not well targeted to address the true disadvantage associated with very high degrees of sensitization.

Responsibility for developing protocols for deceased donor organ allocation in Australia sits with the Transplantation Society of Australia and New Zealand (TSANZ)[34]. The Renal Transplant Advisory Committee (RTAC) is the primary clinical forum for policy design, discussion, review and ratification of kidney transplant allocation policy[310]. This committee reports to TSANZ as well as the Australian and New Zealand Society of Nephrology (ANZSN) and Kidney Health Australia (KHA). Consisting of up to 24 members, RTAC has representation from the local renal transplant advisory committees of each of Australia's five transplanting regions as well as representatives for transplanting surgeons, tissue typing laboratories, the donation sector, consumers and other key stakeholders. The policy changes developed and ratified by RTAC are ultimately recommended by TSANZ for implementation by the Australian Government's Organ and Tissue Authority (OTA).

In the past, development of kidney transplant allocation has been heavily reliant on expert opinion but has also strived to incorporate "all elements of a continuous quality improvement process of kidney allocation"[64]. This process has included comprehensive reviews of outcome data[64] and the commissioning of targeted reports examining specific elements of allocation policy and international practice[44]. However, unlike some other international kidney transplant programs including France[73], the United Kingdom[315] (UK) and the United States[53] (US), who have used various approaches to simulating new allocation proposals prior to implementation, simulation has not previously been used to directly inform policy development in Australia.

Kidney transplant allocation is a complex process that must balance a number of competing priorities and has potentially profound impacts of the lives of individuals with end stage kidney disease. The work presented in Chapter 9 of this thesis demonstrates that the priorities of various stakeholders in the principles that should guide allocation do not necessarily align. Interventions aimed at achieving a specific goal, such as improving access to rapid transplantation for children in the US through the Share 35, may result in unintended consequences, in this case a decrease in living donor transplant rates and increase in HLA mismatches for paediatric recipients[70]. Simulation presents an opportunity to harness the potential of technological advances, comprehensive data collection and statistical modelling to estimate the likely effects of proposed policy interventions and screen for unintended consequences prior to implementation[71–74].

We present the methods for developing and validating a kidney transplant allocation simulation platform to model deceased donor kidney allocation in Australia followed by a description of how this simulation has been used to refine new policy proposals in Australia, thus providing proof of concept for the ongoing role of simulation in the future redesign of deceased donor kidney allocation in Australia.

10.3 Aims

1) To create a model capable of simulating the allocation of deceased donor kidneys in Australia in a contemporary cohort of patients whose degree of sensitization is accurately defined by cPRA
2) To demonstrate accuracy of the model compared to actual allocation or kidneys in Australia using the current allocation algorithm
3) To develop a simulation of proposed changes to the Australia deceased donor kidney allocation system as put forward by RTAC and demonstrate the likely impact of the proposed changes
4) To use iterative simulation to refine and improve policy proposals
5) To demonstrate the potential for simulation to play an ongoing role in the development, evaluation and implementation of deceased donor kidney allocation policy in Australia

PART 1: SIMULATION DEVELOPMENT AND VALIDATION

10.4 Part 1 Methods

10.4.1 Overview

Simulations were performed using a modified version of the Kidney Pancreas Simulated Allocation Model (KPSAM) software (version 4.2) which was developed in the United States by the Scientific Registry of Transplant Recipients (SRTR) to simulate proposed changes to the US allocation system prior to the implementation of the new Kidney Allocation System (KAS) in 2014[53]. The software was adapted to simulate deceased donor kidney only transplantation in Australia using historical data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), the National Organ Matching Service (NOMS) and the Australia and New Zealand Organ Donation Registry (ANZOD).

The KPSAM software was first adapted for the Australian context by A/Prof Philip Clayton (PC) and presented in his PhD thesis, Outcomes of Kidney Transplantation for the University of Sydney in October 2013[316]. Further work on these simulations was performed by Ms Aarti Guylani (AG) in her role as statistician at the ANZDATA registry. The work presented in this chapter involved a complete update of simulation performed by the author (MS) using data from March 2016-December 2018 with major revisions of the code used to generate input files and statistical models, however, I wish to acknowledge extensive work performed by SRTR in building this software, and PC and AG in developing the earlier versions of this simulation model for the Australian context. In 2015 the ANZDATA registry database underwent a major revision including the renaming of the majority of variables within the

database, therefore, all files used to develop inputs for the Australian adaptation were revised by the author. Where major changes to the code used in generating input files was required in the process of model validation, these are described in detail below. Methods for prior work are outlined in brief with attribution as appropriate.

The processing and analysis of simulation outcomes also builds on previous work by PC and AG, but major revisions and extensions to this aspect of the simulation were also conducted by the author as reported below.

10.4.2 Software description

The KPSAM software simulates deceased donor kidney and pancreas allocation using an event-sequenced Monte Carlo technique[76]. A number of event handlers process a series of time stamped events that are either input driven based on user created input files, or internally generated as a result of modelled processes in which the probability of an event occurring is calculated based on a user specified formula and then compared to random number between 0 and 1 to determine the outcome of the event within the simulation.

The follow events can occur during the simulations:

1) Organ arrival (input driven)
2) Patient arrival (input driven)
3) Status changes for patients who have not yet received a graft (input driven)
4) Unacceptable antigen changes for wait list candidates (input drive)
5) Relisting events for patients whose grafts fail (sampled by the model)

6) Status changes for relisted graft recipients (sampled by the model)

7) Deaths for graft recipients not on the waiting list (sampled by the model)

Whereas the event handlers related to patient status updates and unacceptable antigen changes simply update the state of the waiting list, the organ arrival event triggers a number of additional processes. Firstly, the event handler performs a match run by reordering the waiting list according to user defined criteria in the allocation rules. Starting with the highest ranked candidate the event handler simulates the organ acceptance process by calculating the probability of acceptance based on a user specified logistic regression model that can include patient, donor and transplant variables. The event handler samples from a uniformly distributed random variable and compares this to the probability of acceptance to determine the outcome of the organ offer. If the offer is accepted, the event handler places the patient on a list of graft recipients and schedules a graft failure event.

The time to graft failure can be determined by either a Cox Proportional Hazards Model or Weibull Survival Model (a Cox Proportional Hazards model was used in the Australian simulations). Again the model samples from a random number from the U(0,1) distribution and uses this to determine the survival time by inverting the complementary cumulative probability distribution of survival time and reading data from a pre-specified step function. Other set pf possible outcomes (death and re-listing events) and their relative probabilities is associated with each graft failure date[317].

If the offer is not accepted, the event handler repeats the above process sequentially down the match list until a specified maximum number of offers at which point the organ is discarded.

A full list of the input files required to run KPSAM is described in

Table 10.1. Each of these input files requires a specific structure as outlined in the KPSAM user guide. Detailed methods for the production of input files from registry data are outlined below.

Table 10.1 User generated input files required by the Kidney Pancreas Simulated Allocation Model (KPSAM)

Original File Name	Description
Patient Input Files	
Waitlist.txt	List of patients active on the waiting list at the beginning of the simulation period, including demographics, HLA typing, cPRA, co-morbidities etc.
Patients.txt	Timestamped list of patients who arrive on the waiting list during the simulation, including demographics, HLA typing, cPRA, co-morbidities etc.
Status.txt	Timestamped list of patient status updates that occur during the simulation period (with updates to demographics, HLA typing, cPRA, co-morbidities etc.)
UnAccAnt.txt	Timestamped list of unacceptable antigens entered for patients on the waiting list and updates during the simulation period
Organ Input Files	
Organs.txt	Timestamped list of all organ arrivals including donor details.
Statistical Models	
DefAccept.txt	Contains the definition for calculation to perform to determine whether a patient accepts an organ offer. This includes the field references and coefficients from the organ acceptance logistic regression model.
DefSurvival.txt	Contains the definition for the calculation to determine how long before graft failure or death after transplantation. This includes the field references and coefficients from the deceased donor graft survival Cox Proportional Hazards model as well as a step function used to assign survival times.
DefNRDeath.txt	Contains the definition for the calculation to perform to determine patient survival after graft failure for a graft recipient who is not relisted.
DefPartRelist.txt	Contains the definition for the calculation to perform to determine whether a kidney-pancreas patient who receives an isolated kidney or an isolated pancreas will immediately relist for the organ not received. Note this was not used in the Australian simulations.
Allocation Rules	
DefMethods.txt	List of allocation method definitions. Separate allocation rules can be specified for subsets of organs (eg organs from a particular region or within a specific donor age group)
DefBoostDef.txt	Contains the definitions of rules to boost allocation scores base on candidate, transplant or donor factors. Note that this was not used in Australian simulations as bonus points (eg for paediatric status) were accounted for in the DefMethods.txt file.
Data Definitions	
DefDataDef.txt	Contains the definitions of default data fields used in the simulation for forming allocation rules, score boost specifications, acceptance calculations, and post-transplant survival calculations. Default definitions must be specified to run the program.
OptDataDef.txt	Contains the definitions of optional user specified data fields used in the simulation for forming allocation rules, score boost specifications, acceptance calculations, and post-transplant survival calculations.
Systems Files	
LocMap.txt	List of all transplanting centre IDs mapped to local and regional areas (not used in Australian simulations)
ABOChart.txt	List of blood group compatibility definitions.
AntigenSplit.txt	Identifies antigen pairs that are not considered a mismatch.
UnAntEquiv.txt	Identifies antigen pairs that are considered equivalent.
Payback.txt	Contains the initial status of payback accounting for kidneys at start of simulation. Note this was not used in Australian simulations.
ZeroMM.txt	Contains a list of recipients in the simulation with zero HLA -A, -B and -DR mismatches for each donor. This is an optional file designed to improve the computational efficiency of the simulation.

In addition to uploading all input files, the user must also specify the period of simulation, the number of iterations to be performed, the number of organ offers prior to organ discard and a seed for random number generation.

A number of output files are produced by the KPSAM software which record events that occurred during the simulation (match lists, transplants, relists, patient removals, deaths), patient characteristics at the time of events, probabilities of acceptance as calculated by the model, and waiting list and patient status lists (transplanted, relisted, removed, deceased) at the end of the simulation.

10.4.3 Construction of input files

All input files used for simulation of deceased donation allocation in Australia were constructed using a de-identified data extract from the ANZDATA registry. Data relating to waiting list status and calculated panel reactive antibody (cPRA) was sourced from NOMS (now OrganMatch). Although separate approval was obtained from NOMS for data use in this project, a NOMS dataset is routinely linked to ANZDATA under the terms of a standing memorandum of understanding between the two bodies and data used for this study was sourced directly from ANZDATA, therefore all analysis was performed using a pre-linked, deidentified data. Data relating to organ donors was sourced from the ANZOD registry which is run and administered by the ANZDATA registry. The ANZDATA and ANZOD datasets are available as a single, linked, deidentified dataset subject to an overarching data governance framework.

The adaptation of the KPSAM software for the Australian context has occurred over three periods: initial adaptation using data from 28/06/2006-31/12/2010, performed primarily by PC; revised simulation using data from 01/01/2010-31/12/2014, performed by AG, MS and PC; and the current (2020) simulation using data from 01/03/2016-31/12/2018, performed by MS. Although the primary purpose of updating the simulation for this project was to incorporate cPRA data that was not available on previous patient cohorts, due to a revision of the ANZDATA database in 2015 that involved a renaming of most variables within the database, all input files were revised for the current simulations. A number of components of input files were refined and optimised during this process as outlined below.
All input files, including statistical models were constructed using Stata version 14 (StataCorp, College Station, Texas).

Patient input files (Initial waiting list, arrival and status updates)

Patient input files were created for all patients listed as active on the NOMS kidney only waiting list at any point between the periods of 01/03/2016-31/12/1018. The period was chosen as 01/03/2016 was the date that cPRA was introduced for defining sensitization in Australian deceased donor kidney allocation. Patients listed for combined kidney-pancreas transplantation and other multi-organ transplants were not included in the simulation as these are allocated separately within Australia.

A dataset of patient demographics, HLA typing, blood group, dialysis start date and other characteristics was constructed from ANZDATA records and merged with a longitudinal dataset of patient comorbidities that is collected on an annual basis by the registry.

Reconstruction of cPRA dataset

As outlined in Chapter 6 of this thesis, a longitudinal dataset of changes in cPRA for patients waitlisted for kidney transplantation in Australia does not exist. Therefore, this was reconstructed using the available data according to the following methods:

Data sources:

1) The NOMS "Waitlist" dataset tracks the status (active, on hold etc) of all patients listed for deceased donor kidney transplant over time.

2) The NOMS "Organ Matches" dataset contains the allocation list for all deceased kidney donors, including the potential recipient cPRA at the time of matching. Since March 2016, cPRA has been calculated using a standardised national calculator based on antibody exclusions as defined by local tissue typing laboratories. Most laboratories have used a standard MFI threshold of 4,000 for defining antibody exclusions (8,000 in some laboratories) with additional curation based on antibody characteristics and clinical circumstances.

3) The NOMS "Antibody List" dataset contain lists of anti-HLA antibodies detected over time for patients registered on the transplant waiting list. The methodology for antibody detection has changed over time and serum treatment and MFI cut off used for antibody exclusions have historically varied across transplant laboratories. Antibody lists in this dataset are separated by HLA class and are accompanied by the "population frequency" or estimated percentage of the donor population excluded by that list of antibodies as entered by the testing laboratory. This dataset is a record of all antibody testing by tissue typing laboratories and it cannot be determined from

this dataset which antibodies were actually used for exclusions at specific historical time points.

As the “Organ Matches” dataset contains the actual cPRA used in allocation at the time of organ offer this was the primary dataset used to re-construct a historical record of changes in cPRA. The following assumptions were used: living donor matches were excluded; if there were multiple matches on the same day the highest cPRA was used; cPRA was assumed to be constant between matches with the most recent cPRA carried backwards to the date of previous match; the last recorded cPRA was carried forward until the end of the follow up period.

Eleven percent of the cohort did not have any cPRA data in the “Organ Match” dataset. For these patients, cPRA histories were reconstructed from the “Antibody List” dataset. The following assumptions were used: cPRA was calculated using class I and class II antibody specificities using the current OrganMatch cPRA calculator (antibodies to HLA -A, -B, -C, -DRB1, -DRB3/4/5, -DQA1 and -DQB1 with MFI≥4000 were included in calculations which were based on HLA frequencies in a panel of 2,115 previous Australian kidney donors); cPRA was assumed to remain constant until a higher cPRA was recorded; the last cPRA recorded was carried forward until the end of the follow up period.

The longitudinal dataset of patient status updates and comorbidities was combined with the reconstructed longitudinal cPRA dataset to create a record of cPRA for all active patients over the study period which was then merged with the patient demographics and comorbidities dataset to produce a timestamped list of all patient status updates throughout the simulation period.

Imputation of patient status updates for patients who received deceased donor transplants

The KPSAM simulation software requires a complete patient waiting list status record for all patients within the simulation across the entire simulation period. For patients who received a deceased donor transplant in ANZDATA records, this is not available between the date of their transplant and the date of graft failure. As we do know what would have happened to an individual if they had not received their deceased donor graft and the simulation requires a complete history for all patients, it was necessary to impute a waiting list history after the date of transplantation for patients who received a deceased donor graft in ANZDATA records during the study period. The methods for waiting list history imputation were developed by PC and outlined in his PhD thesis[316]. In brief, this involved censoring of the waiting list history for each patient who received a deceased donor kidney transplant. Each censored patient was then matched to their nearest neighbour on the basis of their projected survival on the waiting list using the linear prediction from the waiting list survival model described below and the waiting list history from the neighbour was appended to the censored patient's history. This was to ensure that the appended waiting list histories were derived from a patient with similar prognosis. These steps were repeated until no censored patients remained.

Simulation of interstate debt

Australia's deceased donor kidney allocation rules contain a payback mechanism between various transplanting regions based on the balance of kidneys shipped in and out of each region. As the KPSAM software is unable to track the inter-regional balance of kidneys

shipped during the simulation a workaround was developed to account for this allocation rule.

Each patient status record within the simulation was assigned a randomly generated Centre Credit Difference Score based on their waiting list region that was generated according to the Poisson distribution around a distribution mean m, where m varied from -4 to +5 across the five transplanting regions and was determined by review of recent shipping balances and iterative trial and error. A similar process was performed for each donor organ and the Centre Credit Difference Score used in allocation was determined by comparing the candidate and organ scores within the simulation.

Unacceptable Antigen Lists

Due to the availability of more detailed antibody testing data in the period 2016-2018, the methods for defining antibody exclusions were completely revised for the updated simulation. Antibodies were listed as exclusions if they were detected either by complement dependent cytotoxicity (CDC) cell-based assay or by single antigen bead (SAB) solid phase assay with a mean fluorescence intensity (MFI) of 4000. This figure was chosen at is the most common threshold used for defining unacceptable antigens in Australian Tissue typing laboratories. Due to limitations of donor typing available for simulation purposes, only antibodies to HLA -A, -B and -DR were included in antibody exclusions.

Organ Input Files

A list of all organs retrieved for the purpose of transplantation in Australia during the study period with detailed donor characteristics was generated from the Australia and New

Zealand Organ Donor Registry (ANZOD). Organ transplanted as part of multiorgan transplants were excluded.

Centre Credit Difference Scores were randomly assigned to organs according to a Poisson distribution with distribution mean varying across transplanting regions as outlined above. The Kidney Donor Performance Index (KDPI) for each organ was determined by calculating the Kidney Donor Risk Index (KDRI) based on the US Organ Procurement and Transplant Network's (OPTN) donor only formula[59] and scaling this from 1-100 based on a reference population of all utilised donors in Australia during the preceding three years[65]. Donor race was assumed to be non-African American and if hepatitis C status was missing this was presumed to be negative.

In a significant revision compared to previous simulations, organs that were discarded due to surgical or anatomical reasons were excluded from the current simulations. The decision to exclude these organs was based on KPSAMs mechanism for discarding organs based on a set number of organ offer declines. This is highly dependent on the organ offer conversion model outlined below. Organs discarded due to anatomical issues (eg a malignant lesion discovered at retrieval) or surgical issues (eg an irreparable arterial tear at time of retrieval) would not be offered at all and therefore would fall outside the mechanism of discards utilised in the simulation model. We also chose to exclude organs in which the results of a biopsy was listed as the reason for discard. Pre-implantation biopsy for the purpose of assessing organ quality and determining acceptance is a relatively uncommon practice in Australia[247] and once again the simulation model did not have capacity to adequately account for this variable in determining the outcome of organ offers.

Statistical Models

The survival models used in these simulations were initially developed by PC and revised and updated by AG and MS. The description of survival model construction outlined below is adapted from PC's PhD thesis and included here for completeness. The survival model estimates were updated by MS using more contemporary data, however the methods remained unchanged.

Due to issues encountered in validating the simulations in the contemporary cohort, the offer conversion logistic regression model was completely rebuilt by MS and although the methods were similar to those used in earlier iterations, the construction of the offer conversion model outlined below represents original work by the author.

Graft survival after deceased donor transplant

Patients receiving deceased donor kidney only transplants between 01/01/2000 and 31/12/2014 in Australia were used in constructing the graft survival models using Cox proportional hazards regression. The outcome was defined as all cause graft failure, including death with a functioning graft. The cohort was randomly split into 2:1 construction and validation cohorts stratified by age group, ethnicity, diabetes status and donation pathway (donation after brain death vs donation after circulatory death). A clustered robust variance estimator was used to account for some patients receiving more than one deceased donor graft.

Variables tested for inclusion in the model were: 1) recipient variables: age, gender, ethnicity, primary renal disease, body mass index (BMI), diabetes, ischaemic heart disease, cerebrovascular disease, peripheral vascular disease, chronic lung disease, history of smoking, duration of renal replacement therapy, peak panel reactive antibody (PRA) 2) donor variables: age, gender, ethnicity, cause of death (medical vs other), donation pathway, diabetes, hypertension, and 3) transplant factors: HLA mismatch, total ischaemic time and transplant era. Recipient gender, BMI, diabetes status and the presence of ischaemic heart disease were empirically included in the multivariable model with other factors included in the base model if statistically significant at a p value of <0.20 on univariate analysis. All potential 2-way interactions were assessed for statistical and clinical significance. A backward selection procedure was used to remove non-significant factors until all factors were significant at a p value of <0.05 and/or considered clinically significant. The proportional hazards assumption was examined using plots of scaled Schoenfeld residuals. Model discrimination was assessed using Harrell's C statistic and validation performed with the remaining third of patients/transplants. The entire cohort was then combined and the model re-run to produce maximally precise coefficients for survival projections.

Non-relist death after graft failure

Patients experiencing graft failure between 01/01/2010 and 31/12/2014 in Australia who were not relisted during their duration of follow up were used in the construction of the model to predict non-relist death after graft failure using Cox proportional hazards regression. The outcome was defined as death and patients were censored at date of last follow up.

Variables testing for inclusion in the model were: age at graft failure, gender, ethnicity, BMI, primary renal disease, ischaemic heart disease, peripheral vascular disease, cerebrovascular disease, diabetes, chronic lung disease, history of smoking and duration of RRT at graft failure. Factors were included in the base model if significant on univariate analysis at a p value of <0.20. Due to a small number of statistically significant predictors on univariate analysis, limited backward selection was performed and variables were kept in the model if clinically significant.

Organ Offer Acceptance

As described in the overview of the model structure, when an organ is allocated to wait listed candidate in KPSAM, the organ event handler determines whether the offer is accepted by calculating the probability of acceptance based on a user specified logistic regression model and then sampling from a uniformly distributed random variable to compare to the probability of acceptance and determine the outcome of the organ offer.

All kidney only transplant offers of organs retrieved for the purpose of kidney donation in the period 2010-2014 were used in the derivation cohort. Kidneys that were discarded based on surgical or anatomical issues or based on the results of a donor biopsy were excluded as were those used for multiorgan transplantation. Where two kidneys were transplanted en bloc or as a dual kidney transplant, these were considered as a single organ. A binary logistic regression model was used to determine the predictors of offer acceptance. As decisions for each kidney from the same donor are not independent, a panel model was specified with a random intercept for donor.

Variables tested for inclusion in the model were: 1) recipient factors, age, gender, ethnicity, primary renal disease, BMI, duration of RRT, diabetes, ischaemic heart disease, peripheral vascular disease, cerebrovascular disease, chronic lung disease, history of smoking, number of previous grafts, peak PRA at the time of offer; 2) donor factors, age, gender, ethnicity, cause of death (medical vs other), donation pathway, diabetes, hypertension; 3) transplant factors, HLA mismatch, local allocation within each transplanting region. The linear relationship between continuous variables and the log odds of offer acceptance was assessed by comparing the fit of alternative fractional polynomial models and by plotting the linear predictor against the mean of quantiles of each continuous independent variable. As a result of violations of this assumption, recipient age and PRA were modelled as categorical variables and donor age was modelled as a linear spline with knots at 20 and 65 year of age. Variables were considered for inclusion within the multivariate model if statistically significant on univariate analysis at a p values of <0.2 or if clinically significant. All potential 2-way interactions were assessed for statistical and clinical significance. Non-significant factors were removed from the model in a backwards selection procedure until all factors were significant at a level of <0.05 and or considered clinically significant. Model discrimination was tested using the C-statistic.

Variable definitions, allocation rules and systems files

The optional data definitions input file was updated to include all addition variables required for simulation within the Australian context and for the statistical models outlined above. The current Australia deceased donor kidney allocation rules as defined by the Transplantation Society of Australia and New Zealand (TSANZ)[36] were coded according to

KPSAM specifications. ABO blood group compatibility definitions, HLA split antigens and HLA unacceptable antigen equivalents were coded according to definitions used by OrganMatch. Note the Payback.txt and LocMap.txt functions of the KPSAM model were not used in the Australian simulation.

10.4.4 Model specifications

The simulation was run over the period 01/03/2016-31/12/2018 as a single iteration. The number of organ offers prior to organ discard was set at 30 as this produced a reasonable approximation of actual organ discards and was thought to be a clinically plausible number. The random number generator seed was set to 82513044 in order to ensure reproducibility of results.

10.4.5 Assessment of model accuracy

A national deceased donor kidney allocation program represents a highly complex system and no single metric can meaningfully represent the accuracy of simulations.
In order to perform a comprehensive assessment of accuracy and adequacy of our simulations for the purpose of validating the model we developed a multidimensional report based on KPSAM output files using both formal hypothesis testing and graphic representation of outcomes.

The recipient and transplant characteristics of transplanted organs were compared between the simulation and actual transplants performed using ANOVA for normally distributed continuous variables, the Wilcoxon rank-sum test for non-normally distributed continuous variables and the Pearson's chi-squared test for categorical variables.

Patient outcomes were also assessed across the entire population and by relevant subgroups according to: age group, gender, ethnicity, degree of sensitization, region and ABO blood group. For each of these subgroups comparison between the simulation and actual outcomes were presented graphically across the following domains: number of transplants performed, transplant rate (per 100 active waiting years), kidney donor performance index (KDPI) or transplanted organs (presented as the percentage in each KDPI quintile), HLA antigen mismatches of transplants performed (out of 6 potential mismatches at HLA -A, -B and -DR, both the mean and as the percentage at each level of mismatch), and the percentage of transplants allocated through various tiers of allocation (national, regional (HLA matching), regional (waiting time) and national override).

10.4.6 Initial assessment and iterative redesign

The methods outlined above represent a concise presentation of the final methods used in adapting the KPSAM software for the Australian context. In reality, the development and validation of the model required a somewhat challenging process of assessing the simulation output and attempting to find and resolve issues that were producing unacceptable inaccuracies. Initial simulations that were run with input files derived from previous methods used by PC and AG in earlier cohorts produced a number of anomalies that required correction in order for the modelling to be of practical use. Many of these were minor issues relating to the very specific file specifications required by KPSAM and were easily corrected (once the source of the error was able to be detected; this in itself was a challenging task as KPSAM produces relatively limited and non-specific error messages). Four key issues required more elaborate solutions and I expand on these below,

as they include important discrepancies in: number of discards, regional transplant rates and organ shipping, transplants by cPRA and calculated exposure time from the simulation. A number of approaches were employed to address each of these issues, with varying degrees of success which are outlined in brief below:

Organ discards

Initial updated simulations showed that the number of discards was far lower in the simulations compared to reality. As outlined above, mechanism for simulating discards within KPSAM is to permit a certain number of organ offers to be declined before registering the kidney as discarded. By default the software sets this number to 200 offers. The number of discards in the simulation is a function of both the permitted number of organ offers and the equation used to define offer acceptance, and adjusting either of these will increase or decrease the discard rate accordingly. Initial attempts to approximate the discard rate by iteratively adjusting the number of organ offers were successful in achieving accurate results, however when later refinements were made to the offer acceptance model as outlined below, these caused dramatic changes in the discard rate, likely due to overfitting of the permissible number of offers. After investigating a number of alternative solutions to this issue, we decided to exclude organs from the simulation that were discarded for reasons that are not able to be accurately simulated through KPSAM. This included anatomic factors, surgical issues or based on the results of retrieval biopsies (which are performed rarely in Australia). We felt this assumption was justified as these kidneys would likely be discarded, independent of factors included in the offer conversion model and there was no way to accurately simulate this within KPSAM. The number of offer declines prior to

discard was set at 30, which was deemed to be a clinically plausible number of offers made for a marginal kidney.

Regional transplant rates and organ shipping

The mechanisms built into KPSAM to account for regional sharing of organs are specific to the structure of transplanting regions in the US and were unable to be used for the Australian simulations. A novel method of simulating Australia's system of Centre Credit Differences using a region specific random number generated based on the Poisson distribution with the mean varying by transplanting regions was developed by PC and recalibrated for the current simulations by MS. This accounted for the national payback scheme built into the national allocation protocol but did not address the issue of variation in transplanting practices across Australia's five transplanting regions. Australia is a geographically and demographically diverse country with three of the five transplanting regions having relatively smaller populations spread over large geographical area, two of which are serviced by a single adult transplanting centre and one with two adult transplanting centres (each with a single associated paediatric transplanting centre), and two of the regions having larger, more dense populations serviced by multiple transplanting centres. To address inaccuracies in regional transplant numbers and account for variation in offer acceptance practices across regions, a number of region specific variables were tested in the offer conversion model. After iterative review of simulation outcomes, the strategy that produced the most accurate transplant numbers by region was to include a factor for local allocation or local organs within the three states with smaller populations in the offer conversion model, as outlined in the methods above.

Transplants by cPRA

A major update of this simulation was the inclusion of cPRA data that had not been previously available for earlier simulations, and as a key aim of the project was to test proposals to improve transplant rates for highly sensitized patients, attention to the accuracy of transplant rates by cPRA was of particular interest. Early simulations showed excessively high rates of transplantation for highly sensitized patients in the simulation compared to reality (this had also been an issue in earlier cohorts simulated in KPSAM, without an adequate solution found). As previously mentioned, whilst the offer conversion model simulates a clinical decision to accept or decline an organ, it is also simultaneously simulating the likelihood of a positive CDC crossmatch which would exclude a patient from the allocation list. These two processes are quite distinct yet modelled by a single equation in KPSAM. This is of particularly relevance to highly sensitized patients who due to the presence of a number of anti HLA antibodies, are more likely to have a positive cross match. Recognizing that the offer conversion model was derived from a dataset that did not include patients who were excluded due to positive crossmatch but who would have been present on allocations lists in KPSAM, the initial approach to correcting this issue was to manually adjust the coefficients for cPRA categories in the offer conversion model and calibrate this based on iterative simulation. To avoid overfitting the model to the current population, manual adjustment of the coefficients were calibrated through iterative adjustments from simulations using a patient cohort from 2010-2014 before being testing in the contemporary cohort. While this strategy produced reasonably accurate transplantation rates by cPRA category, an alternative approach was later found that was cleaner and more accurate. In review of the file for generating a list of unacceptable antigens for wait listed patients, it was found that the methods for defining these had not been updated with the increased

detail of antibody data that was available in the contemporary cohort compared to previous cohorts. As a result, the methods for generating the unacceptable antigen file were completely revised (as outlined above). The simulation was rerun using the unadjusted coefficients from the original offer conversion model and found to be superior to the manually adjusted approach which likely represented a more accurate modelling of potential positive crossmatches within the simulation due to more accurate unacceptable antigen inputs.

Calculated exposure time from the simulation

On review of simulation outcomes it was noted that despite similar transplant numbers across subgroups in the simulated and actual groups, the calculated transplant rates per 100 active waiting list years were consistently higher in the simulated cohort. On further exploration it was found that the overall calculated exposure time was lower within the simulation, and that the discrepancy between actual and simulated groups increased through the duration of the simulation. This is most likely a result of the methods for imputing waiting list histories for patients who received a deceased donor transplant in reality during the simulation that are outlined above, whereby imputed histories had a bias toward less active waiting time compared to patients who remained on the waiting list in reality but who were transplanted in the simulation. Several strategies were attempted to address this issue including stratifying the propensity matching in the waiting list imputation methods by diabetes or other key patients factors, adjusting the calliper of matching radius, and revising the survival models used in propensity matching and other revision, however, an adequate solution was not discovered and this issue remains a limitation of our simulations as discussed below.

10.5 Part 1 Results

A total of 3,783 transplant candidates and 2,176 organs were included in the simulation.

10.5.1 Graft survival after transplantation

This analysis included 6,254 graft and 32,402 graft-years of follow up. There were 1,558 graft failure events during the follow up period. Results of the Cox proportional hazards model are shown in . The model showed moderate discrimination with a Harrell's C statistic of 0.65 in the derivation cohort, 0.66 in the validation cohort and 0.66 in the combined cohort.

Table 10.2 Cox proportional hazards model for graft survival model: deceased donor kidney transplants 2000-2014

Factor	Hazard Ratio	95% CI	P value
Age (Years)	1.01	[1.01, 1.02]	<0.001
Ethnicity			
Caucasian		Reference	
Indigenous Australian	1.78	[1.44, 2.20]	<0.001
Asian	0.95	[0.78, 1.17]	0.660
Other	1.27	[0.96, 1.67]	0.099
Primary Renal Disease			
Glomerulonephritis		Reference	
Analgesic Nephropathy	1.74	[1.13, 2.67]	0.012
Polycystic Kidney Disease	0.89	[0.74, 1.07]	0.216
Reflux Nephropathy	1.03	[0.84, 1.27]	0.771
Hypertension	0.98	[0.76, 1.27]	0.870
Diabetic Nephropathy	0.96	[0.74, 1.24]	0.743
Other	1.42	[1.17, 1.72]	<0.001
Uncertain	1.36	[1.06, 1.74]	0.017
Body Mass Index			
Underweight	1.23	[0.97, 1.55]	0.083
Normal		Reference	
Overweight	0.96	[0.84, 1.09]	0.534
Obese	1.13	[0.97, 1.32]	0.109
Comorbidities			
Diabetes Mellitus	1.45	[1.18, 1.80]	0.001
Peripheral Vascular Disease	1.46	[1.18, 1.79]	<0.001
Smoking History			
Current Smoker		Reference	
Never Smoked	0.62	[0.53, 0.73]	<0.001
Former Smoker	0.78	[0.66, 0.92]	0.003
Graft Number	1.29	[1.12, 1.48]	<0.001
Donor Age (Years)	1.01	[1.01, 1.02]	<0.001
Donor Hypertension	1.16	[1.02, 1.33]	0.028
HLA Mismatch (per mismatch)	1.07	[1.04, 1.11]	<0.001
Peak PRA	1.01	[1.00, 1.01]	<0.001
Total Ischaemic Time	1.02	[1.01, 1.03]	0.001
Transplant era			
2010-2014		Reference	
2005-2009	1.33	[1.12, 1.57]	0.001
2000-2004	1.38	[1.15, 1.65]	0.001

10.5.2 Non-relist death after graft failure

This analysis included 484 patients whose graft failed during the study period and who were not relisted during the period of follow up. There were 138 deaths. Results of the Cox Proportional Hazards Model are shown in

Table 10.3. The model had good discrimination with a Harrell's C statistic of 0.71.

Table 10.3 Cox proportional hazards model for patient survival after graft failure: patients with failed graft 2010-2014

Factor	Hazard Ratio	95% CI		P value
Age at Graft Failure (Years)	1.06	[1.04	1.08]	<0.001
Male Gender	1.04	[0.73	1.47]	0.835
Diabetes Mellitus	0.94	[0.61	1.47]	0.800
Ethnicity				
Caucasian		Reference		
Indigenous Australian	2.07	[1.11	3.87]	0.022
Asian	0.73	[0.37	1.46]	0.378
Other	1.11	[0.50	2.43]	0.801
Cerebrovascular Disease	2.00	[0.97	4.11]	0.060

10.5.3 Organ Offer Acceptance Model

A total of 9,435 organ offers, 2,657 of which were accepted were included in the organ offer acceptance logistic regression model. Results of the model are shown in Table 10.4.

A large number of statistically significant two-way interactions were retained in this model. Although determined based on a single equation with KPSAM, organ offer acceptance represents two distinct processes. Firstly, the performance of a CDC crossmatch between donor cells and recipient serum and secondly a highly complex and individualised clinical decision by the treating clinician and patient on whether the specific organ should be accepted for that patient. Previous adaptations of KPSAM using Australian data had encountered a number of issues with the offer conversion model. As each of the statistically significant interactions was clinically plausible, and the purpose of the model was for prediction rather than interpretation of causal inference, we felt it was appropriate to retain these interactions in the final model. Discrimination of the final model was good with a C-statistic of 0.75.

Table 10.4 Logistic regression model for kidney offer acceptance: deceased donor kidney only offers 2010-2014

Factor	Label for Interactions	Odds Ratio	[95% CI]		p value
Recipient Factors					
Male Gender	a	1.29	1.16,	1.43	<0.001
Recipient Age					
0-18 years	b	2.62	0.29,	23.29	0.387
19-64 years	c		Reference		
>65 years	d	0.43	0.08,	2.48	0.347
Recipient Ethnicity					
Caucasian	e		Reference		
Indigenous Australian	f	0.71	0.56,	0.89	0.003
Asian	g	0.94	0.80,	1.09	0.397
Other	h	0.71	0.59,	0.86	0.001
Diabetes Mellitus	i	0.49	0.17,	1.37	0.174
Duration of RRT					
<6 months	j		Reference		
6-12 months	k	1.49	0.57,	3.84	0.414
1-5 years	l	1.30	0.56,	2.99	0.544
>5 years	m	0.85	0.35,	2.08	0.718
Sensitization (PRA%)					
0%	n		Reference		
1-79%	o	1.19	0.87,	1.63	0.28
80-94%	p	1.40	0.71,	2.75	0.336
>95%	q	1.29	0.52,	3.22	0.579
Previous Transplant	r	0.58	0.37,	0.92	0.019
Donor Factors					
Donage Age					
Per Year (0-20)	s	1.01	0.99,	1.04	0.334
Per Year (>20-65)	t	1.00	1.00,	1.01	0.77
Per Year (>65)	u	0.91	0.89,	0.94	<0.001
Donation Pathway					
DCD	v	0.20	0.07,	0.55	0.002
Donor Diabetes	w	0.63	0.52,	0.77	<0.001
Transplant Factors					
HLA Mismatch (per MM)	y	0.97	0.78,	1.20	0.784
Donor and Recipient in Same State					
Queensland		0.42	0.36,	0.48	<0.001
South Australia		0.75	0.62,	0.90	0.002
Western Australia		1.84	1.46,	2.30	<0.001
Interactions					
Recipient Age and Donor Age					
b x s		1.01	0.90,	1.14	0.859
b x t		0.95	0.93,	0.97	<0.001
b x u		0.68	0.40,	1.18	0.171
d x s		1.02	0.93,	1.11	0.727
d x t		1.03	1.01,	1.04	<0.001

d x u	1.01	0.96,	1.06	0.738
Recipient Diabetes and Donor Age				
i x s	1.03	0.97,	1.09	0.352
i x t	1.01	1.00,	1.02	0.008
i x u	0.97	0.93,	1.01	0.173
Duration of RRT and HLA MM				
k x y	0.89	0.69,	1.14	0.341
l x y	0.75	0.60,	0.94	0.012
m x y	0.85	0.68,	1.07	0.177
Sensitization and HLA MM				
o x y	0.90	0.84,	0.97	0.006
p x y	0.80	0.64,	0.99	0.044
q x y	0.53	0.35,	0.79	0.002
Previous Transplant and HLA MM				
r x y	0.85	0.76,	0.94	0.003
Donation Pathway and Donor Age				
v x s	1.10	1.04,	1.16	0.001
v x t	0.98	0.97,	0.99	<0.001
v x t	0.92	0.82,	1.03	0.17

10.5.4 Validation

No single metric is adequate in assessing the ability of the simulation to accurately reproduce transplants that actually occurred over the study period. The purpose of building this simulation is to develop a tool that can model the potential impacts of changes in the allocation rules. These impacts can affect a number of different subpopulations in distinct way and therefore a multidimensional assessment framework is required to meaningfully appreciate the impacts of change. The data presented below show a series of comparisons of organ, patient and transplant factors between what actually occurred during the period 01/03/2016-31/12/2018 (labelled “ANZDATA” to reflect the source of this data) and what occurred during the KPSAM simulation of the same period (labelled “Simulation”).

A total of 3783 patients were active on the deceased donor only waiting list at some point during the study period and are included in the analysis. Figure 10.1 shows the patient outcomes at the end of the study period for actual data and in the simulation. The number of patients with functioning deceased donor transplant was similar between ANZDATA and the simulation (2128 vs 2149) as were the number of patients who had died (77 vs 75). There were a higher number of living donor grafts in ANZDATA compared with the simulation (226 vs 77).

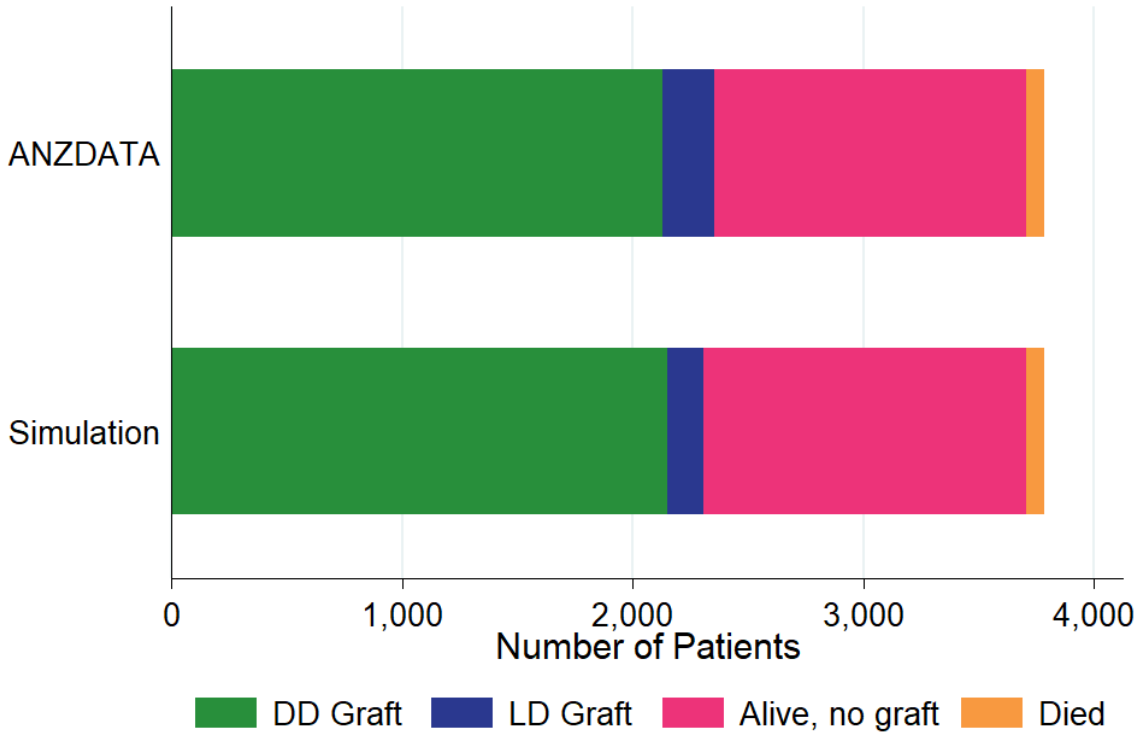

Figure 10.1 Overall patient outcomes comparing KPSAM simulation and actual events (ANZDATA)

Of the 2176 kidneys included in the study period, 2135 were transplanted in ANZDATA and 2165 in the simulation, resulting in a discard rate of 1.8% in ANZDATA and 0.5% in the simulation (note that the actual discard rate in Australia was 4.76% in 2016[227] with all organs included).

Table 10.5 *shows a comparison of recipient and transplant characteristics for* transplanted organs in ANZDATA compared to the simulation. Overall, characteristics were very similar with no significant difference in recipient age, gender, ethnicity, primary renal disease or comorbidity profile (apart from slightly higher rate of recipient coronary disease in the simulation, 19.3 vs 16.9%, p=0.037). There was no significant difference in HLA mismatches for transplants between ANZDATA and the simulation. A significant difference is noted in the proportion of kidneys going to very highly sensitized patients (cPRA ≥99%), 2.7% in ANZDATA vs 4.8% in the simulation, p=0.004. Fewer kidneys were shipped interstate in the simulation (17.6% vs 20.9%, p=0.006) and there were minor difference between ischaemic time and ABO compatibility profiles as shown below. Overall, the recipient and transplant characteristics for kidneys transplanted in the simulation were very similar to ANZDATA, however, it is important to note areas of difference when interpreting subsequent simulation of policy proposals. Discrepancies in transplants by cPRA and interstate shipping were improved through the methods outlined above but remain imperfect in the final model.

Table 10.5 Comparison of recipient and transplant characteristics for organs transplanted in the KSPAM simulation compared with actual transplants (ANZDATA)

Factor	Level	ANZDATA	Simulation	p-value
N		2135	2165	
Discarded kidneys, mean (SD)		41 (0)	11 (0)	
Waiting time (months), median (IQR)		30.8 (16.6, 49.1)	31.7 (16.8, 50.7)	0.38
Age (years), median (IQR)		54.8 (43.6, 63.5)	54.0 (42.8, 62.6)	0.089
Gender	Female	769 (36.0%)	753 (34.8%)	0.40
	Male	1366 (64.0%)	1412 (65.2%)	
Ethnicity	Caucasian	1451 (68.0%)	1489 (68.8%)	0.65
	Indigenous	95 (4.4%)	96 (4.4%)	
	Asian	329 (15.4%)	343 (15.8%)	
	Other	260 (12.2%)	237 (10.9%)	
Primary renal disease	GN	795 (37.2%)	809 (37.4%)	1.00
	Analgesic	5 (0.2%)	4 (0.2%)	
	Polycystic	284 (13.3%)	297 (13.7%)	
	Reflux	122 (5.7%)	124 (5.7%)	
	Hypertension	153 (7.2%)	150 (6.9%)	
	Diabetes	342 (16.0%)	342 (15.8%)	
	Other	297 (13.9%)	305 (14.1%)	
	Uncertain	137 (6.4%)	134 (6.2%)	
Body mass index	<18.5 (underweight)	86 (4.0%)	45 (2.1%)	<0.001
	18.5-24.9 (normal)	836 (39.2%)	926 (42.8%)	
	25-29.9 (overweight)	637 (29.8%)	635 (29.3%)	
	>=30 (obese)	576 (27.0%)	559 (25.8%)	
Diabetes		570 (26.7%)	526 (24.3%)	0.071
Coronary disease		360 (16.9%)	418 (19.3%)	0.037
Cerebrovascular disease		123 (5.8%)	143 (6.6%)	0.25
Peripheral vascular disease		186 (8.7%)	203 (9.4%)	0.45
Chronic lung disease		180 (8.4%)	210 (9.7%)	0.15
Smoking at RRT entry	Never	1259 (59.0%)	1285 (59.4%)	0.89
	Former	692 (32.4%)	702 (32.4%)	
	Current	184 (8.6%)	178 (8.2%)	
Graft number	1	1812 (84.9%)	1842 (85.1%)	0.94
	2	276 (12.9%)	281 (13.0%)	
	3	44 (2.1%)	39 (1.8%)	
	4	3 (0.1%)	3 (0.1%)	
Regraft during simulation		7 (0.3%)	16 (0.7%)	0.065
Donor age (years), median (IQR)		48.0 (35.0, 59.0)	48.0 (35.0, 59.0)	0.67
Donor hypertension		533 (25.0%)	547 (25.3%)	0.82
HLA -A/B/DR mismatch	0	60 (2.8%)	55 (2.5%)	0.080
	1	163 (7.6%)	155 (7.2%)	
	2	445 (20.8%)	430 (19.9%)	
	3	209 (9.8%)	259 (12.0%)	
	4	385 (18.0%)	383 (17.7%)	
	5	542 (25.4%)	595 (27.5%)	
	6	331 (15.5%)	288 (13.3%)	
HLA-A mismatch	0	355 (16.7%)	380 (17.6%)	0.70
	1	994 (46.7%)	1010 (46.7%)	
	2	781 (36.7%)	775 (35.8%)	
HLA-B mismatch	0	271 (12.7%)	260 (12.0%)	0.63

	1	744 (34.9%)	782 (36.1%)	
	2	1115 (52.3%)	1123 (51.9%)	
HLA-DR mismatch	0	583 (27.4%)	544 (25.1%)	0.071
	1	723 (33.9%)	803 (37.1%)	
	2	824 (38.7%)	818 (37.8%)	
cPRA Categories	0-49	1722 (80.7%)	1711 (79.0%)	0.004
	50-79	129 (6.0%)	149 (6.9%)	
	80-94	154 (7.2%)	136 (6.3%)	
	95-98	72 (3.4%)	66 (3.0%)	
	≥99	58 (2.7%)	103 (4.8%)	
Ischaemic time (hours), mean (SD)		10.9 (4.6)	11.7 (4.3)	<0.001
Shipped interstate		447 (20.9%)	382 (17.6%)	0.006
ABO status	Identical	1963 (91.9%)	2055 (94.9%)	<0.001
	Compatible	169 (7.9%)	110 (5.1%)	
	Incompatible	3 (0.1%)	0 (0.0%)	

In order to facilitate a comprehensive and nuanced interpretation of simulation outcomes we developed a series of graphical panels that provide a summary of outcomes and transplant characteristics for subpopulations within the transplant candidate pool. The panels below presents the number of transplants (a), transplant rate per 100 active waiting years (b), algorithm level through which transplants were allocated (c), proportion of transplanted kidneys by KDPI quintile (d), mean HLA mismatch (at HLA -A, -B and -DR) of transplanted kidneys and proportion of transplanted kidneys by HLA mismatch (at HLA -A, -B and -DR) for all transplant candidates and then for subpopulations based on age group, gender, blood group, transplanting region, ethnicity and cPRA categories.

Overall, these figures support the accuracy of the simulations across a broad range of populations and metrics, however, they also highlight some limitations of the simulation which should be noted in interpreting subsequent modelling. As noted above in the methods section, despite attempts to improve known issues with the calculation of exposure time in the simulation a discrepancy remain such that despite a similar number of overall transplants performed in ANZDATA and the simulation, the overall transplant rate per 100 active waiting years for all patients was lower in ANZDATA compared to the simulation, 78.8 (95% CI 75.5-82.2) vs 87.8 (95% CI 84.2-91.6). This error is reflected in all figures below showing transplantation rates when comparing ANZDATA to the simulation. Despite this limitation, the relative transplant rates across subgroups are similar between ANZDATA and the simulations and in most cases the 95% confidence intervals for each subgroup overlap across models. An important exception to this is the transplant rate per 100 active waiting years for candidates with a cPRA of ≥99% (13.8 (95%CI 10.5-17.9) in ANZDATA vs 29.9 (95%CI 24.4-36.3) in the simulation) which reflects both the lower

exposure time in the simulation and the higher number of transplants in this subgroup as discussed above.

An additional discrepancy noted between the simulation and ANZDATA is the percentage of transplants allocated through the national algorithm compared to regional algorithms. In ANZDATA, national allocation accounts for 19.6% of all transplants compared to 14.5% in the simulation. This is also reflected in subsequent presentation of allocation pathways for subpopulations.

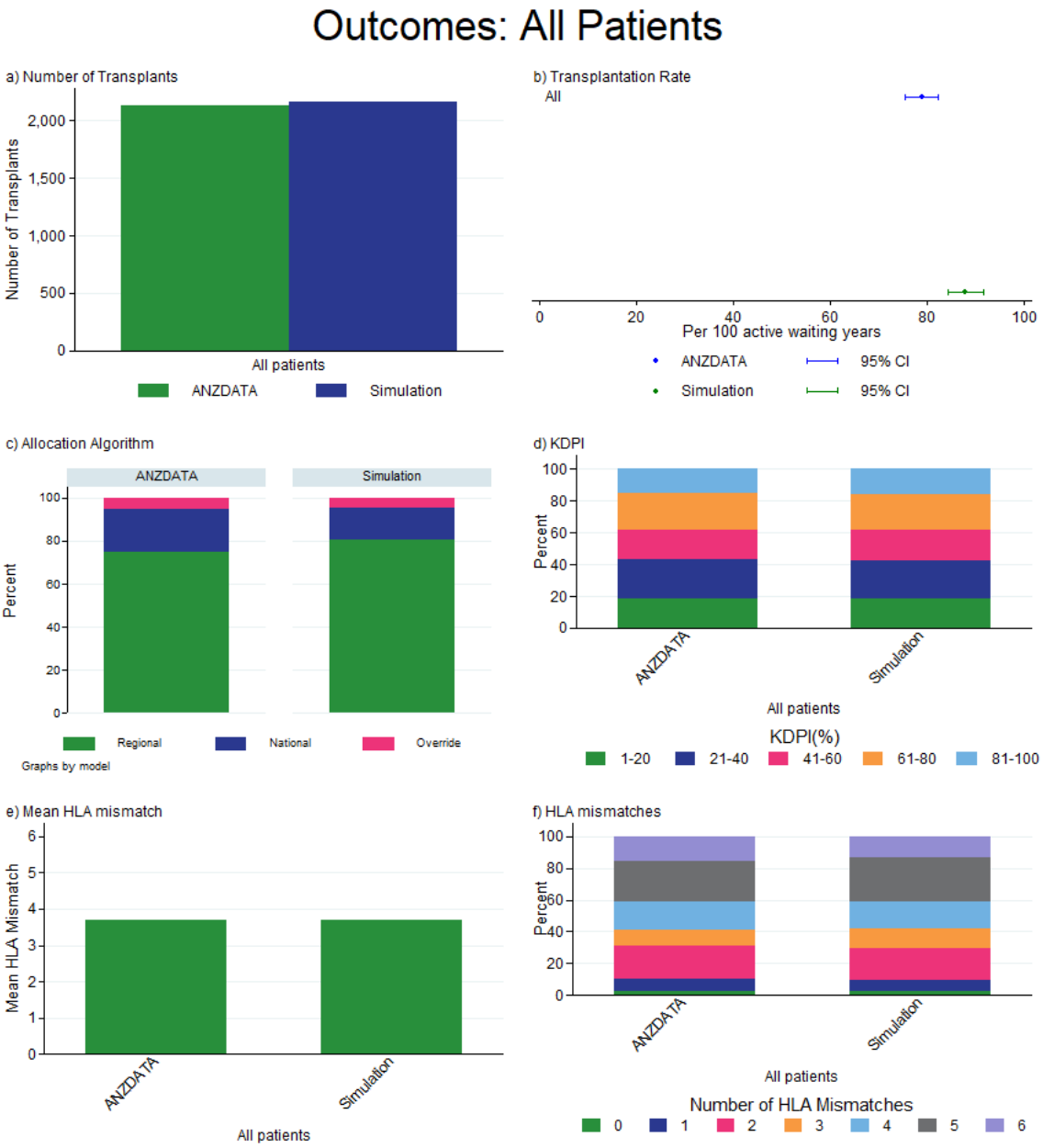

Figure 10.2 Comparison of outcomes between KPSAM simulations and actual events (ANZDATA) for all recipients

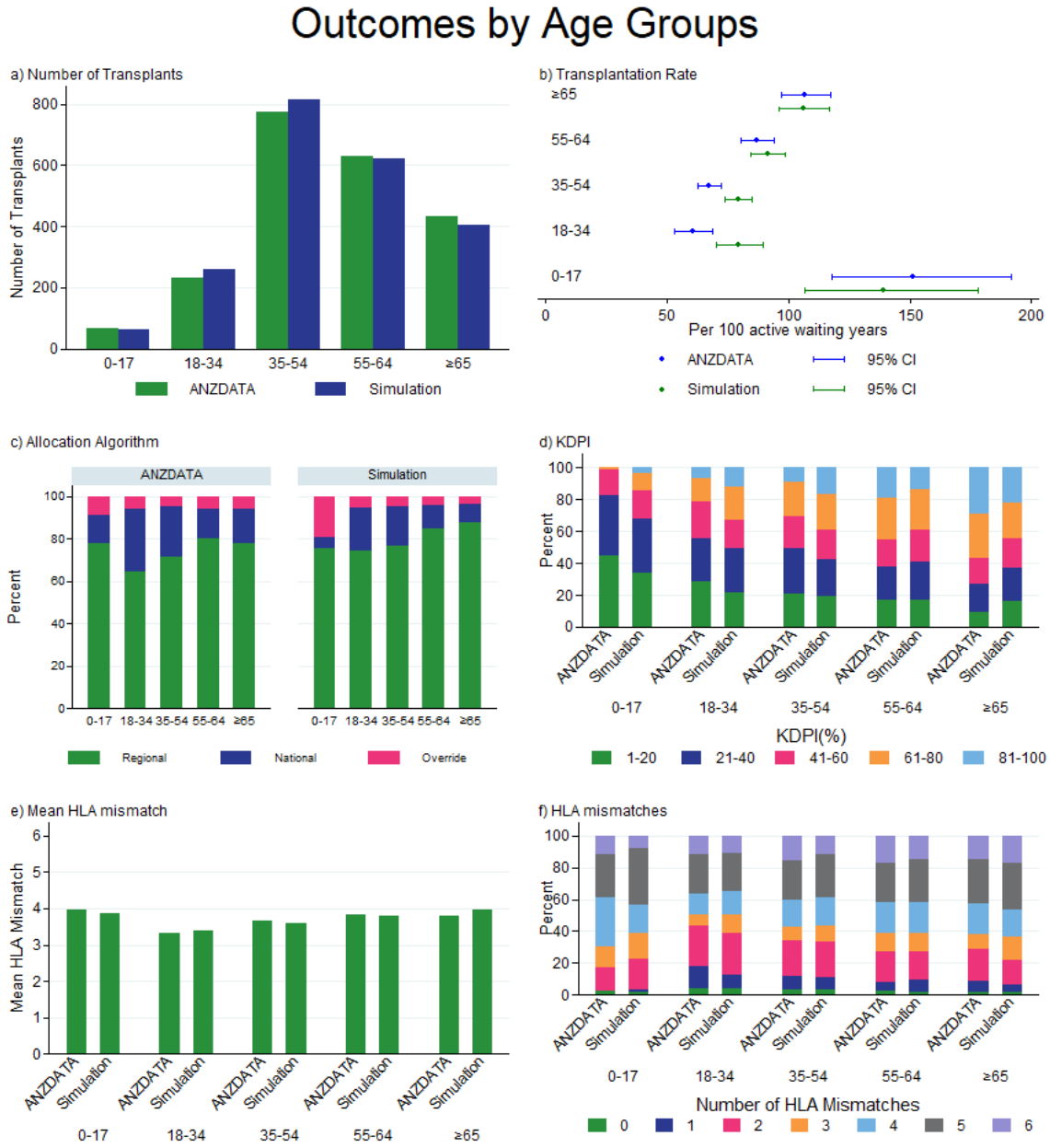

Figure 10.3 Comparison of outcomes between KPSAM simulations and actual events (ANZDATA) by recipient age group

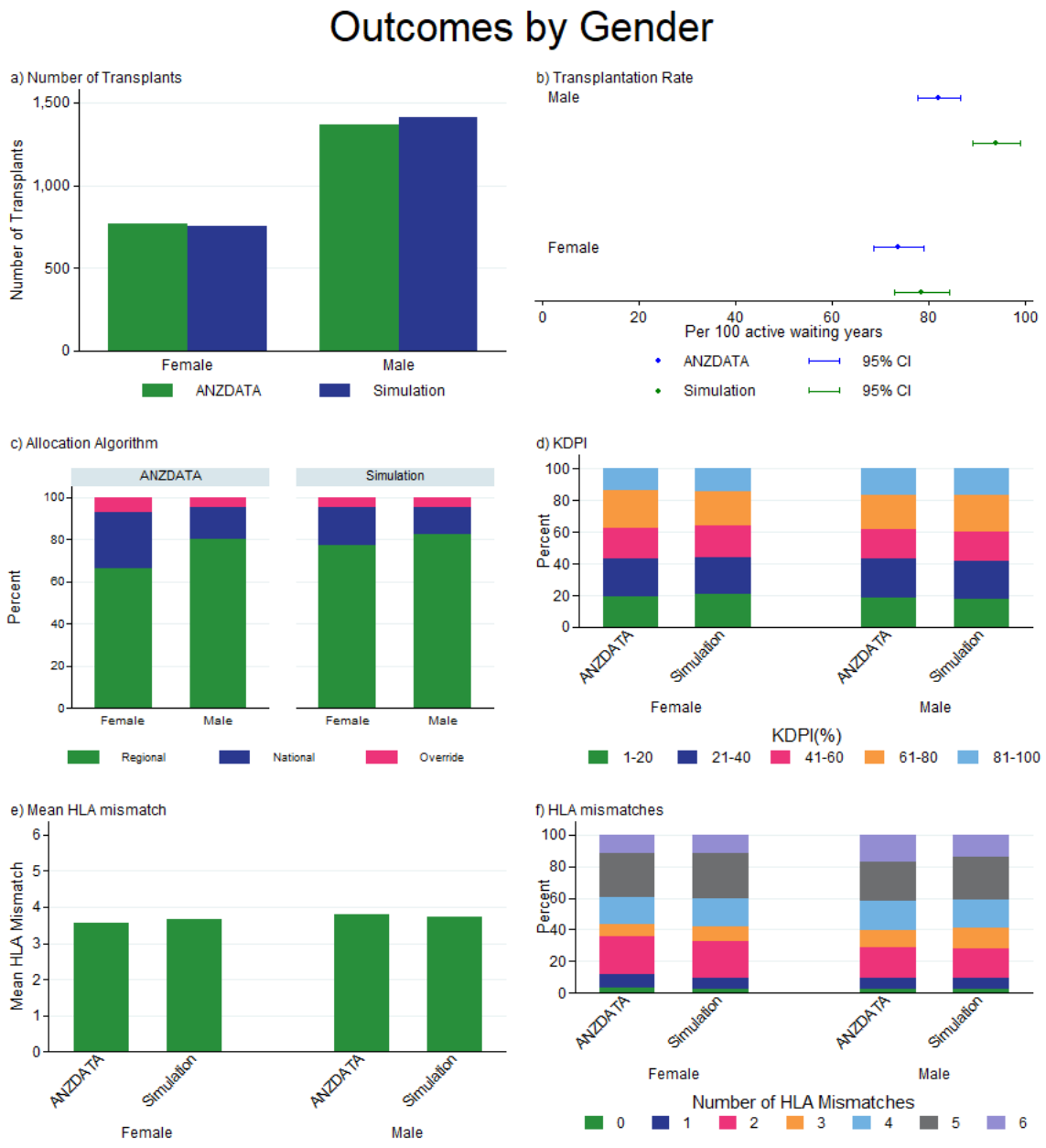

Figure 10.4 Comparison of outcomes between KPSAM simulations and actual events (ANZDATA) by recipient gender

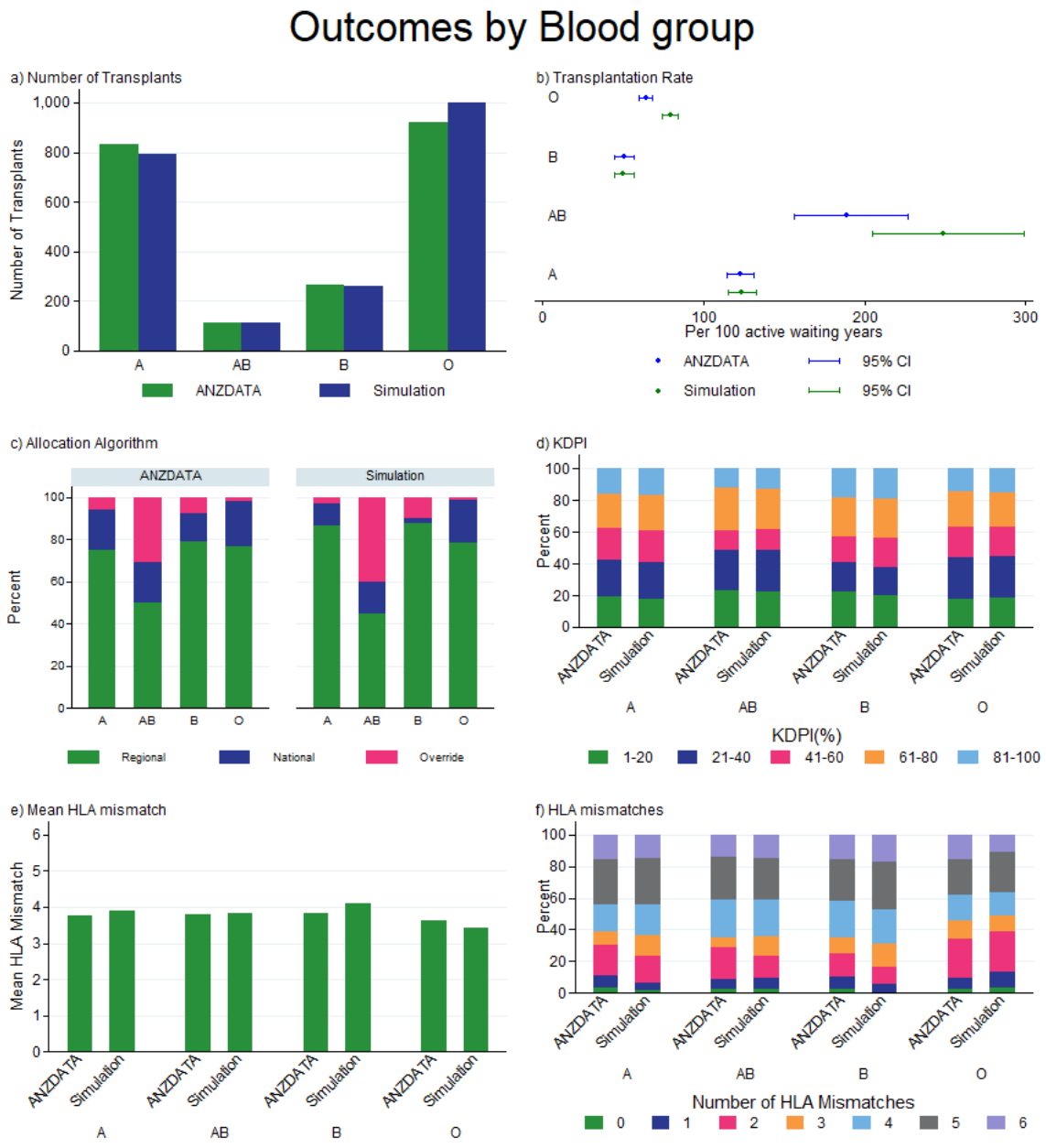

Figure 10.5 Comparison of outcomes between KPSAM simulations and actual events (ANZDATA) by recipient ABO blood group

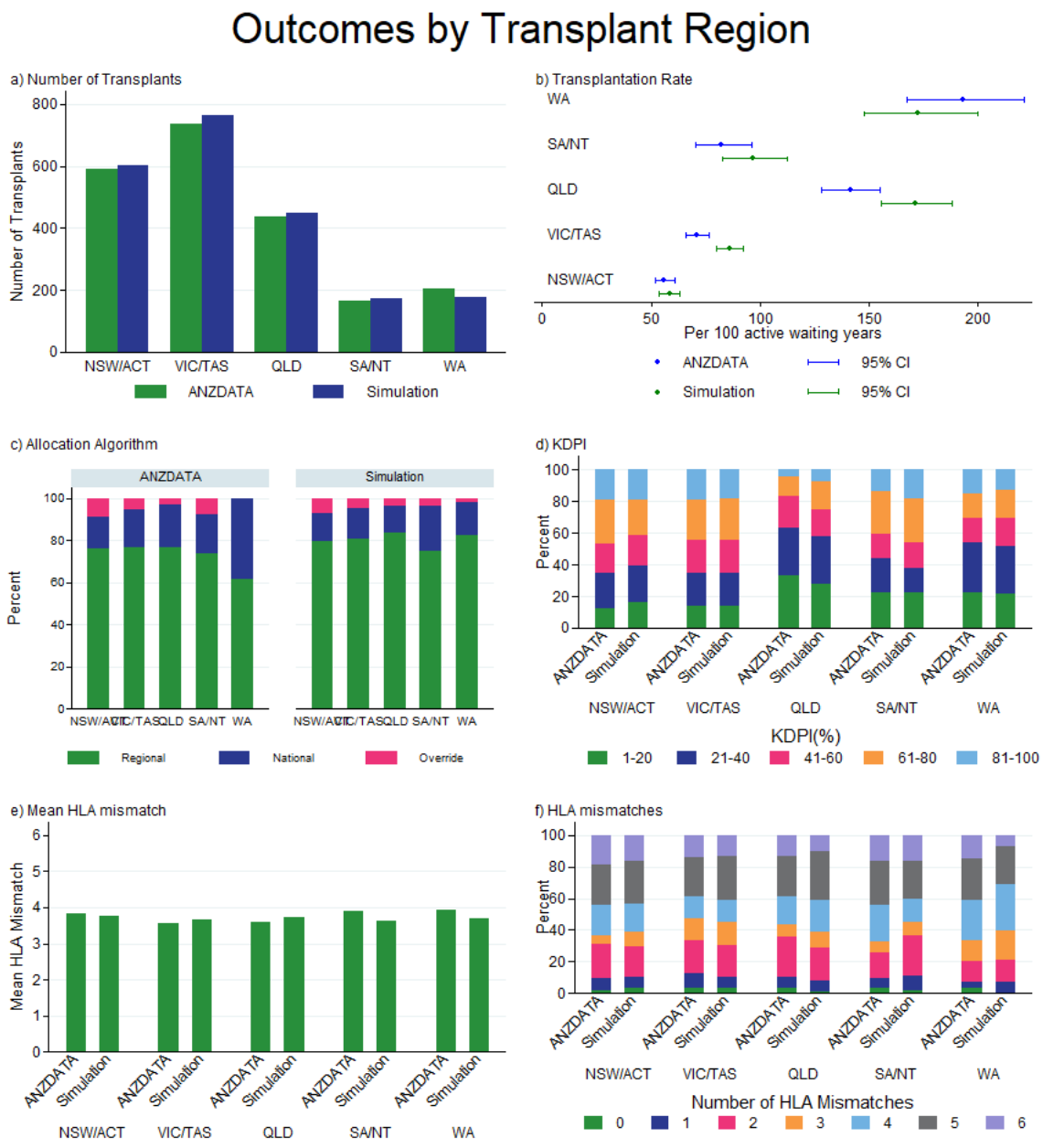

Figure 10.6 Comparison of outcomes between KPSAM simulations and actual events (ANZDATA) by the transplanting region in which the recipient was waitlisted

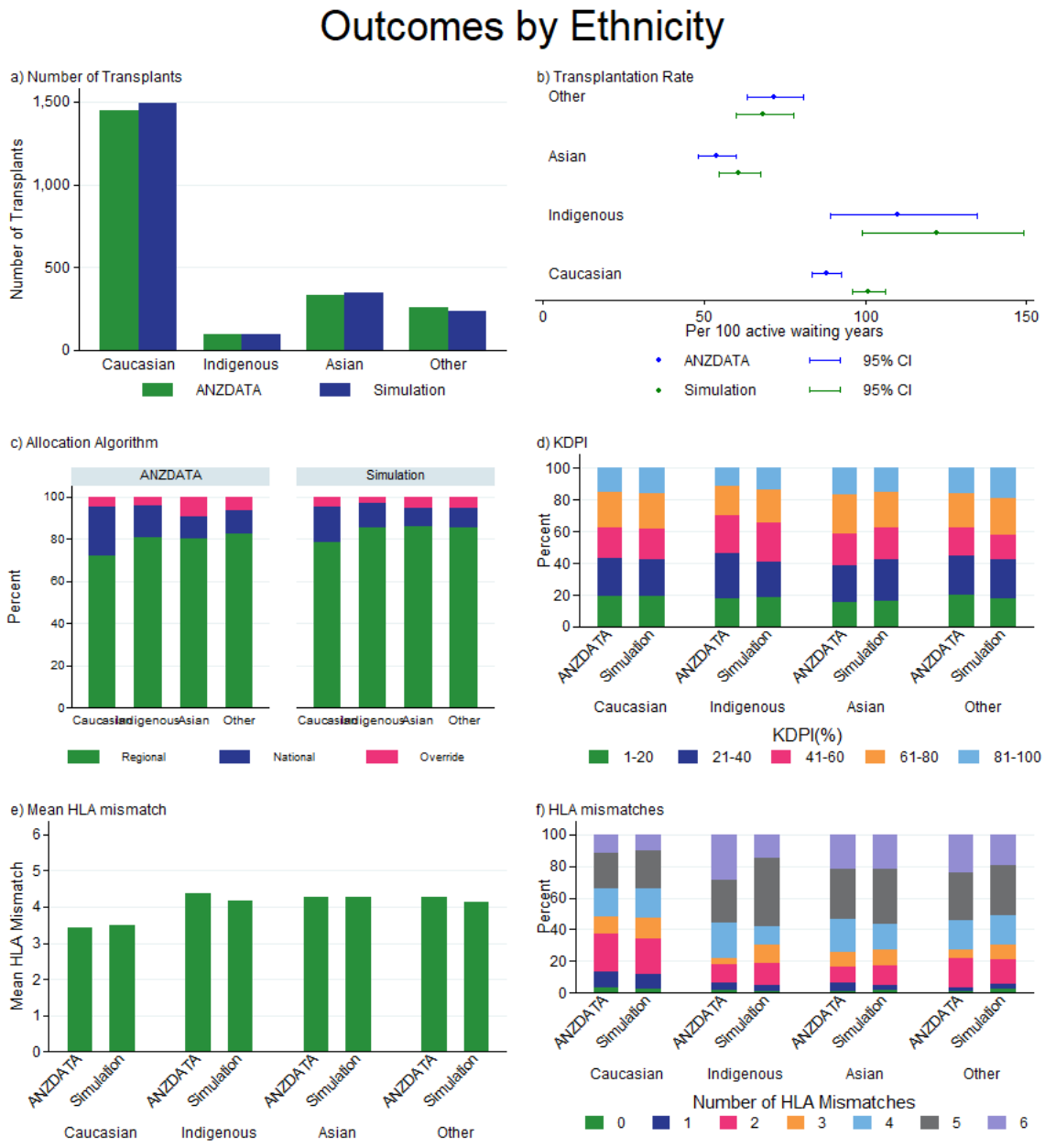

Figure 10.7 Comparison of outcomes between KPSAM simulations and actual events (ANZDATA) by recipient ethnicity

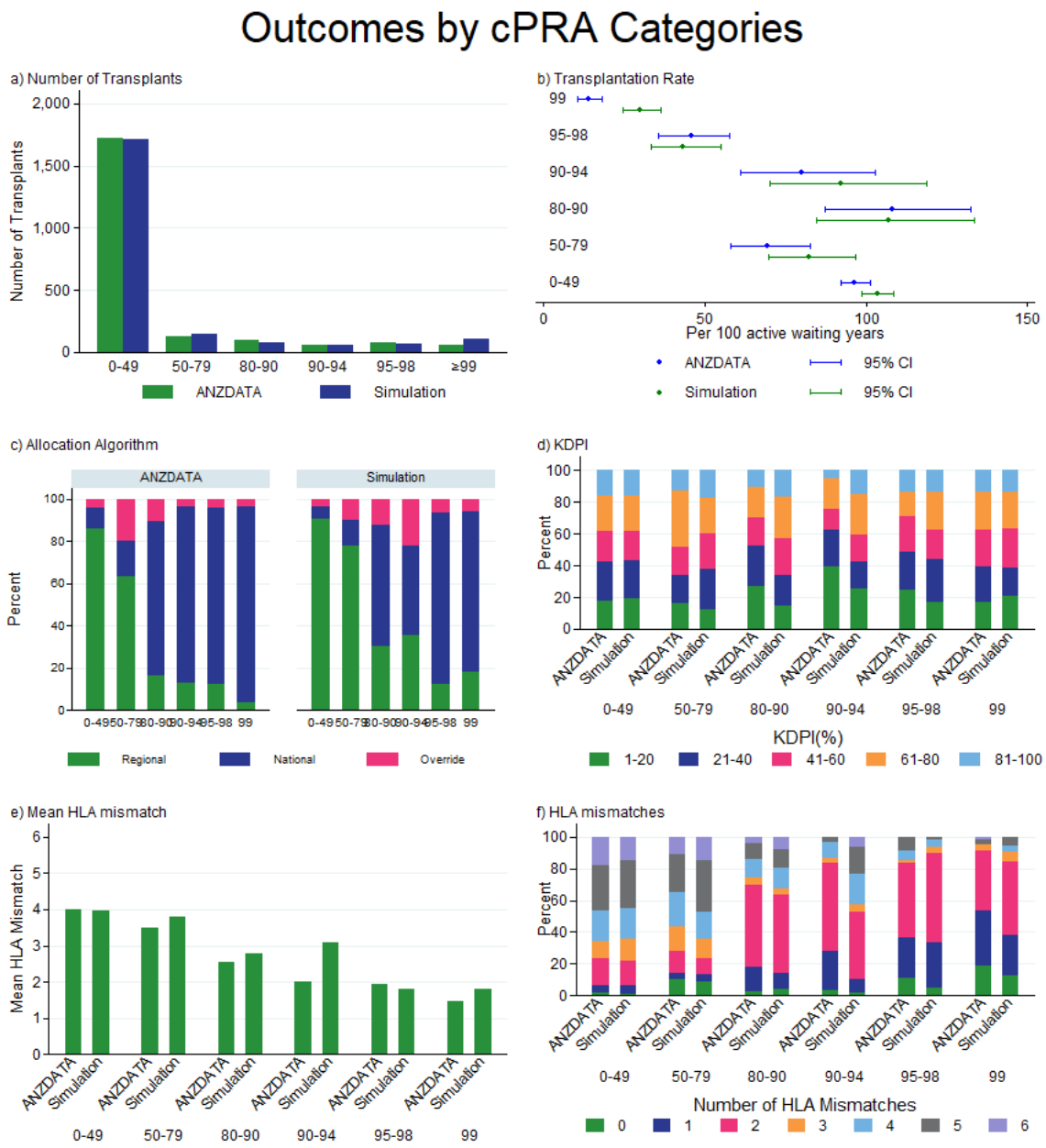

Figure 10.8 Comparison of outcomes between KPSAM simulations and actual events (ANZDATA) by recipient sensitization (defined by categories of calculated panel reactive antibody (cPRA) (%))

Overall a comprehensive and multidimensional comparison between simulation outcomes and actual transplant activity during the study period indicates that the adapted KPSAM model produces an acceptably accurate representation of the Australia deceased donor transplant allocation system. Subtle absolute differences between the simulation and ANZDATA are identified, however the patterns of differences across patient populations are highly preserved in the simulation which supports the validity of this tool in assessing the relative impacts of proposed allocation changes across a broad range of subpopulations and outcome measures. Transparency around the limitations of adapting modelling software developed to simulate the US allocation system to the Australian context and the challenges of modelling complex clinical decision making using a static logistic regression equation, allow for nuanced interpretation of the findings presented in part 2 of this chapter.

PART 2: ITERATIVE SIMULATION OF POLICY PROPOSALS

10.6 Part 2 Methods

Following development and validation of the baseline simulation outlined above, the authors undertook a series of iterative simulations using the validated model to assist in the assessment and refining of new deceased donor kidney allocation rules proposed by RTAC. The following narrative and results highlight key events and illustrative examples of the modelling, assessment and design process involved in this practical application of simulation in re-designing deceased donor kidney allocation in Australia.

It is important to note that the changes proposed by RTAC were designed to represent an interim measure only, targeted to deal with particular urgent issues within the limitations of the current allocation structure. These issues were: 1) improving access to deceased donor transplantation for very highly sensitized patients; 2) improving access to well matched kidneys for paediatric candidates and younger adults who are likely to require re-transplantation in the future; 3) Restricting the use of the kidneys with the best predicted survival in recipients with the poorest post-transplant predicted survival; and 4) Developing a standard regional allocation algorithm across transplanting regions. A longer-term goal to complete re-design the structure of the allocation system is planned, however, it was felt that the timeframe on which this could be achieved would be excessive and adapting the current system to achieve the urgent short term goals above was an appropriate interim step.

10.6.1 Timeline of key events

- ***July 2019:*** Face to face meeting of RTAC at the TSANZ annual scientific meeting, Sydney, Australia: a draft of new deceased donor allocation rules is discussed and MS and PC are requested to provide results of simulations of these new rules at the following meeting:
- ***August-November 2019:*** Proposed allocation rules are coded and simulated. Based on review of these simulation outcomes, refinements are made to the rules producing a number of alternative allocation proposals.
- ***November 2019:*** Teleconference between MS, PC and the Chair of RTAC to present initial findings.
- ***November-December 2019:*** Further simulations performed
- ***December 2019:*** MS presents at face to face meeting of RTAC, Sydney Australia: model structure, construction and validation are presented to the committee. Results of simulation of proposed new rules presented along with alternative rule proposals demonstrating specific concerns with new proposal. Significant alterations made to allocation proposal. Request for additional simulations of new proposal and alternatives submitted by RTAC.
- ***May 2020:*** Revised simulations presented to RTAC via teleconference
- ***July 2020:*** Final policy endorsed by RTAC for implementation

10.6.2 Iterative simulation process

In order to maintain integrity of the validated baseline model, all statistical model input files were locked and no further alterations were made to model specifications. Where new allocation rules required addition variables in the organ or patient input files these were

regenerated from the ANZDATA data set using the original Stata .do files with minor changes to include the required variable but no other alterations, and the optional data definition files were updated accordingly.

The new allocation rules proposed by RTAC were coded using KPSAM specifications and the simulations performed. Comprehensive outcome reports as detailed above were produced for each simulation comparing the proposed new allocation rules to the base simulation using the current allocation rules.

Outcome reports were qualitatively reviewed and where issues were identified, rule adjustments were recoded and the simulation rerun. Revised simulations were compared to either the base simulation or previous iteration as appropriate.

The key findings of iterative simulations were collated into a narrative presentation and communicated to RTAC along with the full simulation reports for each substantial iteration (either out of session through email and teleconferences with the Chair, or to the sitting committee through face to face and teleconference meetings). Further iterations were performed with the results communicated to the committee in an ongoing cycle of redesign and testing.

New national algorithm initial proposal

The current national allocation algorithm for deceased donor kidneys used in the base simulation is shown below in Figure 10.9.

The initial draft of a new national allocation algorithm as proposed at the July 2019 RTAC meeting is summarized in Table 10.6. It is important to note that these rules represented the core features of new proposals but did not specify a number of finer details such as the priority for multi-organ donor allocation or handling or urgent patient listings. For the purpose of simulation, when details were unspecified in the proposed new rules, the definitions from existing rules were used.

National Allocation formula

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

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

Figure 10.9 Current national formula for the allocation of deceased donor kidney transplants in Australia

Reproduced from: TSANZ (Transplantation Society of Australia and New Zealand). Clinical Guidelines for Organ Transplantation from Deceased Donors. http://www.tsanz.com.au/TSANZ_Clinical_Guidelines_Version 1.3%5B6986%5D.pdf. Published 2019. Accessed April 4, 2020.

Table 10.6 Initial draft proposal of new national allocation rules proposed by the Renal Transplant Advisory Committee

Level	Definition	Score
National Level 1		
1a	cPRA≥99%	100 000 000
1b	cPRA 98-98.9%	99 000 000
1c	cPRA 97-97.9%	98 000 000
1d	cPRA 96-96.9%	97 000 000
1e	cPRA 95-95.9%	96 000 000
1f	cPRA 94-94.9%	95 000 000
1g	cPRA 93-93.9%	94 000 000
1h	cPRA 92-92.9%	93 000 000
1i	cPRA 91-91.9%	92 000 000
1j	cPRA 90-90.9%	91 000 000
Paediatric bonus	Age <18 years	+5 000 000
Homozygous Bonus	Recipient homozygous at HLA -A, -B, and -DR	+4 000 000
*Note that further levels above 99% were proposed but could not be simulated as cPRA data was only available in integers within simulations		
National Level 2		
2a	HLA A/B/DR 0 MM & EPTS <60	70 000 000
2b	HLA DR 0 MM, A/B 1 MM & EPTS<60	59 000 000
2c	HLA DR 0 MM, A/B 2 MM & EPTS<60	58 000 000
Paediatric bonus	Age <18 years	+5 000 000
DR Homozygous Bonus	Recipient homozygous at HLA -DR	+3 000 000

New regional algorithm initial proposal

The current regional allocation formulas used in the base simulation are contained in Appedix A of the thesis.

The initial draft of a new unified regional allocation algorithm as proposed at the July 2019 RTAC meeting is summarized in Table 10.7. The key goals of this reform were firstly to harmonize allocation algorithms with a single local allocation formula across the various transplanting jurisdictions, and also to prevent kidneys with the best predicted long term survival from being transplanted into candidates with poorer post-transplant predicted survival, unless a suitable fitter transplant candidate could not be found. It was hoped this second goal could be achieved by initially restricting allocation at the regional level to transplants in which there was a difference in KDPI-EPTS of <60 before running the allocation algorithm without this restriction if the kidney had not been accepted.

National override

When a suitable recipient is not identified through national of regional allocation the national override algorithm is run to minimise the changes of organ wastage. This algorithm is contained in Appendix A of the thesis and was not changed in the initial simulations.

Table 10.7 Initial draft proposal of new regional allocation rules proposed by the Renal Transplant Advisory Committee

Level	Definition	Score
Allocation is initially restricted to candidates with an EPTS-KDPI of <60 and then re-run unrestricted		
Regional (HLA Matching)		
	HLA mismatch (-A, -B, -DRB1)	
1a	0 0 0	49 000 000
1b	1 0 0 / 0 1 0	48 000 000
1c	1 1 0	47 000 000
1d	0 0 1	46 000 000
1e	2 0 0 / 0 2 0	45 000 000
1f	1 0 1 / 0 1 1	44 000 000
1g	2 1 0 / 1 2 0	43 000 000
1h	1 1 1	42 000 000
1i	2 2 0	41 000 000
Paediatric bonus	Age <18 years	10 000 000
DR Homozygous bonus	Recipient homozygous at -DRB1	+3 000 000
Regional (Waiting time)		
	Base score	40 000 000
	Waiting time	+1 x waiting time (months)
	Paediatric Bonus	+10 000 000

10.7 Part 2 Results

The process of progressive rule modification and refinement was responsive to both the analysis of authors and specific requests from members of the RTAC committee, and a large number of trial simulations were performed with iterative adjustments made based on interim analysis. Select results and figures from various simulation iterations are shown below with an accompanying narrative for illustrative purpose, however, a large number of trial simulations are not shown. It should also be noted that full reports on simulations for each substantial modification of allocation rules were produced and provided to RTAC for review.

Table 10.8 provides a summary of rule modifications used in iterations of the simulation that are discussed in the narrative description below; this is not designed to be meaningful in isolation, but is rather provided as a reference when interpreting the figures presented below.

Table 10.8 Reference table for rules used in example simulations presented below

Model Name	National Rules	Regional Rules
RTAC v1	New national rules outlined in Table 10.6	Current rules
RTAC v1a	New national rules outlined in Table 10.6with levels 1f-1j removed	Current rules
RTAC v3	New national rules outlined Table 10.6with levels 1f-1j removed and addition of new national levels 3a-3e (based on level 2,3,4,6 and 7 of the current allocation rules shown in Figure 10.9)	New regional rules outlined in Table 10.7
RTAC v3a	New national rules outlined in Table 10.6 with levels 1f-1j removed and addition of new national levels 3a-3e (based on level 2,3,4,6 and 7 of the current allocation rules shown in Figure 10.9	Current rules
RTAC v3b	New national rules outlined in Table 10.6 with levels 1f-1j removed, the EPTS threshold for eligibility for national level 2 reduced to <25% and the addition of new national levels 3a-3e (based on level 2,3,4,6 and 7 of the current allocation rules shown in Figure 10.9	Current rules
RTAC v4	New national rules outlined in Table 10.6 with levels 1f-1j removed, the EPTS threshold for eligibility for national level 2 reduced to <25% and the addition of new national levels 3a-3e (based on level 2,3,4,6 and 7 of the current allocation rules shown in Figure 10.9)	New regional rules outlined in Table 10.7

10.7.1 Improving access to deceased donor transplantation for very highly sensitized patients

Initial simulations were run with the new proposed national rules as outlined above with the existing regional allocation rules, to assess the impact of proposed national changes independently.

From early simulations, two key issues arose with the proposed system that gave absolute national priority for patients with a cPRA ≥ 99% and then in a step wise manner to patients with cPRA 90-90.9%. As shown in Figure 10.10 below, whilst this strategy did effectively improve transplantation rates for patients with cPRA ≥99% and cPRA 95-98%, there was a dramatic overcorrection for patients with cPRA 90-94%, with a new transplantation rate in this population over 3 fold greater than unsensitized patients. There was also a substantial reduction in transplant rates for patients with cPRA 80-90% such that this was now below the rate of patients with cPRA ≥99%.

Based on the work presented in Chapter 6 of this thesis and iterative trials of various cut offs for the level 1 national bonus, it was found that a threshold of cPRA of ≥95% for applying the new national level 1 bonus appeared to be effective in addressing the disadvantage experienced by very highly sensitized patients without producing excessively high transplantation rates compared to other groups (see Figure 10.11).

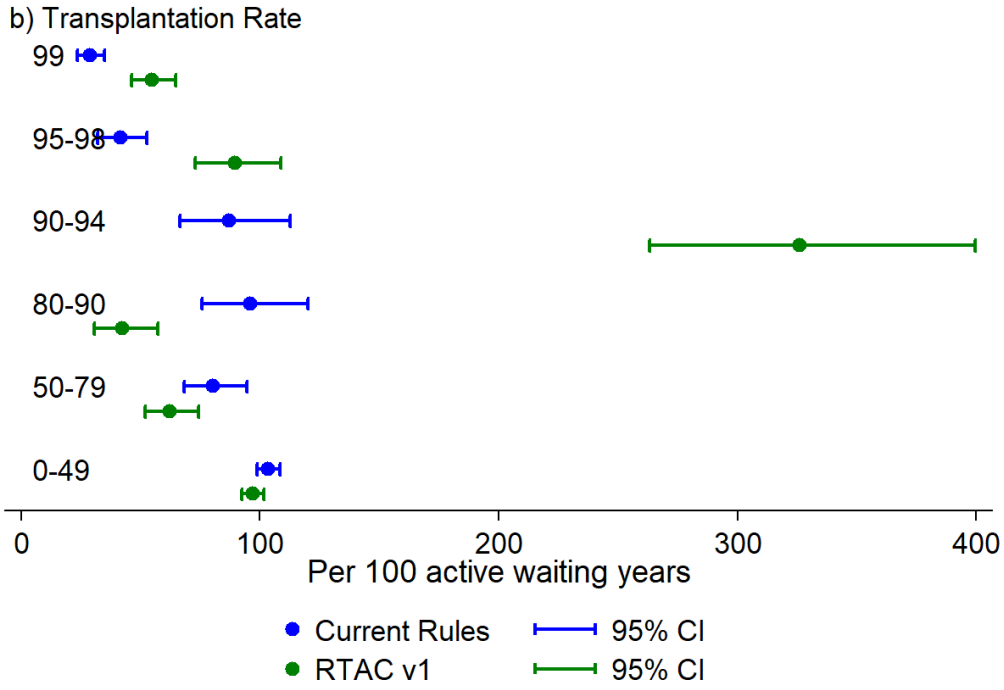

Figure 10.10 Comparison of transplant rate in KPSAM simulations between current rules and proposed new rules by cPRA (%) category

RTAC v1 model includes new national rules outlined in Table 10.6 *and current regional rules*

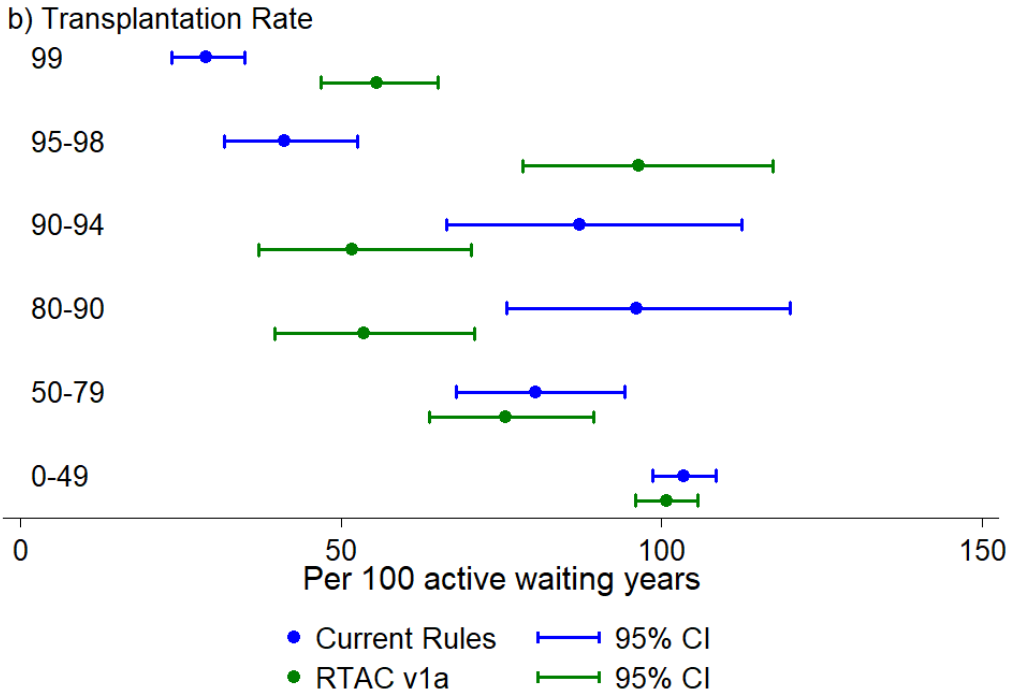

Figure 10.11 Comparison of transplant rate in KPSAM simulations between current rules and modified proposed new rules by cPRA (%) category

RTAC v1a includes new national rules outlined in Table 10.6 *with levels 1f-1j removed and current regional allocation rules*

This did not address the issue with the reduction in transplantation rate for patients with cPRA 80-90% under the proposed new rules. As shown in Chapter 6 of this thesis and in figure 17 below, under the current allocation rules, the majority of patients with cPRA 80-94% transplanted with a deceased donor kidney in Australia, receive their organ based on the national allocation program. The simulations demonstrated that removing this priority in the new allocation proposal would likely result in a substantial reduction in access to deceased donor transplantation for this population as they were no longer likely to access the national donor pool.

In addition, the simulations showed that an improved transplantation rate for very highly sensitized patients due to increased national shipping of kidneys resulted in a reduction in transplant rates for the three single centre transplanting regions with smaller populations and a lower proportion of very highly sensitized patients (Figure 10.13). Whilst transplantation rates remained higher than the larger transplanting regions, it may have been politically challenging to get some regions to accept reductions in their local transplant rates.

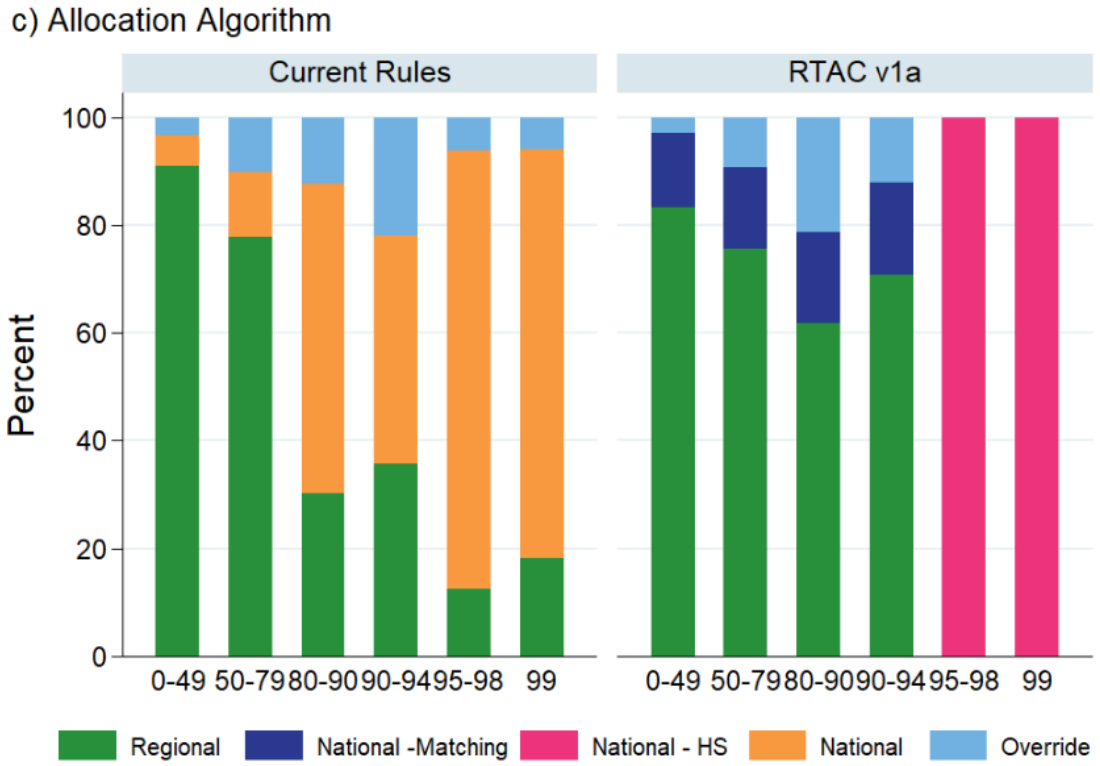

Figure 10.12 Comparison of algorithm used to allocate transplanted kidneys in KPSAM simulations between current rules and modified proposed new rules by cPRA (%) category

RTAC v1a includes new national rules outlined in Table 10.6 *with levels 1f-1j removed and current regional allocation rules*

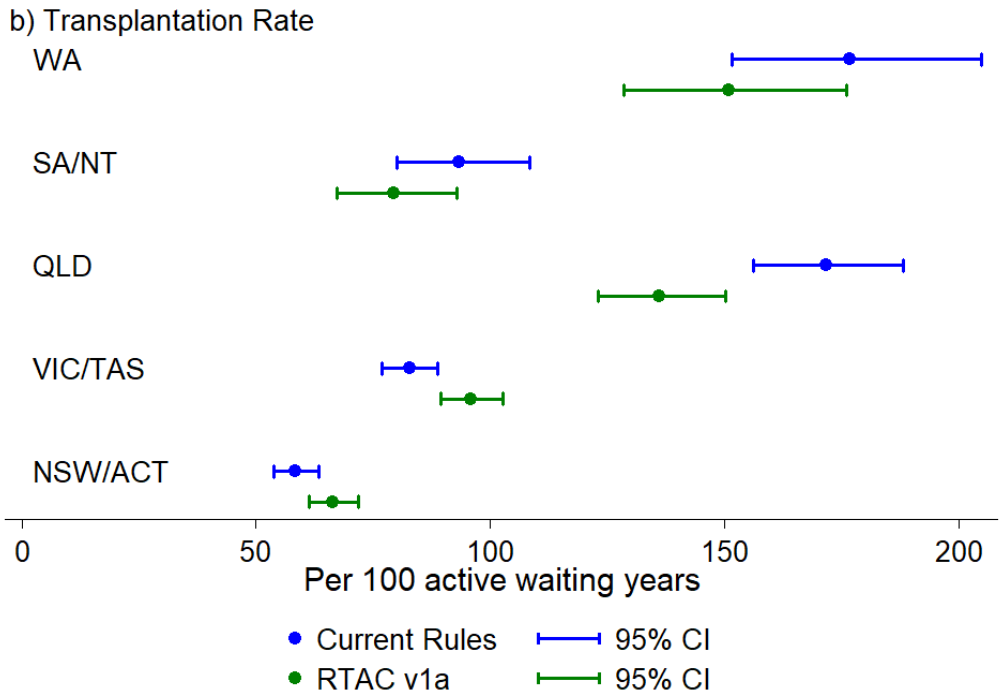

Figure 10.13 Comparison of transplant rate in KPSAM simulations between current rules and modified proposed new rules by region in which the recipient was waitlisted

RTAC v1a includes the new national rules outlined in Table 10.6 *with levels 1f-1j removed and current regional allocation rules*

Various solutions to these two issues were proposed, however, within the limitations of the structure of the current allocation system and in the interests of progressing forward on the implementation of a new policy, the option of reintroducing the former national levels 2,3,5,6 and 7 as a third tier of national allocation (levels 3a-3e) to the new proposal was considered. Simulation of this algorithm demonstrated a slight but not excessive improvement in transplantation rate for patients with cPRA 80-90% and 90-95% (Figure 10.14) and minimal changes in transplantation rates across the various transplanting regions when compared to the current system (Figure 10.15) which was likely to be politically acceptable to most parties.

Figure 10.14

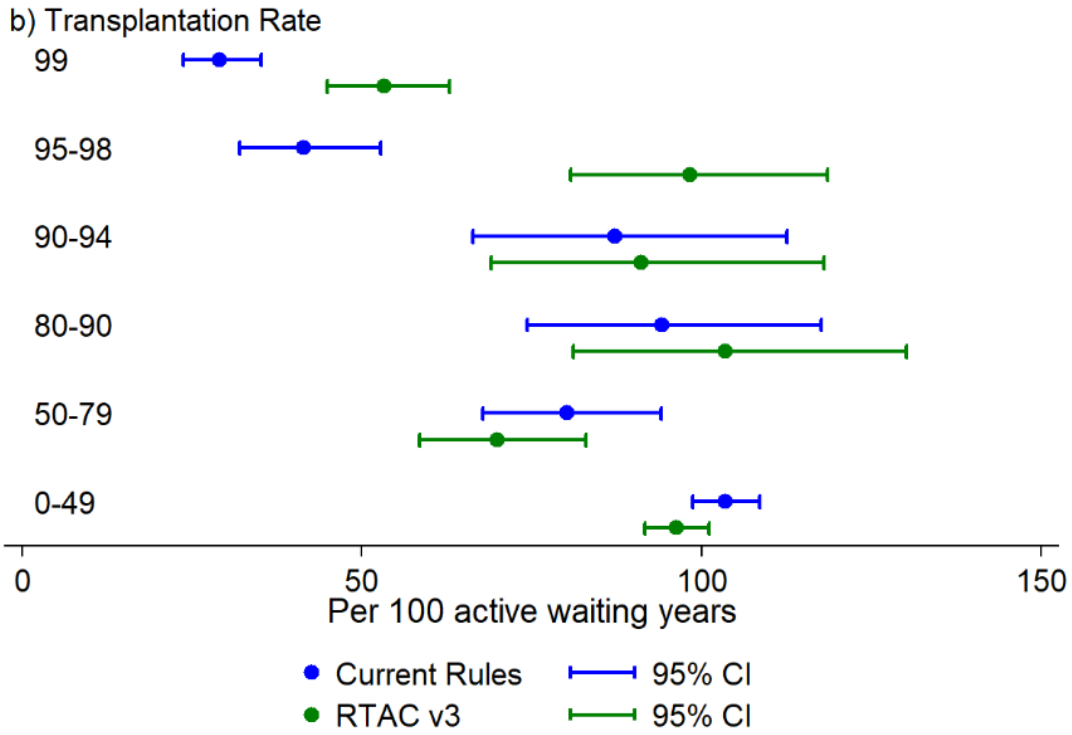

Figure 10.14 Comparison of transplant rate in KPSAM simulations between current rules and modified proposed new rules by cPRA (%) category

RTAC v3 includes new national rules outlined in Table 10.6 with levels 1f-1j removed, the addition of new national levels 3a-3e (based on level 2,3,4,6 and 7 of the current allocation rules shown in Figure 10.9) and new regional rules outlined in Table 10.7

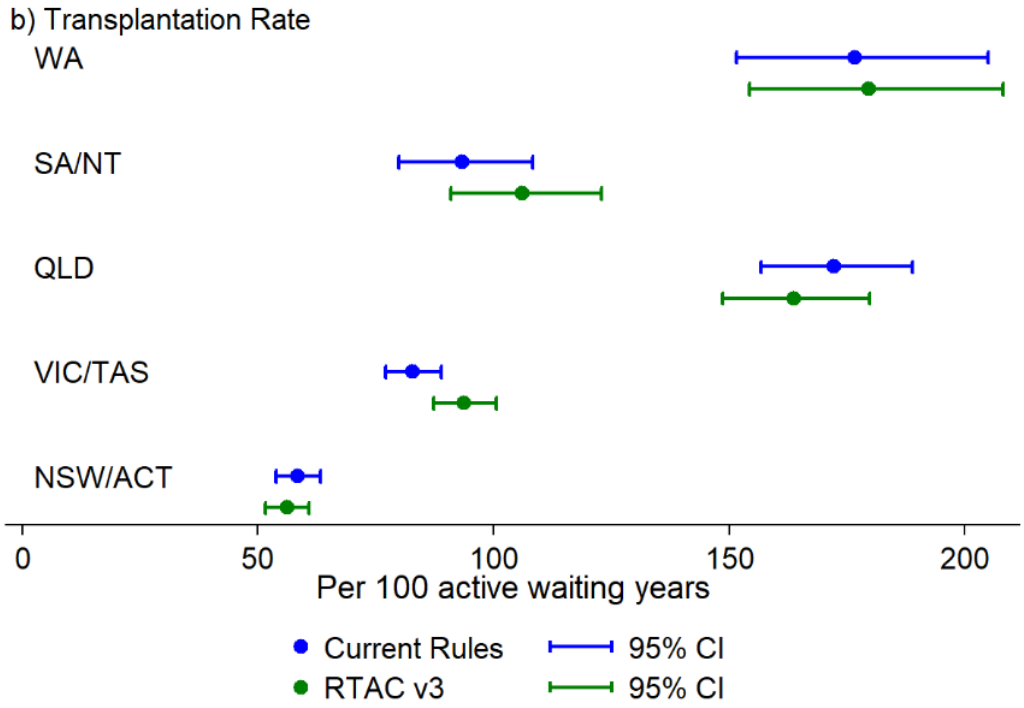

Figure 10.15 Comparison of transplant rate in KPSAM simulations between current rules and modified proposed new rules by region in which the recipient was waitlisted

RTAC v3 includes new national rules outlined in Table 10.6 *with levels 1f-1j removed, the addition of new national levels 3a-3e (based on level 2,3,4,6 and 7 of the current allocation rules shown in Figure 10.9) and new regional allocation rules outlined in* Table 10.7

Improving access to well matched kidneys for paediatric candidates and younger adults

Level 2 of the proposed new national allocation algorithm was also refined as a result of simulation findings. The intention of this rule was to give patients with a high predicted post-transplant survival access to well matched kidneys (either 0 MM or 1 or 2 AB MM). The initial proposal restricted allocation at this level to patients with an EPTS <60%. Simulation of this proposal showed that it was effective in improving the percentage of transplants with 2 or few HLA mismatches from 29.6% under the current rules to 34.7% under the proposed rules. However, as Figure 10.16 shows, this was a relatively untargeted measure, with all age groups apart from recipients aged 65 years and older seeing an improvement in the proportion of well-matched kidneys. In the new simulation, kidneys transplanted through national level 2 allocation made up 18.2% of all transplants, which when combined with the 11.8% transplanted through national level 1 transplants (levels 1a-1e, only) meant that 30% of all transplanted were being transplanted through the national allocation system compared to 14.5% in the simulation under the current rules (and before adding the old levels 2,3,5,6 and 7 as described above).

The threshold of an EPTS<60% for this allocation level was an arbitrary figure proposed by RTAC. As shown in Figure 10.18 below, the use of this cut-off results in some patients up to the age of 65 years being included in what was intended to be a targeted priority for children and young adults to reduce the risk of sensitization for future transplants.

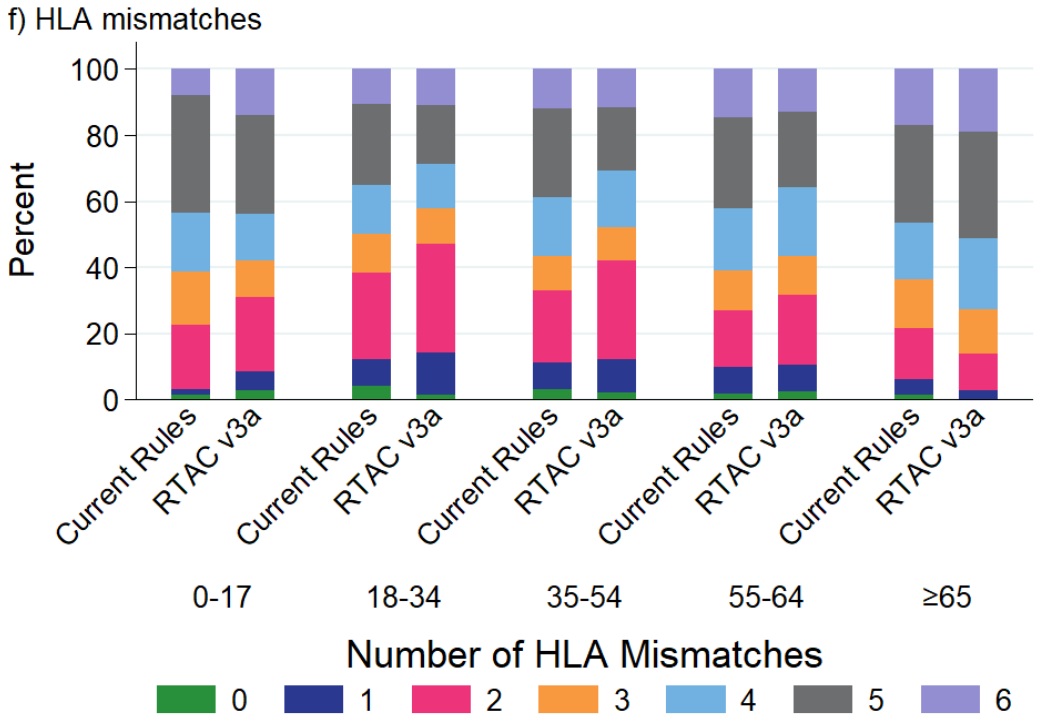

Figure 10.16 Comparison of HLA mismatches for transplants in KPSAM simulations between current rules and modified proposed new rules by recipient age

RTAC v3a includes new national rules outlined in Table 10.6 *with levels 1f-1j removed, the addition of new national levels 3a-3e (based on level 2,3,4,6 and 7 of the current allocation rules shown in Figure 10.9) and current regional rules*

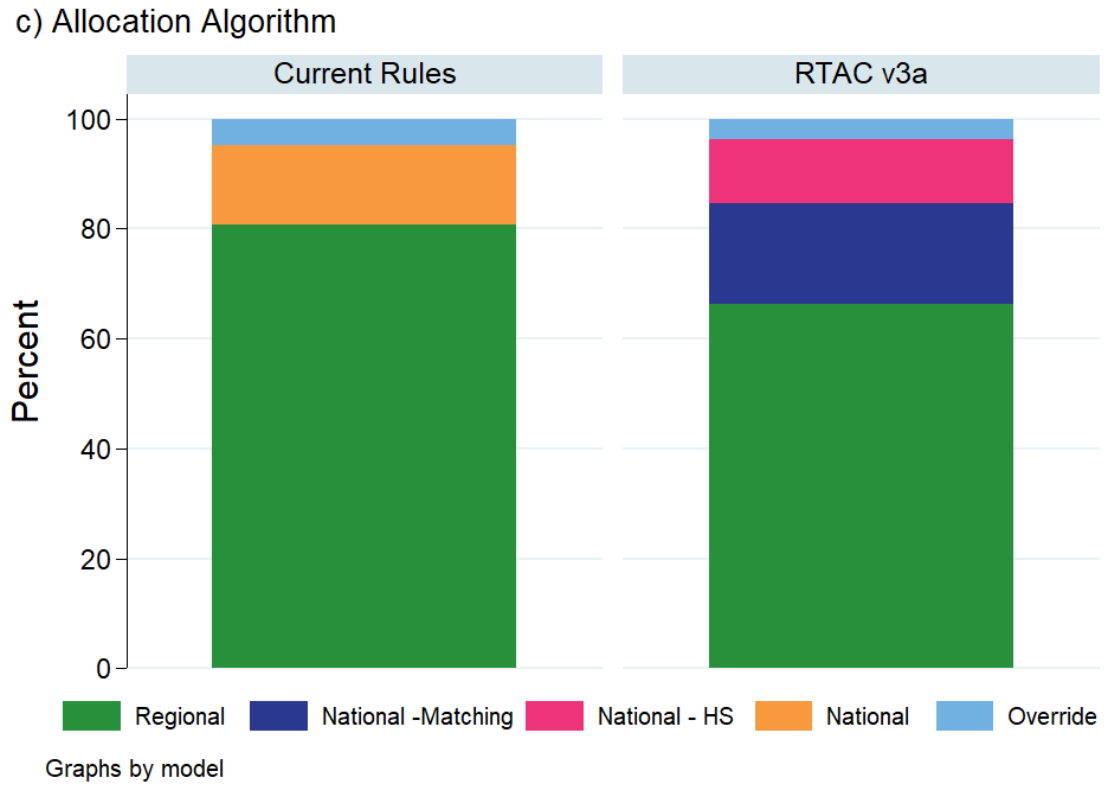

Figure 10.17 Comparison of algorithm used to allocate transplanted kidneys in KPSAM simulations between current rules and modified proposed new rules

RTAC v3a includes new national rules outlined in Table 10.6 *with levels 1f-1j removed, the addition of new national levels 3a-3e (based on level 2,3,4,6 and 7 of the current allocation rules shown in Figure 10.9) and current regional rules*

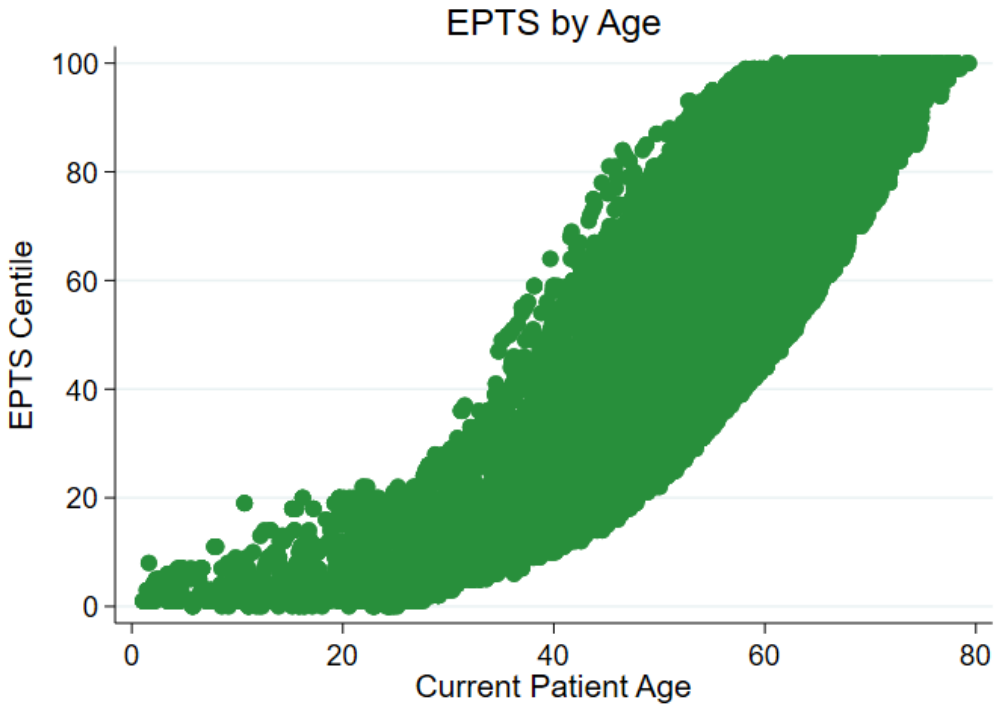

Figure 10.18 Expected Post Transplant Survival (EPTS) score plotted against patient age for all patients wait listed for kidney only transplant (March 2016-December 2018)

A number of alternative thresholds were tested through a process of iterative simulation. For example, reducing the EPTS threshold to <25% for national level 2 allocation resulted in a much more targeted effect. The percentage of transplants with 2 or fewer HLA mismatches improved for paediatric recipients (from 22.6% to 31.2%) and for young adult recipients aged 18-34 (from 38.6% to 51.2%) compared to the simulation of current allocation rules. Conversely, there was little change in the proportion of well matched kidneys for adults aged 35-54 (33.1% vs 31.9%) and a slight drop for older adults as shown in Figure 10.19 below. This was associated with a significant reduction in the percentage of kidneys allocated through the national algorithm when compared to the simulations using the EPTS threshold of <60%. Using the EPTS threshold of <25% the percentage of kidneys transplanted through national allocation level 2 was 8.3%, giving a total of 20.9% of kidneys being transplanted through national allocation under the new rules, compared to 14.5% in simulations using the current rules.

Following discussion amongst the allocation committee and review of simulations of a number of alternative EPTS thresholds, agreement was reached on a threshold of EPTS<25% for national levels 2a, 2b and 2c, with the addition of a level 2e for patients with a 0 HLA mismatch and EPTS <60%.

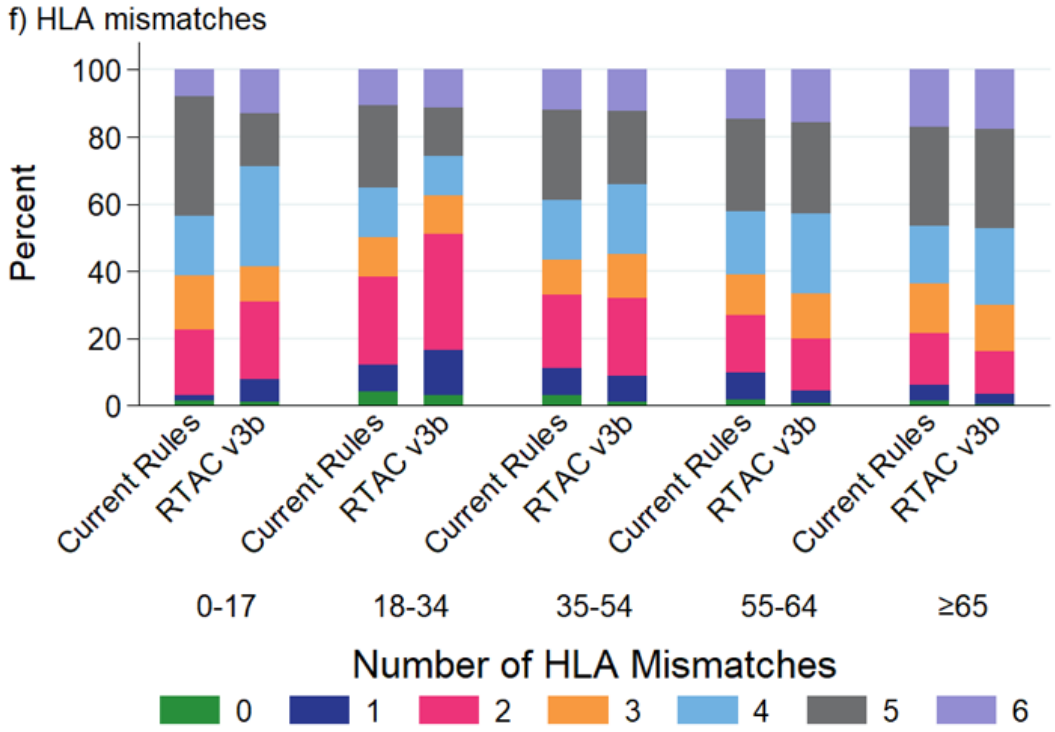

Figure 10.19 Comparison of HLA mismatches for transplants in KPSAM simulations between current rules and modified proposed new rules by recipient age

RTAC v3b includes new national rules outlined in Table 10.6 *with levels 1f-1j removed, the EPTS threshold for eligibility for national level 2 reduced to <25%, the addition of new national levels 3a-3e (based on level 2,3,4,6 and 7 of the current allocation rules shown in Figure 10.9) and current regional rules*

Restricting the use of the kidneys with the best predicted survival in recipients with the poorest post-transplant predicted survival

The addition of a two step regional allocation process in which kidneys offers were first restricted to an EPTS-KDPI difference of <60 (meaning that a patient with an EPTS of 100% would be excluded from offers of kidneys with KDPI <40%, and so forth) and then allocated without restriction was also proposed. This is intended to reduce the likelihood of kidneys with a very good predicted post-transplant survival (as defined by a low KDPI) being allocated to recipients with a poor predicted post-transplant survival (as defined by a high EPTS). The simulations demonstrated that the allocation system was able to achieve this goal, as shown in Figure 10.20 which plots KDPI vs EPTS across simulations. It was beyond the scope of the study to assess whether this policy is likely to result in improved overall utility of the deceased donor transplant system or what impact this may have on patient and graft survival for candidates with higher EPTS. Iterative simulations of alternative restriction thresholds were not undertaken as part of this study.

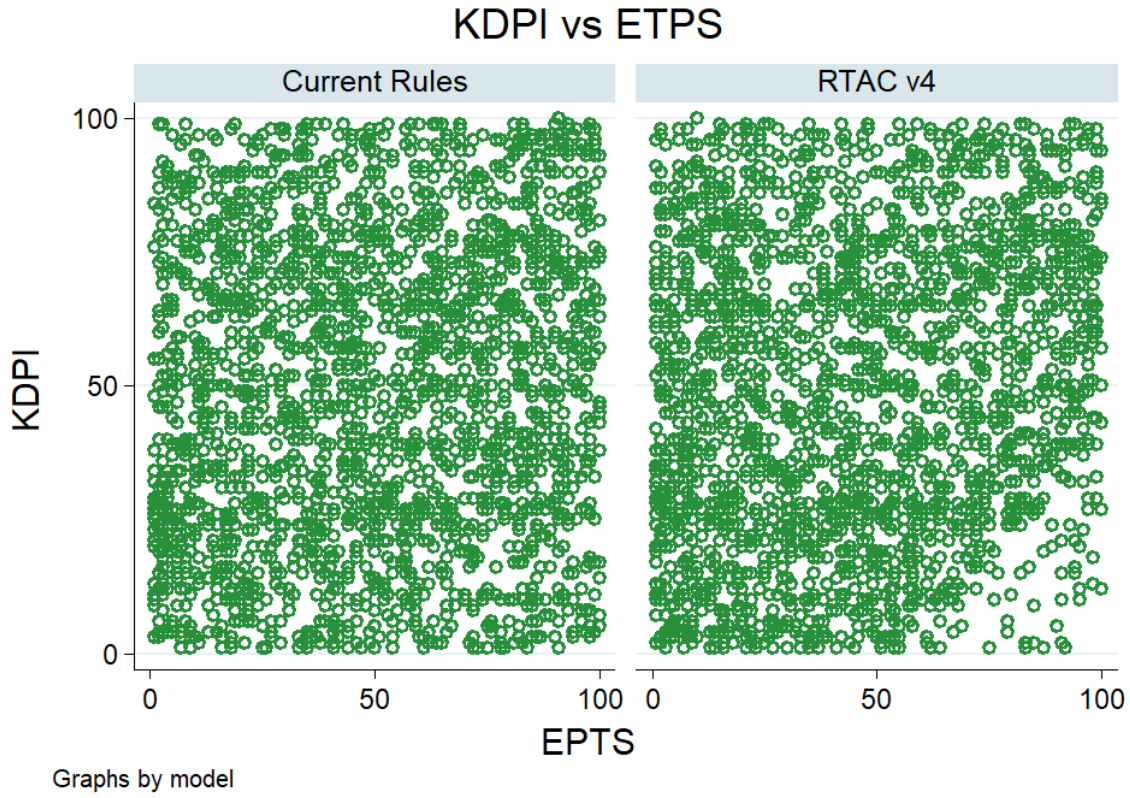

Figure 10.20 Kidney Donor Performance Index (KDPI) plotted against Expected Post Transplant Survival (EPTS) for transplants in KPSAM simulations, comparison between current rules and modified proposed new rules

RTAC v4 includes new national rules outlined in Table 10.6 *with levels 1f-1j removed, the EPTS threshold for eligibility for national level 2 reduced to <25%, the addition of new national levels 3a-3e (based on level 2,3,4,6 and 7 of the current allocation rules shown in Figure 10.9) and new regional rules outlined in* Table 10.7

Developing a standard regional allocation algorithm

Currently each transplanting region in Australia uses a different local allocation algorithm with varying emphasis on HLA matching, waiting time and other factors. One aim of RTAC's policy revision was to harmonize regional allocation algorithms across the country. While there has been general agreement across transplanting jurisdictions regarding the structure of the proposed new regional allocation system, debate exists on the balance between HLA matching and waiting time in allocating kidneys locally. The option was presented to each transplanting region to elect at which level of HLA matching the local algorithm would switch to waiting time based allocation.

The main role of the KSPAM simulations in informing this debate was to provide feedback on the likely impact of using various cut-offs for levels of HLA matching. Simulations of the proposed new system including regional allocation levels 1a-1i as shown in Table 7 resulted in a dramatic shift in the proportion of kidneys being transplanted through HLA matching algorithms (Figure 10.21). (Note that under the current allocation algorithm in Western Australia there is overlap between points awarded based on HLA matching and points awarded based on waiting time, such that the group groups cannot be cleanly separated and are therefore presented as one category). This increase was most marked in the two larger transplanting regions as shown in Figure 10.22.

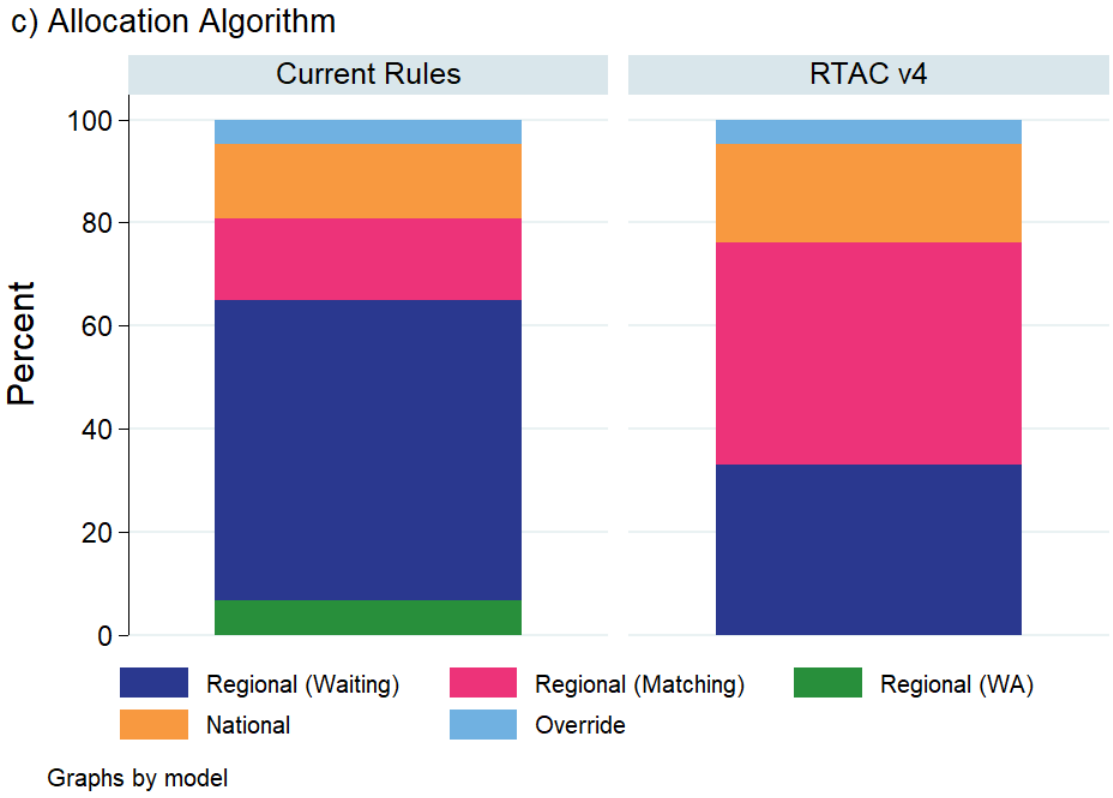

Figure 10.21 Comparison of algorithm used to allocate transplanted kidneys in KPSAM simulations between current rules and modified proposed new rules

RTAC v4 includes new national rules outlined in Table 10.6 *with levels 1f-1j removed, the EPTS threshold for eligibility for national level 2 reduced to <25%, the addition of new national levels 3a-3e (based on level 2,3,4,6 and 7 of the current allocation rules shown in Figure 10.9) and new regional rules outlined in* Table 10.7

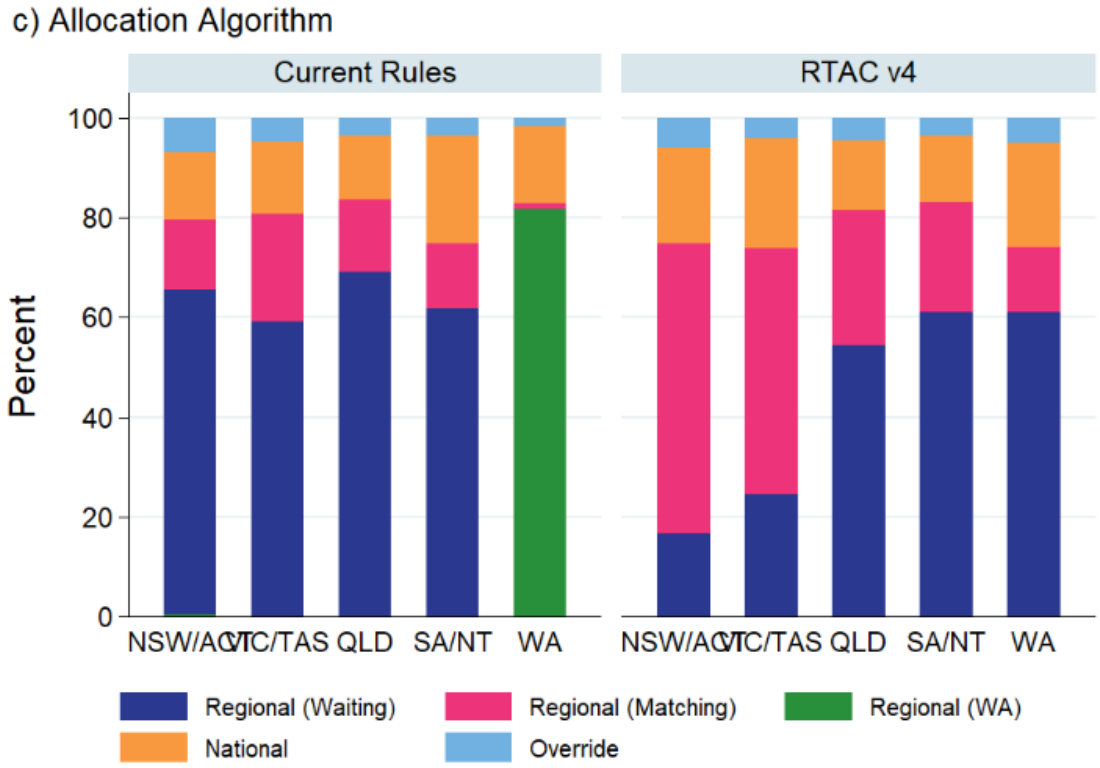

Figure 10.22 Comparison of algorithm used to allocate transplanted kidneys in KPSAM simulations between current rules and modified proposed new rules

RTAC v4 includes new national rules outlined in Table 10.6 *with levels 1f-1j removed, the EPTS threshold for eligibility for national level 2 reduced to <25%, the addition of new national levels 3a-3e (based on level 2,3,4,6 and 7 of the current allocation rules shown in Figure 10.9) and new regional rules outlined in* Table 10.7

Analysis of simulation outcomes showed that not only would the proposed new regional allocation rules result in a substantial reduction in the proportion of kidneys allocated based on waiting time, but that the increased emphasis on HLA matching would likely have a different effect on patient groups based on ethnicity. Figure 10.23 shows that under the new regional allocation rules the transplant rate the dominant ethnic group (Caucasian) increased whereas there was a reduction for Indigenous Australians, and although there was little change for other minority ethnic groups, transplant rates in these populations remained well below those of the majority population.

Through iterative simulations of various alternative cut-off levels for HLA matching base allocation we were able to provide feedback on the likely impact of various thresholds to representatives on the allocation committee in order to assistant each region with defining the preferred local cut-off based on local population demographics and other regional priorities.

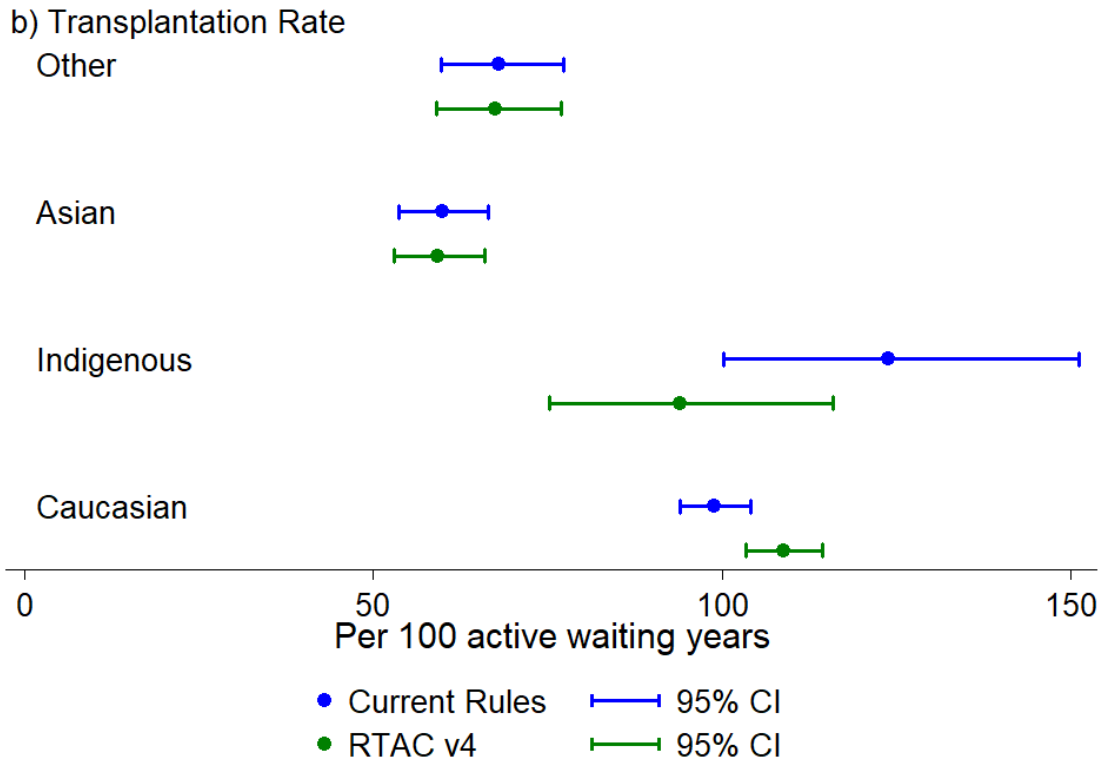

Figure 10.23 Comparison of transplant rate in KPSAM simulations between current rules and modified proposed new rules by recipient ethnicity

RTAC v4 includes new national rules outlined in Table 10.6 *with levels 1f-1j removed, the EPTS threshold for eligibility for national level 2 reduced to <25%, the addition of new national levels 3a-3e (based on level 2,3,4,6 and 7 of the current allocation rules shown in Figure 10.9) and new regional rules outlined in* Table 10.7

Comment

The results presented above represent some illustrative examples of the process of simulation, analysis, discussion and redesign that occurred over the 10 months of this process. In reality this involved a continual process of minor adjustments to models, assessment of outcome reports, consultation with members of the RTAC committee and further adjustments. The dynamic and flexible nature of this approach is challenging to portray in a static description of outcomes and the results presented should not be taken as a complete report of all policy improvements that resulted from the analysis of simulation outcomes.

10.7.1 Final policy proposal

Following a number of adjustments based on simulation and discussion among members of the committee, a final revised allocation protocol was agreed upon and endorsed by RTAC in July 2020. This will now be forwarded to the Organmatch Strategic Governance Committee for final review and implementation. Details of the final algorithm are shown in Figure 10.24 (reproduced with permission).

DRAFT ALLOCATION PROPSAL

National

"Urgent" multiorgan (heart/lung/liver)- TBD

5 new levels for sensitisation (Blood group compatible)

#Level 1Ai: cPRA ≥99.7%	99 700 000
#Level 1Aii: cPRA ≥ 99%	99 000 000
#Level 1B: cPRA ≥ 98%	98 000 000
#Level 1C: cPRA ≥ 97%	97 000 000
#Level 1D: cPRA ≥ 96%	96 000 000
#Level 1E: cPRA ≥ 95%	95 000 000

"Non urgent" multiorgan (heart/lung/liver)- TBD

Orphan ANZKX

4 new levels for well matched patients with low EPTS (Blood group matched)

# Level 2A: 0 HLA MM and EPTS <25	89 000 000
# Level 2B: 1 A/B HLA MM and EPTS <25	88 000 000
# Level 2C: 2 A/B HLA MM and EPTS <25	87 000 000
# Level 2D: 0 HLA MM and EPTS <60	86 000 000

SPK- TBD

cPRA >80% (Blood group matched)

# Level 3A: cPRA >80% 1 MM	79 000 000
# Level 3B: cPRA >80% 2 MM	78 000 000
# Level 3C: cPRA <=80% 1 A or B MM (centre credit difference <-3)	77 000 000
# Level 3D: cPRA <=80% 2 A or B MM (centre credit difference <-6)	76 000 000
# Level 3E: Centre credit difference ≤-20 (No DR homozygous bonus)	75 000 000

All National levels have a 250 000 bonus for paediatrics and 500 000 bonus if donor DR homozygous

State

State urgent (Base score 60 000 000)

Allocation initially restricted to EPTS-KDPI<60, then unrestricted KDPI max at clinicians discretion

State Matching

# 1a 0 0 0	49 000 000
# 1b 1 0 0 / 0 1 0	48 000 000
# 1c 1 1 0	47 000 000
# 1d 0 0 1	46 000 000
# 1e 2 0 0 / 0 2 0	45 000 000
# 1f 1 0 1 / 0 1 1	44 000 000
#1g 2 1 0 / 1 2 0	43 000 000

500 000 bonus if donor DR homozygous

Ability for States to determine at which level to move from "matching" to "waiting"

State waiting (Base score 40 000 000)

Waiting time (months) *1

Paediatric State Bonus

Paediatric bonus of 10 000 000

Interstate utilisation

Use state matching criteria with base score 10 000 000

Figure 10.24 Final draft of the new transplant allocation rules for kidneys from deceased donors in Australia (July 2020)

Reproduced with permission from the Renal Transplant Advisory Committee (RTAC)

10.8 Discussion

We present a validated method for simulating deceased donor kidney allocation in Australia and demonstrate how this tool has been utilised in recent policy development to refine and improve new allocation proposals. A long-standing debate about how to improve access to deceased donor kidney transplantation for very highly sensitized patients in Australia has been accelerated by our recent work showing the scale of this disadvantage. Through our simulations we were able to demonstrate that the initial proposals were likely to result in a marked overcorrection of the decreased transplantation rate for patients with cPRA 90-95% and had the unintended consequence of increasing disadvantage for patients with cPRA 80-90%. As a direct result of these findings and the likely impact of alternative algorithms that were modelled and presented to RTAC, this policy was substantially revised to produce a more targeted priority for patients with cPRA ≥95% and retain existing bonuses for patients with cPRA 80-95%. This and a number of other policy revisions based on results of our simulations provide tangible evidence to support the role of simulation in the re-design of the deceased donor kidney allocation system in Australia.

10.8.1 Limitations of the model

While KPSAM is a mature software platform that has been successfully used in the US context in the design of the updated kidney allocation scheme[53], there are inherent limitations to the software and specific issues with adapting it to the Australian context. Early in this project, the authors investigated the possibility of building an alternative simulation program rather than adapting the KPSAM platform, however, sufficient

resources to design, program, test and validate a de novo simulation platform were not available.

A key issue with any simulation of human behaviour (such as in the acceptance of an organ offer) or a complex organic process (such as graft survival) is the difficulty in representing the complexity of factors contributing to these outcomes through a mathematical formula. In KPSAM, this is particularly relevant for the logistic regression model used to determine offer acceptance. As outlined in the methods above, this statistical model attempts to represent at least two distinct processes that contribute to the conversion of an organ allocation to a successful transplant, that of performing a cross match and the clinical decision to accept or decline the organ. KPSAM uses a Monte-Carlo technique to introduce a stochastic element into this simulation and multiple approaches were used to refine and optimise the logistic regression model used to calculate the probability of offer acceptance, as outlined above. Nonetheless this remains an important limitation of the simulation model, particularly in that clinical decision making is likely to be influenced by changes in allocation rules themselves, an impact that cannot be accounted for in our simulations[74].

The use of the offer conversion model as the mechanism for determining organ discards is another limitation of our simulations. The mechanism was defined for the US context, where discard rates approach 20% of all kidneys retreived[91], more than four times the rate seen in Australia[225]. We found that titration of the permissible number of organ offers before discard to achieve simulations that approximated the actual number of discards in Australia produced a model that was overly sensitive to changes in allocation rules in terms of discarded organs. Our solution to this problem was to exclude kidneys from the model

that were likely to be discarded regardless of acceptance behaviour. As a result the ability of our simulations to accurately model discard rates is limited and should be recognized in interpreting the simulation output.

As KPSAM was designed and built for the US context, the data input specifications reflect data available to the SRTR and in some cases variables were not available in which cases imputation methods were developed. Two key examples of this are the imputation of a record of cPRA changes over time for transplant waiting list candidates and a curation of the raw anti HLA antibody data available into a list of unacceptable antigens updated for each candidate throughout the simulation. Although we are confident in the rigour of our imputation methods, the reliance on specific assumptions and the limitations in available data introduce a potential source of error in our simulations. The inability of KPSAM to track inter-regional shipping debit during the simulation also meant that we were unable to directly simulate Australia's current system for balancing inter-regional sharing of kidneys. A novel method of assigning a Centre Credit Difference to each candidate and organ based on a random number generated according to a Poisson distribution with the distribution mean varying across regions was developed to address this and was adjusted to reflect current organ sharing patterns.

In analysing our simulation outcomes, we found that overall exposure time for years active on the transplant waiting list was around 9% lower in our base model simulations compared to ANZDATA data, resulting in an overestimation of transplant rates in our simulation. The difference in calculated exposure time was not uniform throughout the simulation period, with the bias increasing as the simulation progressed, indicating that the error resulted from

an issue with appended waiting time histories. Our methods for imputing waiting list histories for those patients who received actual deceased donor transplants during the study period involved appending histories from patients with similar projected survival as it was assumed that predicted survival on the waiting list would be associated with a pattern of ongoing waiting list status changes. Multiple alternative strategies were explored in an attempt to address the discrepancy in exposure time, including stratification of the population by comorbidity profile in the imputation methods and revising the patient survival model used for calculating propensity scores, however a satisfactory solution was not found. Although this limitation should be appreciated, as simulations of the current allocation rules rather than actual ANZDATA data was used as the comparator for simulations of alternative rules, the systematic bias in exposure time was present in both the intervention and comparator populations and is therefore less likely to impact overall conclusions.

10.8.2 Benefit and limitations of study design

The aim of this study was to demonstrate a proof of concept, firstly that simulation techniques could accurately model the Australian deceased donor allocation system, and secondly that these models could be used to assist in optimising policy design. The serendipitous timing of the current round of policy revision being undertaken by RTAC that coincided with the final validation of our base simulation offered an opportunity to directly influence policy development. However, this timing meant that rather than the authors designing an allocation algorithm to optimise transplantation rates for very highly sensitized patients and using simulations to test this, as had been the plan at the inception of this project, rules proposed by RTAC were used as the starting point for a series of progressive

refinements. As a result of the political realities that constrain policy development and implementation the proposed rules were designed to be a pragmatic and achievable interim solution, able to be implemented within the current framework of the allocation system, rather than an optimal redesign. In some ways this constraint has limited the ambition of this project in developing an optimised allocation system, however, this trade-off has been balanced by the opportunity for this work to result in meaningful changes that will have direct impact for highly sensitized patients on the waiting list.

With the goal of achieving consensus among stakeholders, the key focus of outcome reporting in this project has been determining the effectiveness of proposed targeted interventions in achieving the intended goals whilst assessing the potential impacts on equity within the system, rather than a more ambitious goal of also optimising utility. Our reporting has focussed primarily on access to transplantation for various populations and the characteristics of the organs for subpopulations, however we have not attempted to examine the likely impact these changes will have on graft and patient survival either across the entire system or for individual patient groups.

Some of the proposed changes, such as improving access to well matched kidneys for younger recipients and restricting kidneys with the best predicted survival from being allocated to recipients with poorer predicted survival, are clearly intended to improve the utility of the system, either for specific patient groups or for the system as a whole. In this project, we have intentionally chosen not to address questions related to what improvements in utility might be expected from these interventions or at what threshold (of EPTS-KDPI, for example) overall utility gains might be maximised.

This limitation of scope was intentional, for a number of reasons. Firstly, the pragmatic aim of this study was to inform policy development within a limited time frame and by limiting the scope of reporting we were able to provide targeted and direct answers to specific questions. Secondly, assessing the utility of the transplant system involves long term projections of graft outcomes, patient survival and other phenomena such as the risk of sensitization. Such predictive modelling on a timeframe of decades with models trained on historical data and the requirement for extensive extrapolation of predictions would introduce substantial uncertainty to the simulation outcomes. Whilst this is valuable as a research objective, we did not feel we would be able to develop models of sufficient reliability to be informing policy debate within the required timeframes. Finally, it is not clear that the maximisation of utility is necessarily desirable. As discussed in Chapter 9 of this thesis, the design of a deceased donor kidney transplant allocation system involves the balancing of many competing priorities and that may differ across various stakeholders. The maximisation of utility at the expense of equity for a specific population may be unacceptable to some stakeholders, or alternatively the goal may be to avoid large opportunity costs rather than the maximisation of benefit. These remain interesting and valuable research questions, which will be pursued in future studies.

In taking a pragmatic approach to the scope of this study, our findings have significantly shaped the next iteration of deceased donor kidney transplantation in Australia. Despite the intentions of the initial policy proposals to improve transplantation rates for very highly sensitized patients in Australia, it is likely that without the evidence presented through our simulations that the new policy would have overcorrected the disadvantage for some

patients and produced new, unintended inequities for others. Similarly, we have assisted in defining a more targeted population for a new system aimed to improve access to well matched kidneys for patients who are most likely to benefit from this, in comparison to the initial proposal which would have resulted in a dramatic increase in organ shipping and reduced access for long waiting patients. These and other important modifications made to the initial proposals provide tangible evidence of the benefits of simulation as a tool in deceased donor allocation policy design.

10.8.3 Future research

A key element in the cycle of policy change is post implementation auditing and policy revision. While simulation provides a powerful tool, due to the inherent uncertainties in predictions and the potential for changes in clinical decision making based on new conditions, is it essential the impacts of the new allocation rules be closely monitored and if necessary, alterations made to correct unforeseen and unintended consequences. As part of this body of work we plan to develop a comprehensive and transparent auditing process to both feed back to the allocation committee and to assess the accuracy of our simulations.

Having demonstrated the value of simulation in a process of policy design using this adapted platform, we plan to develop a custom-built simulation that will address many of the limitations of the model outlined above and allow for more flexible, comprehensive and dynamic simulating capacity. By nature of its design, KPSAM uses a bespoke language for coding data definitions, allocation rules and other inputs as well as very specific file specifications for patient and organ input files. The separate process required to generate statistical models and input files using external statistical software (Stata) with additional

manual formatting to fit KPSAM specifications dramatically reduced efficiency of running iterative simulations and were prone to errors.

In building an integrated simulation tool that can directly process registry data to produce input streams and update statistical models within the simulation, we aim to not only improve the efficiency of manual iterative adjustment but to also build the capacity for internal optimisation to achieve defined targets. Rather than specifying allocation rules and manually interpreting the outcome of a simulation of those rules, the ultimate goal of this project will be to define the goals that the system aims to achieve and allow the simulation to iteratively adjust the allocation rules in order to determine optimised thresholds and scaled bonus points, for example. We have demonstrated how our current simulation model can help us understand if proposed interventions are likely to achieve what is intended; the next step is to build a tool that will define the allocation formulas that will achieve the intended outcomes.

Chapter 11 Conclusions and Future Directions

The projects presented in this thesis demonstrate the value of clinical epidemiology in understanding, evaluating and reshaping a national deceased donor kidney allocation program. In considering the breadth of interconnected processes that constitute the deceased donor kidney transplantation system, this body of work has provided insight into current practice, assessed impacts of previous interventions and provided evidence to guide future policy development. I have demonstrated the feasibility of using simulation to redesign and refine new allocation proposals and used these tools to directly impact policy implementation. Each of these studies addressed a separate aspect of this complex system. Taken together, I hope that they collectively contribute to the overall goal of improving the effectiveness, efficiency and equity of deceased donor kidney transplantation in Australia that will ultimately result in better long term outcomes for patients living with end stage kidney disease.

11.1 Summary of findings

In responding to key gaps in knowledge identified by registry reporting, Chapters 3 and 4 shed light on aspects of the current deceased donor allocation system. The first reported comprehensive analysis of predictors of deceased donor kidney transplant waitlisting in Australia, presented in Chapter 3, identifies demographic characteristics that are associated with reduced access to transplantation. Whilst it may be expected that comorbidities contributing to poor post-transplant outcomes are associated with a lower likelihood of waitlisting, the identification of gender, Indigenous ethnicity, socio-economic status and remoteness as independent determinants of access to transplantation, highlight an urgent need to address these inequities. In demonstrating the association between age and waitlisting under current practice in Australia, this study reveals the potential for a dramatic increase in waiting list numbers as a result of the recent changes in eligibility criteria for deceased donor kidney transplant waitlisting, depending on how the re-wording is interpreted by clinicians. Although this may provide the opportunity to access the benefits of transplantation to a broader range of patients, the impacts on to allocation of organs to other populations and the overall outcomes of the system need to be considered in order to enable appropriate planning and policy adjustment.

The analysis of potential causes of the increase in kidney non-utilisation in Australia observed in 2013 also provides insights that not only assist the donation sector in optimising donor assessment processes, but also help to inform the design of allocation policy. This study found that, unlike in the United States (US) where increases in kidney non-utilisation can be largely explained by changes in donor characteristics, in Australia the observed

increase in recent years is independent of donor factors. This strongly suggests that alongside an expanding donor pool, clinician offer-acceptance behaviour has also changed. An algorithm that allocates kidneys to recipients for whom the offer is likely to be declined, increases donor coordinator workload and may have detrimental clinical impacts by increasing ischaemic time and potentially exacerbating the rise in organ non-utilisation.

Chapters 5, 6 and 7 each assist in the process of redesigning the allocation system by exploring the impacts of recent policy interventions. In assessing the effects of Kidney Donor Performance Index (KDPI) reporting with deceased donor kidney offers in Australia, Chapter 5 builds on the findings of Chapter 4 to give further insights into offer acceptance behaviour and organ non-utilisation. This analysis identified that the reporting of this metric (without it having any role in the allocation algorithm itself) was associated with an increase in the number of offer declines for kidneys with a higher risk of graft failure post-transplant but not a significant change in non-utilisation for these organs. A small improvement in donor/recipient age matching and risk indices alignment for the higher risk kidneys implied that the reporting of KDPI may be contributing to more targeted utilisation of these grafts, however, these findings suggested that optimising the utility derived from lower risk kidneys would likely require targeted changes in allocation.

In Chapter 6, I report on the effectiveness of the targeted priority for highly sensitized patients within the current allocation system in the context of evolving technology used in defining HLA sensitization for candidates on the Australian deceased donor kidney waiting list. The findings of this study show that the somewhat procedural changes from panel reactive antibody (PRA) to calculated panel reactive antibody (cPRA), introduced in 2016,

resulted in a dramatic increase in the proportion of patients on the waiting list defined as highly or very highly sensitized. Furthermore, that the current priority for highly sensitized patients, based on a cPRA of >80% and linked to HLA matching, was both poorly targeted and ineffective at addressing the inequities in the transplantation rate according to sensitization as defined by cPRA. Although these findings were expected based on international studies and clinical experience, demonstrating the magnitude of change with the introduction of cPRA, together with the degree of disadvantage experienced by the most highly sensitized candidates within the current Australian context, has propelled this debate and had a direct impact on advancing the implementation of changes to address this issue.

The study presented in Chapter 7 was commissioned as part of a process of planned reform and also aims to audit the impact of previous allocation changes and assist in optimising the effect of targeted priority for a specific population. This 30 year review into paediatric deceased donor transplantation and the impact of paediatric allocation bonuses was undertaken as part of my role in the National Review of Paediatric Kidney Transplant Recipients in Australia conducted by the Transplantation Society of Australia and New Zealand (TSANZ). While in the setting of a staggered introduction of bonuses at national and regional levels over a period of decades and small event numbers, it is difficult to ascribe causation to the implementation of specific bonuses. This study found that under the current allocation system, some, but not all, goals are being achieved for paediatric kidney transplant recipients. Although current rules facilitate rapid access to high quality donors for paediatric candidates, immunological matching (insofar as this is indicated by the number of HLA -A, -B and -DR antigen mismatches) has not improved in recent years and remains

suboptimal. These finding suggest that Australia, like a number of other international transplanting jurisdictions, should consider implementing paediatric bonuses that are explicitly tied to immunological HLA matching or potentially include more novel strategies to reduce immunological risk of paediatric transplant recipients.

Whereas the five chapters described above examine outcomes under the current allocation system in order to find evidence for how a revised system should be optimised, Chapter 8 and 9 use two different strategies to investigate what novel aspects might be included in a redesigned algorithm. In order to build towards a proposal to implement HLA epitope based allocation into the Australian's algorithm, the study presented in Chapter 8 aimed to expand on a promising but limited evidence base for the benefits of HLA epitope matching (reviewed in Chapter 2). The potential benefit of reducing immunological risk associated with kidney transplantation, including prolonging graft survival, minimising immunosuppression exposure and reducing the risk of sensitization that may hinder future transplant opportunities are most pronounced for paediatric recipients. Due to the limitations in data available to conduct this study, the overall conclusions are limited. Depsite these limitations, this analysis showed that HLA eplet mismatches (EpMM) are a strong predictor of the surrogate endpoint of donor specific antibody formation in paediatric kidney transplant recipients. There was a signal that EpMM are associated with important hard clinical endpoints of graft failure, and a reduction in re-transplantation, although these finding were attenuated on adjusted analysis. This study is one of the first to consider the impacts of antibody-verified EpMMs specifically and indicated a stronger association with clinical endpoints fort this subset of EpMMs when compared with all EpMMs. Rather than providing conclusive evidence that EpMMs should be considered in

kidney allocation for paediatric recipients, this study further highlights the need for high quality evidence based on robust data collection and larger studies to support an argument for this promising but yet unproven and novel approach to defining histocompatibility for solid organ transplantation.

Chapter 9 stands out from the rest of the thesis, both in its methodology, that departs from the use of registry data to perform retrospective analysis, and in that it addresses a more fundamental question of what the allocation algorithm should be trying to achieve, rather than the more narrowly focused specific questions that frame preceding chapters. This collaboration with researchers from the University of Sydney's School of Public Health uses a quantitative technique for eliciting preferences to compare and contrast the priorities of two key groups of stakeholders in what principles should be guiding the design of Australia's deceased donor kidney allocation program. We found that whilst healthcare professionals working in transplantation and donation tended to preference principles that maximised the utility of the transplant system, members of the general community, who represent the population of potential donors, had a higher preference for equity based principles. This observation and other findings that are explored in further detail in Chapter 9, are a reminder to the healthcare professionals who design and implement policy changes that their experience and knowledge may produce biases in their own viewpoints that may not necessarily reflect the priorities of other stakeholders. On a general level this supports the value of consultation and stakeholder engagement in the process of policy revision and more specifically, may help guide the design process when decisions are being considered that involve trade-offs between utility and equity, for example when the overall survival

benefits of optimising longevity matching is being weighed against the potential reduced access to organs for certain sub-populations.

Finally, Chapter 10 reports on a large body of work that brings together many of the findings of earlier studies in building, validating and demonstrating the value of a simulation platform to test and refine new deceased donor kidney allocation policies in Australia. Using software developed by the US Scientific Registry of Transplant Recipients (SRTR) and building on previous work adapting this for the Australian context, we have established a model capable of simulating allocation proposals to address the key issues being debated in deceased donor kidney allocation at present. While the initial intention of this project was to demonstrate a proof of concept and test novel allocation algorithms developed to correct system deficiencies outlined in previous chapters of this thesis, a serendipitous opportunity arose to demonstrate the role of simulation in a real-world application and directly impact policy implementation. Although the ambition of the simulations presented in Chapter 10 was limited by the practical realities faced in policy development, what was lost in working within the constraints of the current allocation framework and the initial draft policy, was more than made up for in the opportunity to impart meaningful improvements in the policy that will actually be implemented and therefore produce tangible benefits for transplant candidates. The findings of these simulations have had a direct influence on 1) defining a more targeted national priority for very highly sensitized patients, 2) ensuring the inclusion of a priority for patient with lesser, but still clinically significant, degrees of sensitization, 3) defining a more targeted national priority for paediatric and young adult recipients to achieve better access to well matched kidneys, 4) deprioritising the use of kidneys with the best predicted survival in those with the poorest post-transplant predicted survival and 5)

assisting transplanting regions in defining thresholds to balance the proportion of kidneys allocated according to HLA matching compared to primarily on waiting time. In taking a holistic approach to the redesign of deceased donor kidney transplant allocation in Australia, this body of work has not only helped facilitate the implementation of policy changes that directly address some of the most urgent unmet needs of the Australian deceased donor kidney allocation system, but in doing so has hopefully demonstrated the value of an evidence based framework for allocation policy design and laid the foundations for this in Australia.

11.2 Future directions

The work presented in this thesis represents initial steps in an ambitious agenda of research and engagement that hopes to build towards an innovative, evidenced based, transparent and flexible approach to continuous improvement in deceased donor kidney allocation policy in Australia. The main features of this strategy are summarized in Figure 11.1.

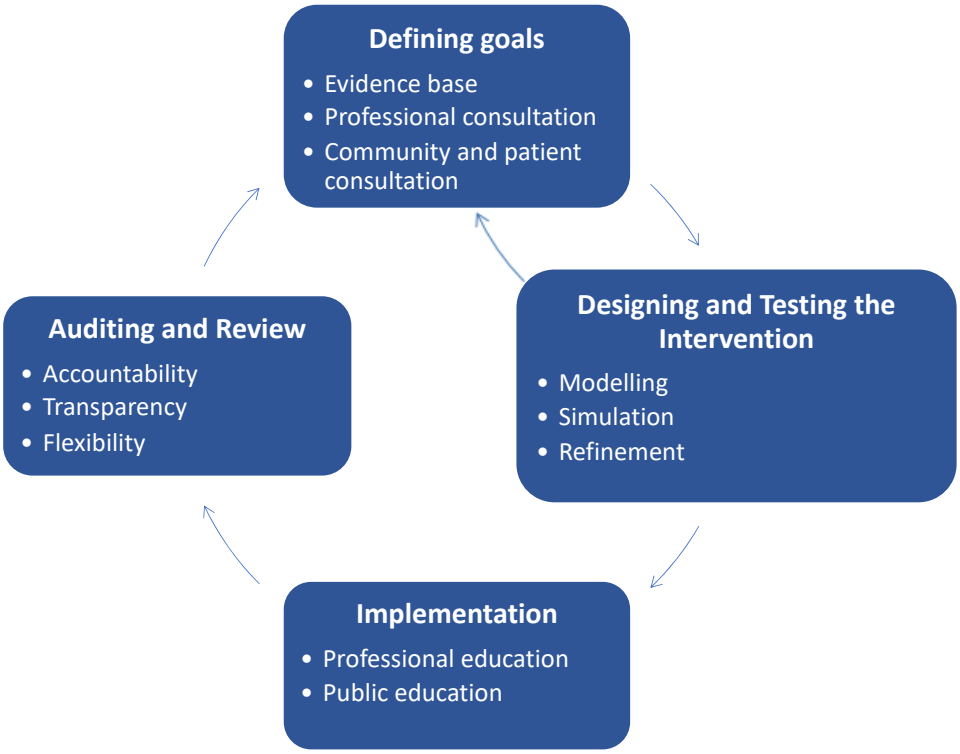

Figure 11.1 Framework for a process of continuous improvement in deceased donor organ allocation policy.

A key element of the design and development of allocation policy is to continuously revisit the goals that the system is trying to achieve. I have highlighted examples of how registry reporting can help identify deficiencies and anomalies in current practice and provide the impetus for targeted research to explore their causes and potential interventions to improve outcomes. Many of the studies I have presented, themselves raise questions that will inform an ongoing body of research. For example, identifying areas of inequity in access to deceased donor waitlisting in Chapter 3 highlights the need for both epidemiological and clinical auditing studies to understand the causes of this disadvantage and interventional research to investigate how to ameliorate it. Following completion of my role as the ANZDATA Epidemiology fellow I will be taking on the position as editor of the ANZDATA Annual Report. In reviewing, summarizing, presenting and communicating the rich data collected through the binational registry, the registry's annual report provides a powerful mechanism for identifying key research questions for targeted inquiry.

While investigating the potential role of HLA epitopes in deceased donor kidney allocation was initially a core aim of this thesis, due to limitations in historical data, this question was only partially explored in Chapter 8 and remains a key area for ongoing study. As reviewed in Chapter 2, the current systems for defining HLA epitope matching are imperfect and further laboratory research is required to better identify immunologically relevant HLA epitopes. Although this work is best left to those with a different skill set to my own, registry based epidemiological studies do have an important role in validating laboratory findings and expanding on clinical trials that often use surrogate end points and have a limited

duration of follow up. Key strengths of registry based studies include the ability to avoid selection bias by capturing the entire population at risk, the low cost achieved by leveraging existing infrastructure and the extended duration of follow up that can capture events occurring on a timescale of decades. Strategies to approach registry based analysis to further validate the utility of HLA epitope based matching include: 1) targeted analysis of groups for whom existing data quality is much higher, such as patients participating in the paired kidney exchange who have mandatory extended high resolution typing available, 2) development of computational methods for imputing high resolution typing from historical serological data using population data from a well profiled dataset such as the national bone marrow donor registry, 3) performing high resolution typing for previous recipients and donors from prospective sample collection or stored serum (although this would be costly and logistically challenging). As high resolution, extended HLA typing rapidly becomes standard of care in deceased donor kidney transplantation, our current approach to allocation based on HLA -A, -B and -DR mismatches at the antigen level is already outdated and evidence to guide the use of a more nuanced approach is needed.

In developing an evidence base for redesigning deceased donor kidney allocation in Australia, this work focused primarily on questions of equity and effectiveness, leaving scope to extend future research into quantifying utility gains of allocation proposals and developing metrics for balancing these two principles. The focus primarily on equity in this work was in part driven by the sense of urgency that arises when the scale of inequity is appreciated (for example in the dramatic reduction in transplantation rates for the 15% of the waiting list with a cPRA of ≥99%) and from the recognition that these principles are a core priority for the broader community, but also from a desire to provide reliability and

accuracy in simulations that had a direct impact on policy development. Due to the excellent long-term graft and patient survival achieved post kidney transplantation, assessing the utility of the deceased donor transplant systems involves modelling on a scale of decades. The prediction models required to simulate long term outcomes must be trained on historical data from periods where surgical techniques, immunosuppressive medication and management of comorbidities were significantly different from current practice, and methods for extrapolation add further uncertainty into prediction models. Expanding the evidence base on strategies to improve the overall utility of the allocation system is a clear priority in continuing to work towards a framework for continuous improvement in organ allocation.

A key component of redesigning the allocation system is not just to ask what can be achieved, but more importantly to ask what we should be trying to achieve. In Chapter 9 I begin to examine these fundamental questions from the perspective of two groups of key stakeholders, however there is a great deal more to be explored. The tools developed in behaviour economics to elicit and quantify preference can be further applied. While the use of a best worst scaling experiment provided a method to efficiently capture and quantify preferences in two separate populations, a follow up study is currently underway using a multilevel discrete choice experiment to estimate quantitative acceptable trade-offs between competing principles. This study will not only help inform the design of the system but will also offer additional quantitative metrics by which simulation outcomes can be assessed. Research into the broader role of community members and patients in the process of policy development and assessment is also required. ANZDATA has recently

established a Consumer Advisory Board providing an ideal forum in which to co-design this research agenda.

I have described the development, validation and practical application of a simulation platform modelling deceased donor kidney transplant allocation in Australia, however, as detailed in Chapter 10 these simulations are not without their limitations and the scope for improvements and optimisation is significant. Leveraging the proof of concept reported in this thesis, I aim to develop a custom-built simulation platform for the Australian context. This would not only address the shortcomings of our simulations that were limited by the structure of KPSAM simulations, but by directly integrating the simulation capacity into the ANZDATA data structure, this would dramatically improve the flexibility and responsiveness of simulation capacity. The goal of this project would not only be to perform static simulations testing user defined changes to the allocation rules, but by incorporating equity and utility metrics into a process of outcome assessment within the simulation platform, to enable the capacity for automated optimisation of the allocation formulas in order to achieve specified outcome targets. Preliminary meetings with the Melbourne Bioinformatics at the University of Melbourne have established the feasibility of this project and produced initial design concepts that will be used to explore funding opportunities for this body of work.

The findings reported in Chapters 5 ,6 and 7 of this thesis demonstrate the importance of post implementation auditing which should ideally be performed prospectively. Vital components of the framework presented in Figure 11.1 are accountability, transparency and flexibility post implementation. As discussed in Chapter 10, even if simulations were

able to perfectly predict the impact of allocation policy changes based on historical conditions, they cannot account for future changes in patient and donor characteristics, laboratory techniques, medical and surgical interventions or clinical decision making that may occur independently or as a direct result of allocation policy changes. Post-implementation auditing not only ensures the intended outcomes are achieved and screens for unintentional effects of policy change, but also provides a mechanism for validating simulation techniques and optimising the accuracy of future simulations. Any change can be confronting as we are often more accepting of the failings of the status quo than we are of deficiencies in a new system, even if these are outweighed by novel improvements. Transparency in reporting the impacts of policy interventions and flexibility in revising the policy to correct unforeseen issues are critical in both optimising outcomes and in gaining trust in the methods of policy redesign, which is an essential prerequisite if we are to promote a more ambitious reimagining of deceased donor kidney allocation in Australia.

11.3 Concluding remarks

The act of organ donation from a deceased donor offers the opportunity for a profoundly positive life-changing event to be born out of another's moment of sorrow. The value of this gift and its potential to be transformative for the person who receives it, places a weight of responsibility on organ allocation systems to ensure it is used justly and effectively. Only in being cognisant of the complex factors that contribute to waiting list access and organ usage, appreciating the competing ethical principles that must be balanced, and taking an evidence based approach to understanding the impacts of the formulae we use to distribute these organ can we ensure that our allocation system does justice to this responsibility.

Epilogue

Of course, kidney transplantation is not a panacea and it is not the only treatment we have to offer our patients. A few months after I met Charlotte, she transitioned from peritoneal dialysis to home-based haemodialysis. Later that year I was pleasantly shocked when a vibrant young woman bounded into my dialysis clinic, freshly returned from a 3 month holiday touring the north of Australia. Thanks to the creativity and hard work of her family, a team of dialysis technicians and nursing staff, the decommissioned bus that Charlotte's family had converted to a portable holiday home had been kitted out with a state of the art portable haemodialysis system and she had driven off to sunny Queensland to escape the cold of a Melbourne winter. It was a pleasure to see her full of energy and regaling me with stories from her adventures. She was still hoping to find her twin kidney, but living life to the fullest whilst she waited.

Charlotte has transitioned to adult services now and I still see her a couple of times a year in the transplant assessment clinic. Typically I check in that her dialysis is going well and that no new issues have come up, and we chat about life – there are never any organ offers to discuss. I'm hopeful that if the bureaucratic wheels turn swiftly enough and the new allocation algorithm that this thesis has helped shape are implemented, the next time Charlotte comes for her transplant assessment clinic I can offer her the reassurance that if, by chance, her twin kidney appears she will be at the very front of the line for that once in a lifetime opportunity. At least that's a start.

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Appendix A: Australian Deceased Donor Kidney Allocation Algorithms

T • S • A • N • Z

The Transplantation Society of Australia and New Zealand

Clinical Guidelines for Organ Transplantation from Deceased Donors

Version 1.3 – May 2019

Produced in partnership with

Australian Government
Organ and Tissue Authority

donatelife

Kidney allocation algorithms

National Allocation formula

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

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

National override list

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

Base score		0
Paediatric bonus	If age <18	+30 000
Peak PRA >50%		+1000*(Peak PRA%-50)
Patient dialysis waiting period >0		+Wait in months*100

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

New South Wales formula (NSW, ACT)

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

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

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

Victorian formula (VIC, TAS)

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

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

Queensland formula

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

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

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

South Australian formula

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

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

West Australian formula

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

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