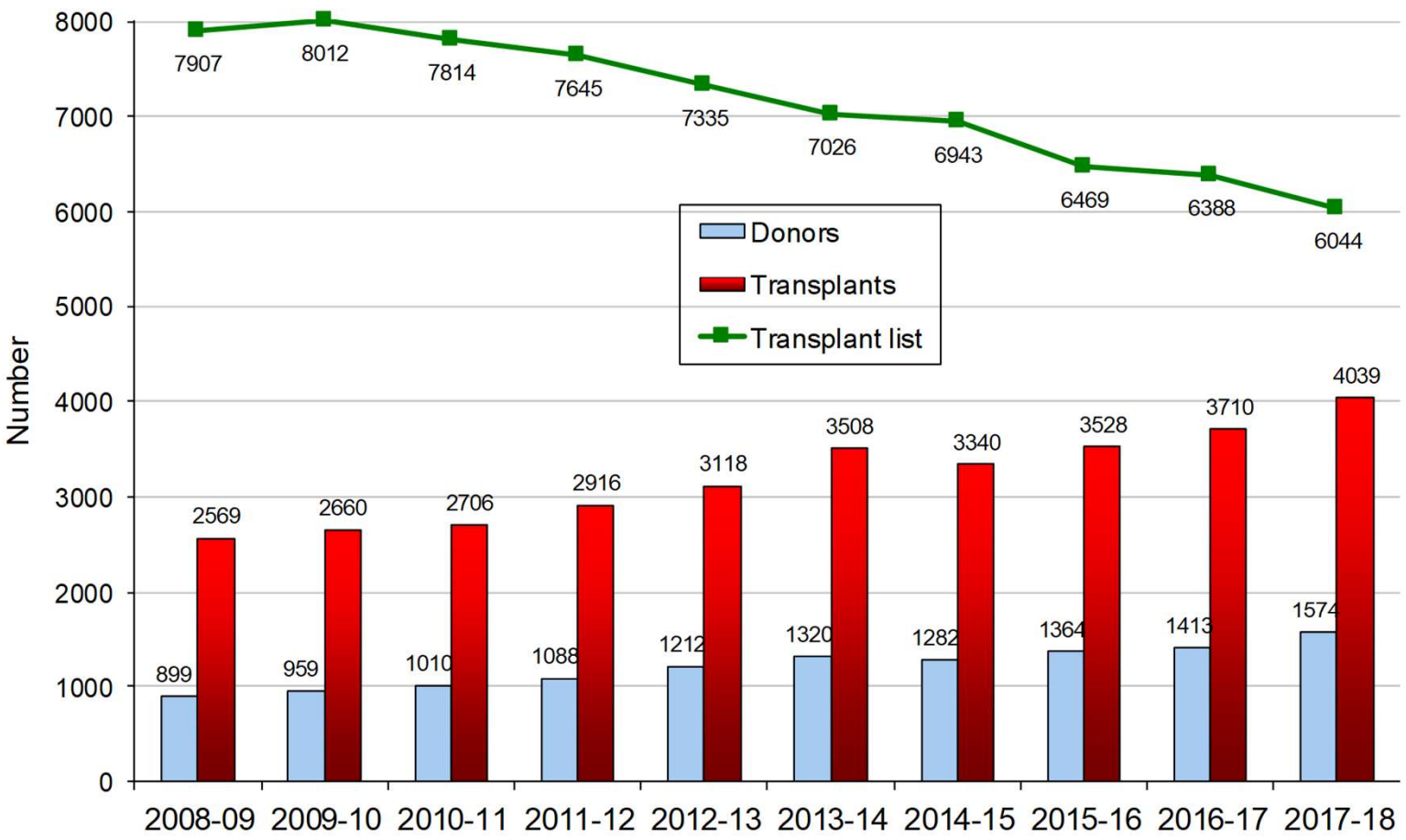
National Histopathology Service for Transplantation

The PITHIA Trial

A stepped-wedge cluster registry randomised trial

@PITHIA_trial

Trends in donation and transplantation



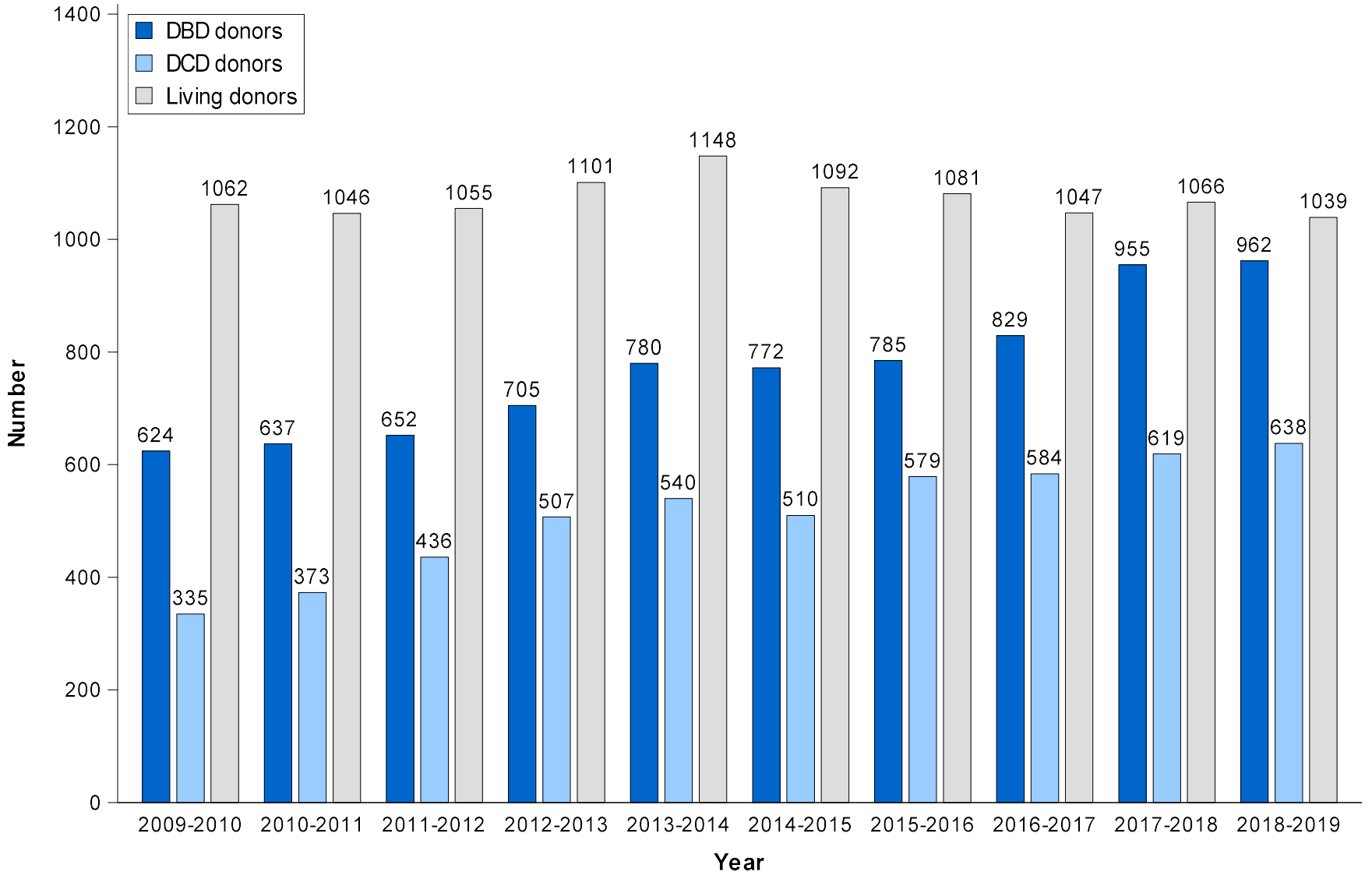
Over the last ten years

24% fall in waiting lists

57% increase in transplants (all organs)

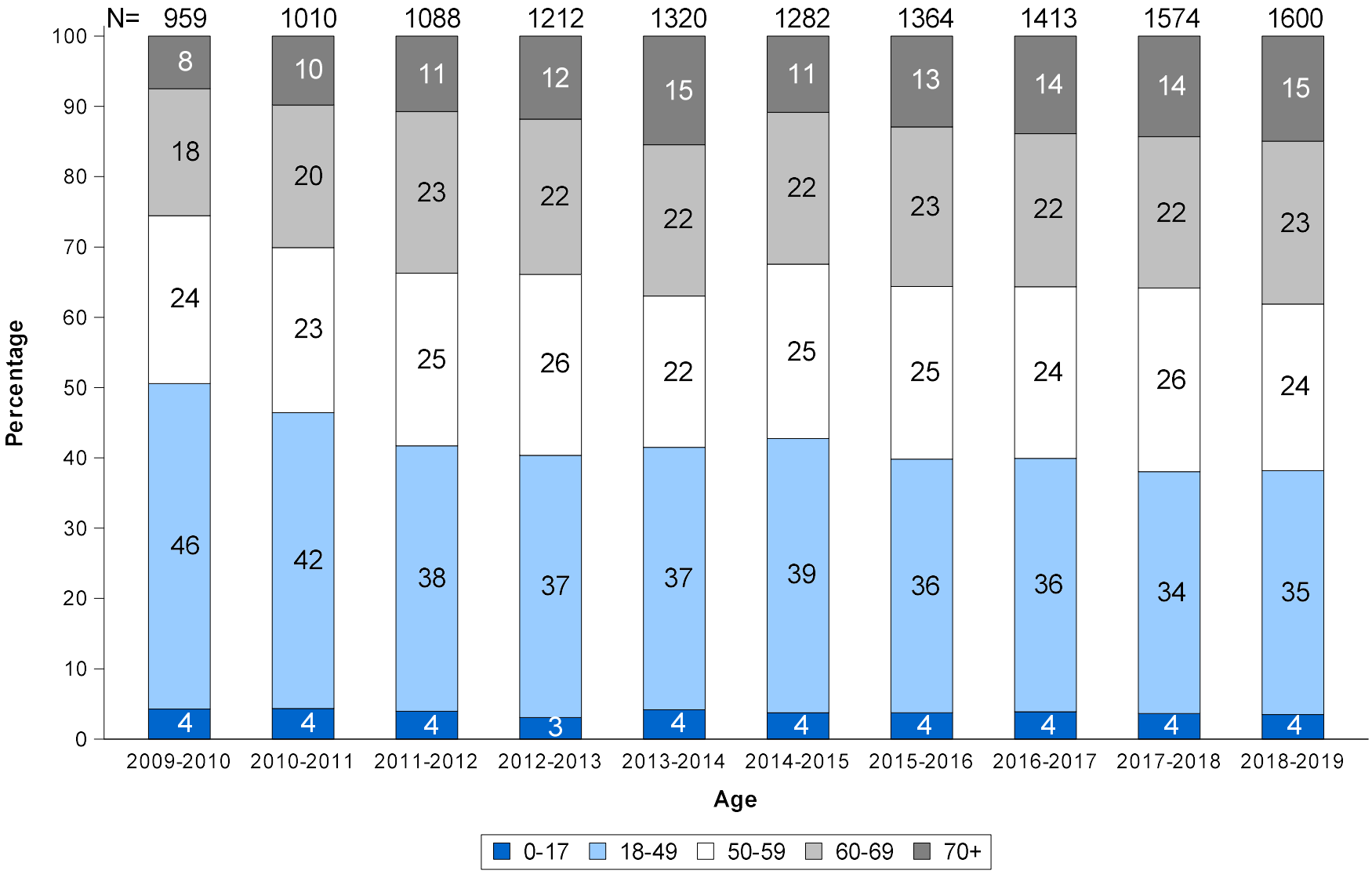
75% increase in deceased organ donors

Number of deceased and living donors in the UK, 1 April 2009 - 31 March 2019



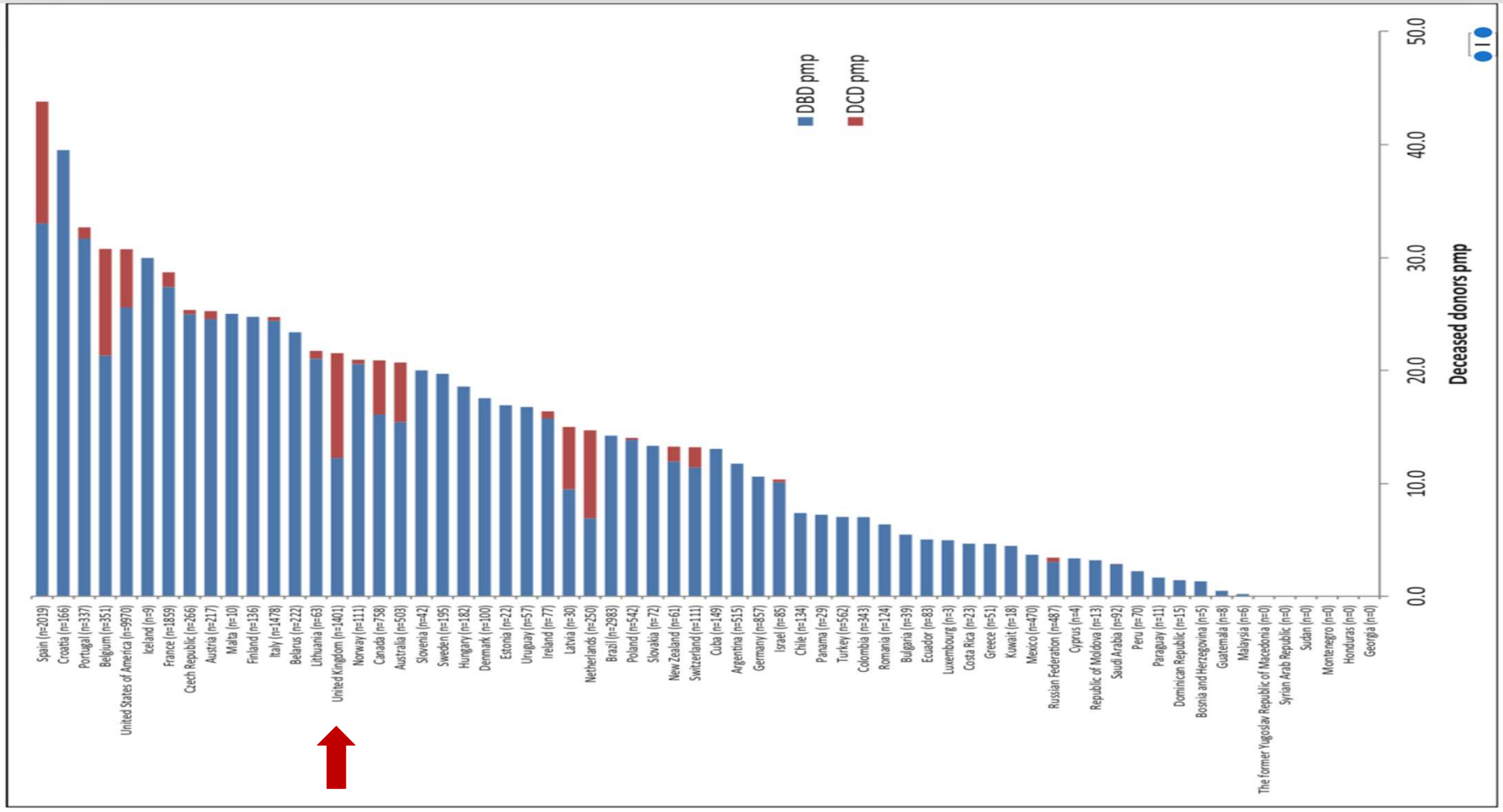
Source: Transplant activity in the UK, 2018-2019, NHS Blood and Transplant

Age of deceased donors in the UK, 1 April 2009 - 31 March 2019



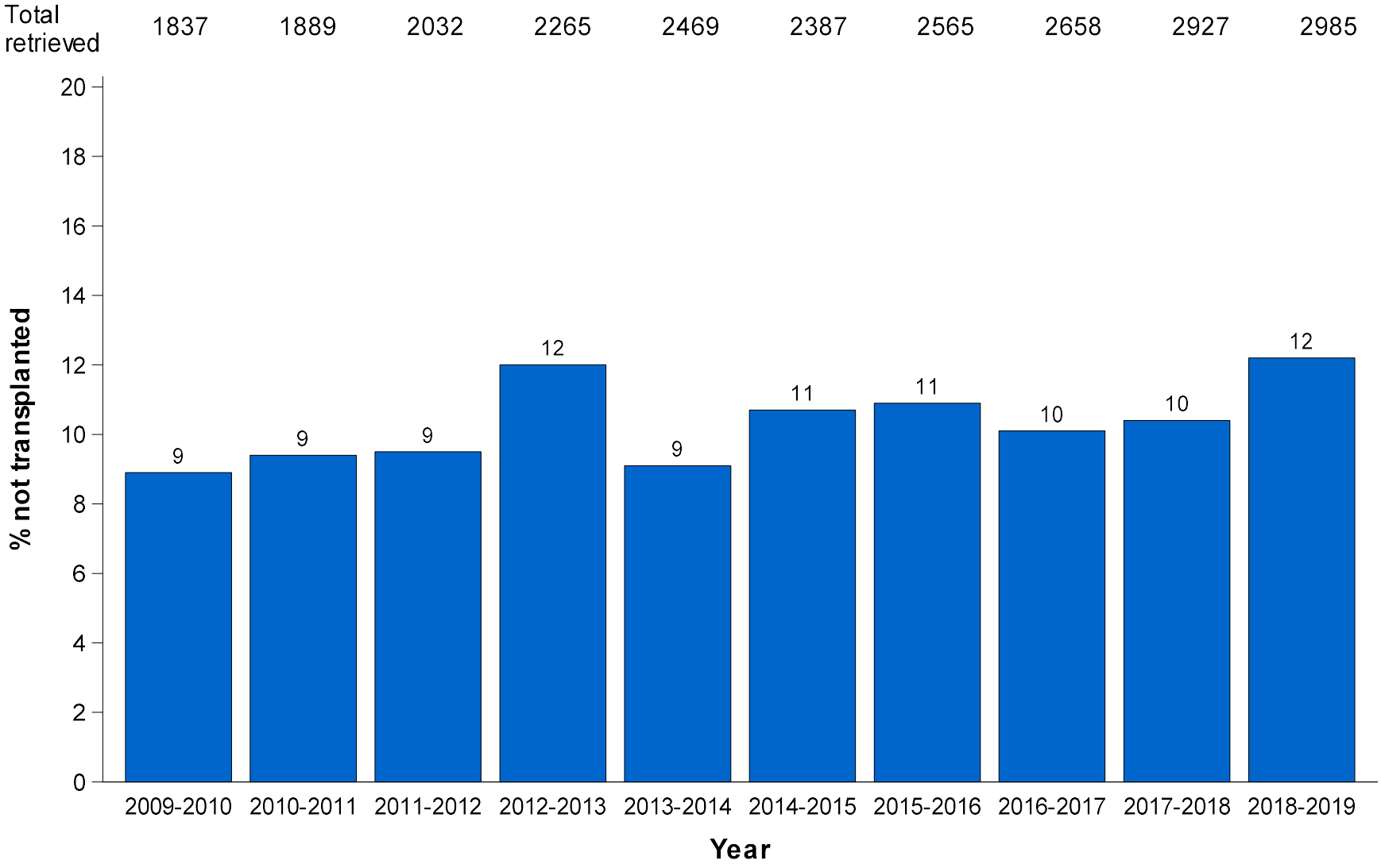
Source: Transplant activity in the UK, 2018-2019, NHS Blood and Transplant

International donor rates 2016



Minambres et al

Percentage of kidneys retrieved that were not transplanted from deceased organ donors in the UK, 1 April 2009 - 31 March 2019



Source: Transplant activity in the UK, 2018-2019, NHS Blood and Transplant

The oracle in transplantation?

> 70% people dying in critical care >50 years

Use of kidneys from older donors has increased donation

Only 28% of offered kidneys from donors >60 years are transplanted

Shortage of kidneys

More than 3 times as likely to lose kidney if donor > 60 years

Primary non-function (PNF) 4.2% vs 1.9%

PNF mortality – 25% at 1 year

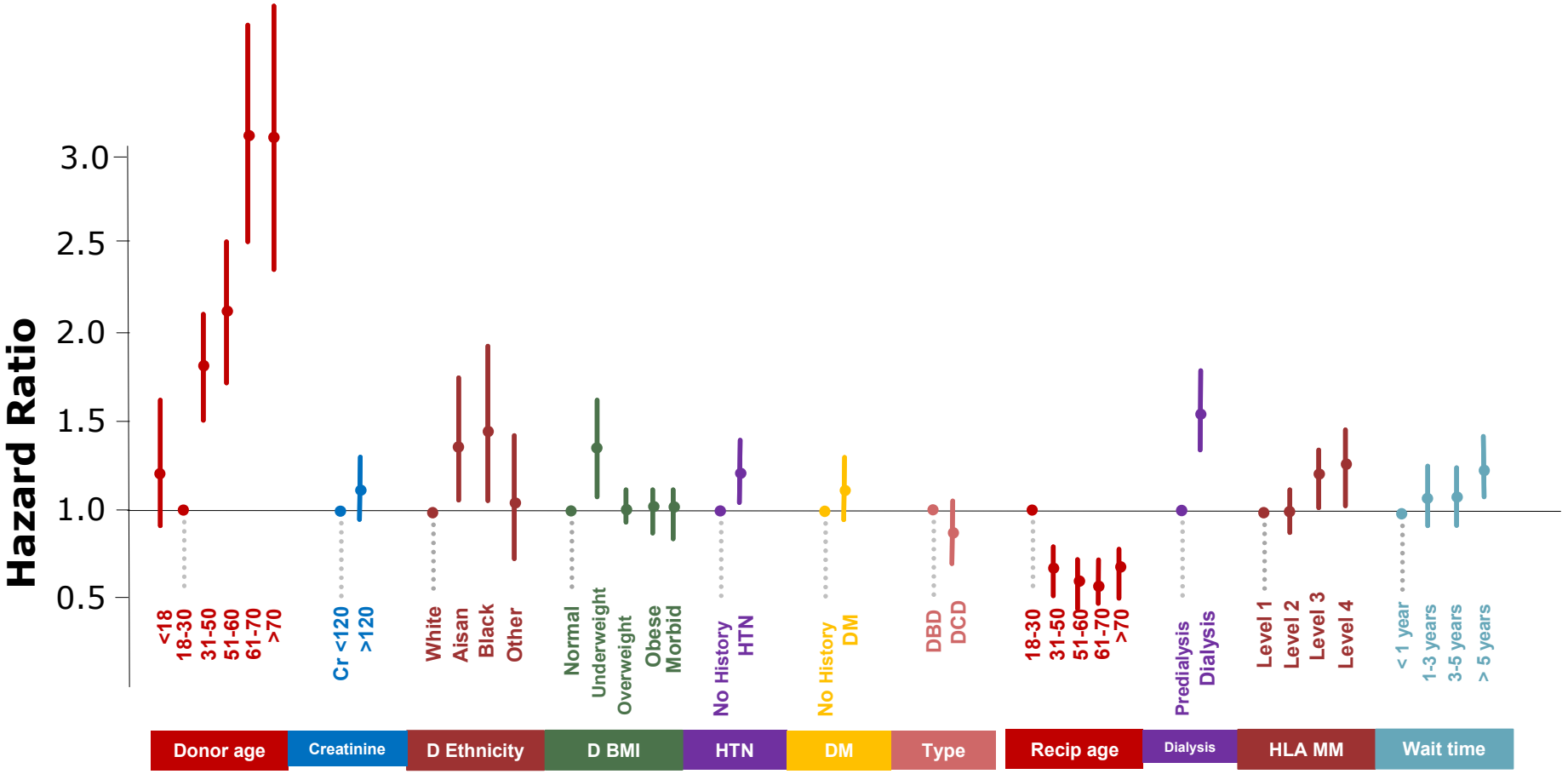
How to sort the transplantable from the not?

Biomarkers

Machine perfusion

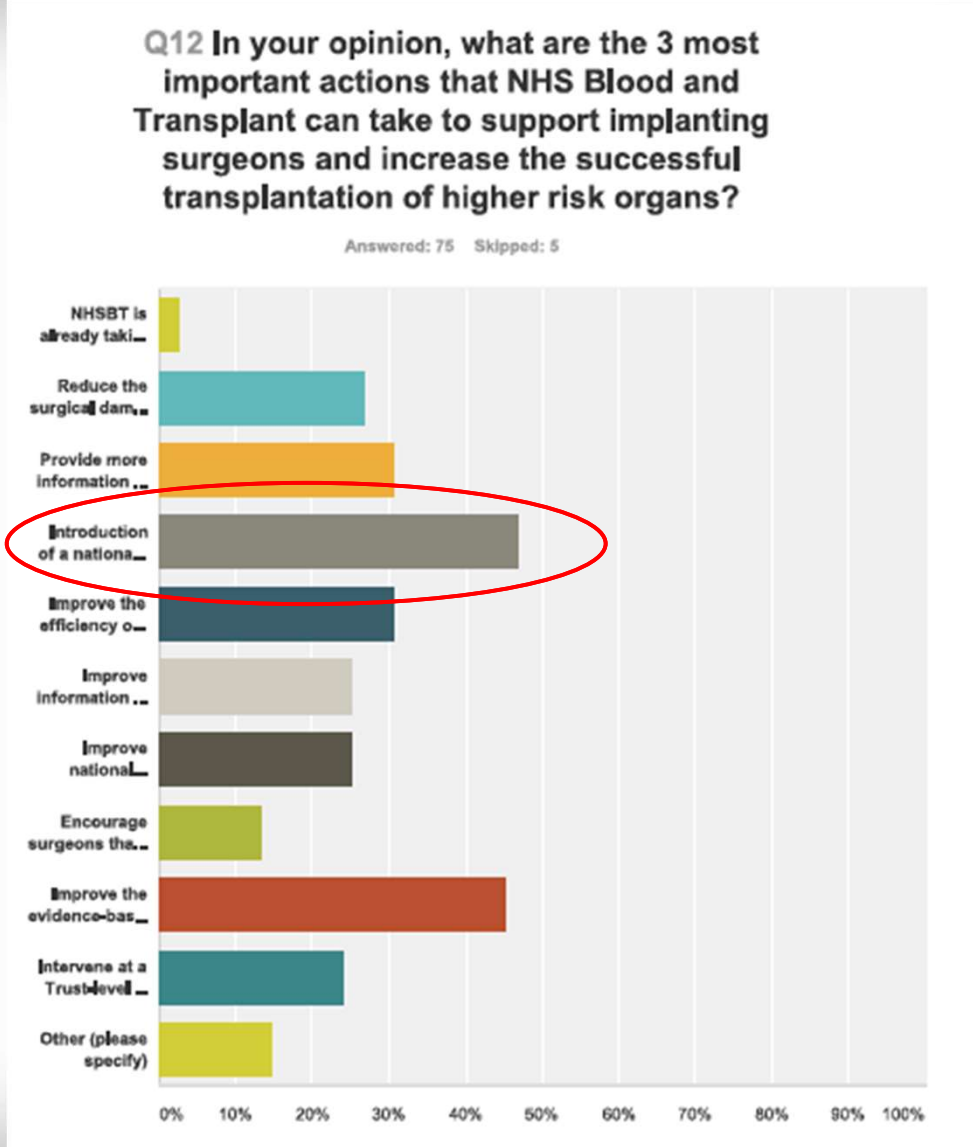
Risk modelling

10 year death-censored graft survival model



Results – NHSBT actions

- Support for:
  - National 24/7 histopathology service
  - Improved evidence-base
  - Improved offering, allocation, and transport
  - More information on organ appearance



National Histopathology – the Consortium

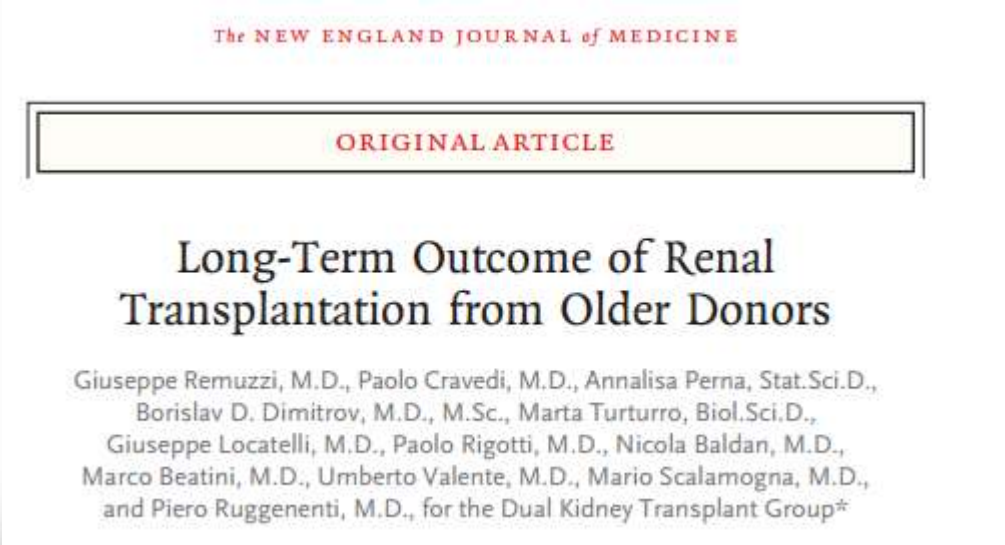
- *NHSBT John Forsythe, Rutger Ploeg, Claire Williment*
- *NHSBT Trials Unit Rachel Johnson, Alison Deary*
- *Clinical Lead for Organ Utilisation Chris Callaghan*
- *NHS England*
- *Histopathology – Desley Neil, Cambridge, Leeds, London*
- *Health Economist Ed Wilson*
- *Implementation Design Dr Karla Hemming*
- *Lay person representation*
- *Surgeons Roberto Cacciola, Gavin Pettigrew, Dom Summers*
- *Transplant Nephrologists Nick Torpey*

Cambridge Histopathology Service

- 24 hour availability of consultant renal pathologists (only centre)
- Routine
- pre-implantation biopsy on kidneys from donors >65
- Biopsy processing takes 4-5 hours
- Graded according to the Remuzzi system

Histopathology assessment of chronic injury

- Age associated histological features of injury
- Correlation with outcome
- Grade or score the severity of baseline injury



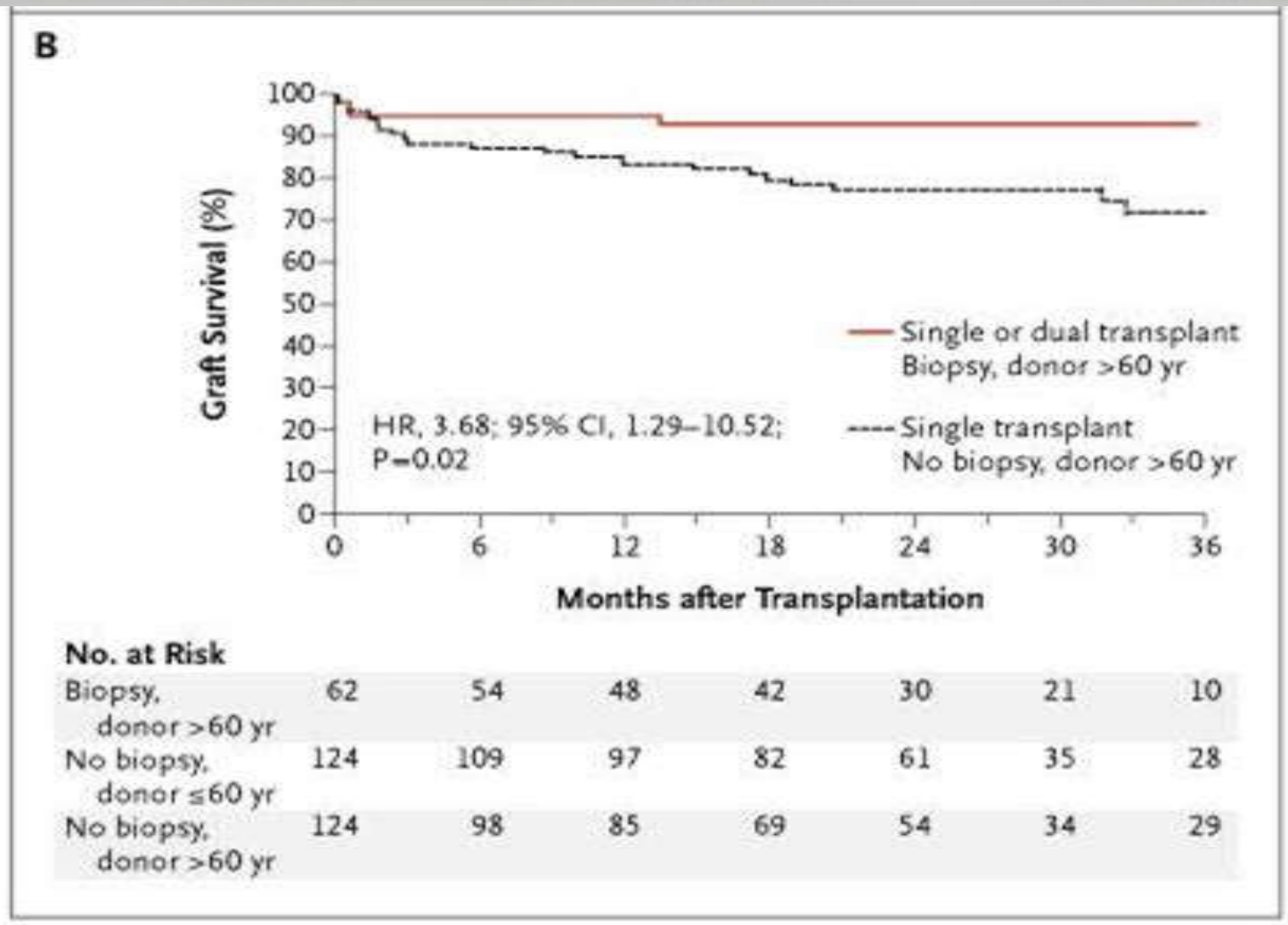
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Outcome of Renal Transplantation from Older Donors

Giuseppe Remuzzi, M.D., Paolo Cravedi, M.D., Annalisa Perna, Stat.Sci.D., Borislav D. Dimitrov, M.D., M.Sc., Marta Turturro, Biol.Sci.D., Giuseppe Locatelli, M.D., Paolo Rigotti, M.D., Nicola Baldan, M.D., Marco Beatini, M.D., Umberto Valente, M.D., Mario Scalamogna, M.D., and Piero Ruggenenti, M.D., for the Dual Kidney Transplant Group*

The Remuzzi score



No. at Risk							
Biopsy, donor >60 yr	62	54	48	42	30	21	10
No biopsy, donor ≤60 yr	124	109	97	82	61	35	28
No biopsy, donor >60 yr	124	98	85	69	54	34	29

Remuzzi G et al. N Engl J Med 2006;354:343-352.

The Remuzzi score

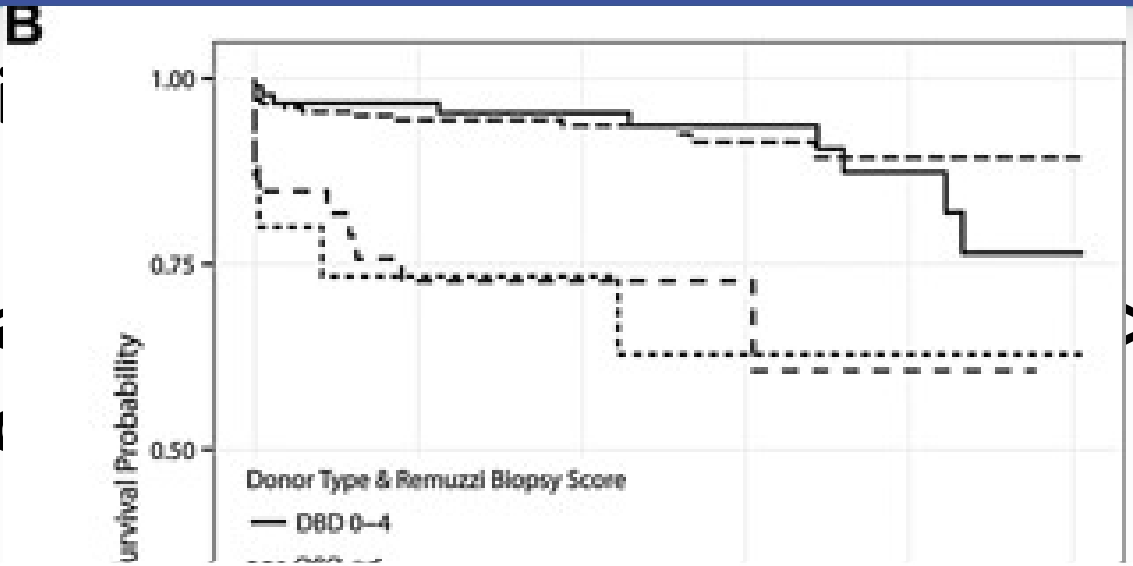
PITHIA

Pre-Implantation Trial of
Histopathology In renal Allografts

BETTER **QUALITY**
ASSESSMENT IN
TRANSPLANTATION

Cambridge Histopathology Service

- Confi ble to DCD
- Impl >4 is asso



American Journal of Transplantation 2015; 15: 754–763
Wiley Periodicals Inc.

doi: 10.1111/ajt.13009

Baseline Donor Chronic Renal Injury Confers the Same Transplant Survival Disadvantage for DCD and DBD Kidneys

DBD 0–4	91	77	37	35	19	1
DBD >4	15	10	8	3	2	1
DCD 0–4	180	152	94	52	16	3
DCD >4	33	20	13	6	2	0

Numbers at risk

Current Practice

1 2
3 4

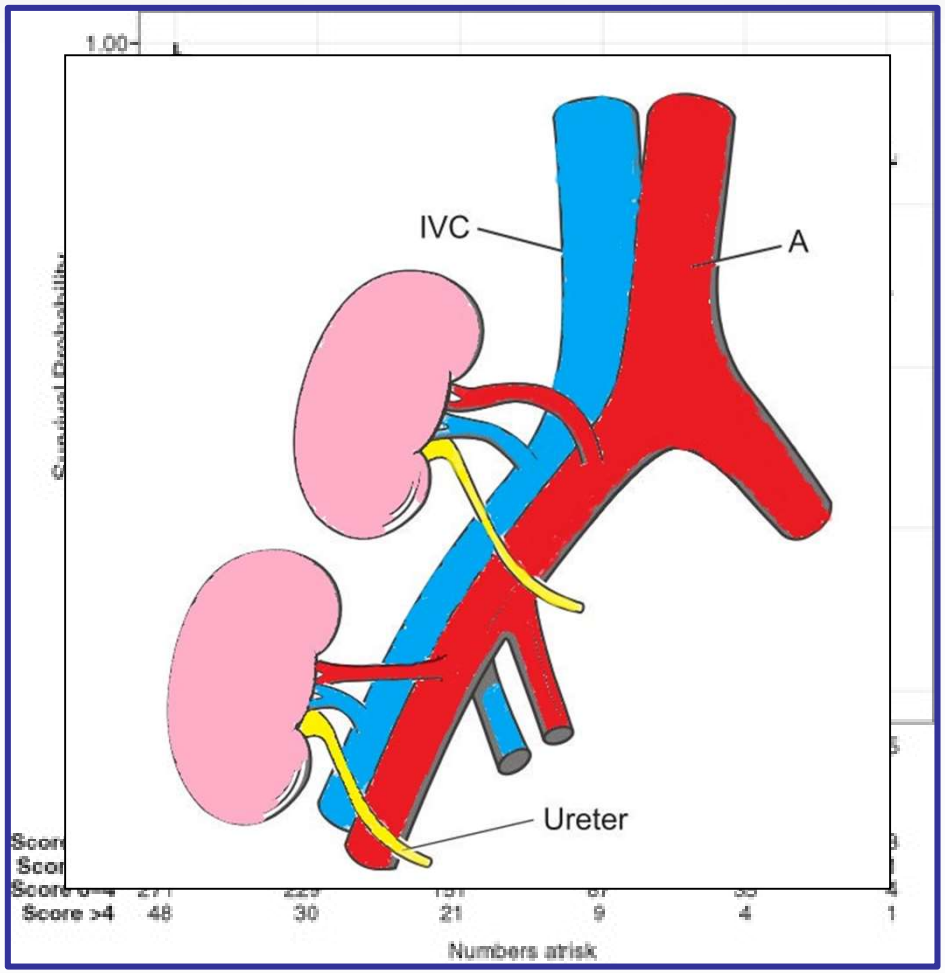
Single

5 6

Double

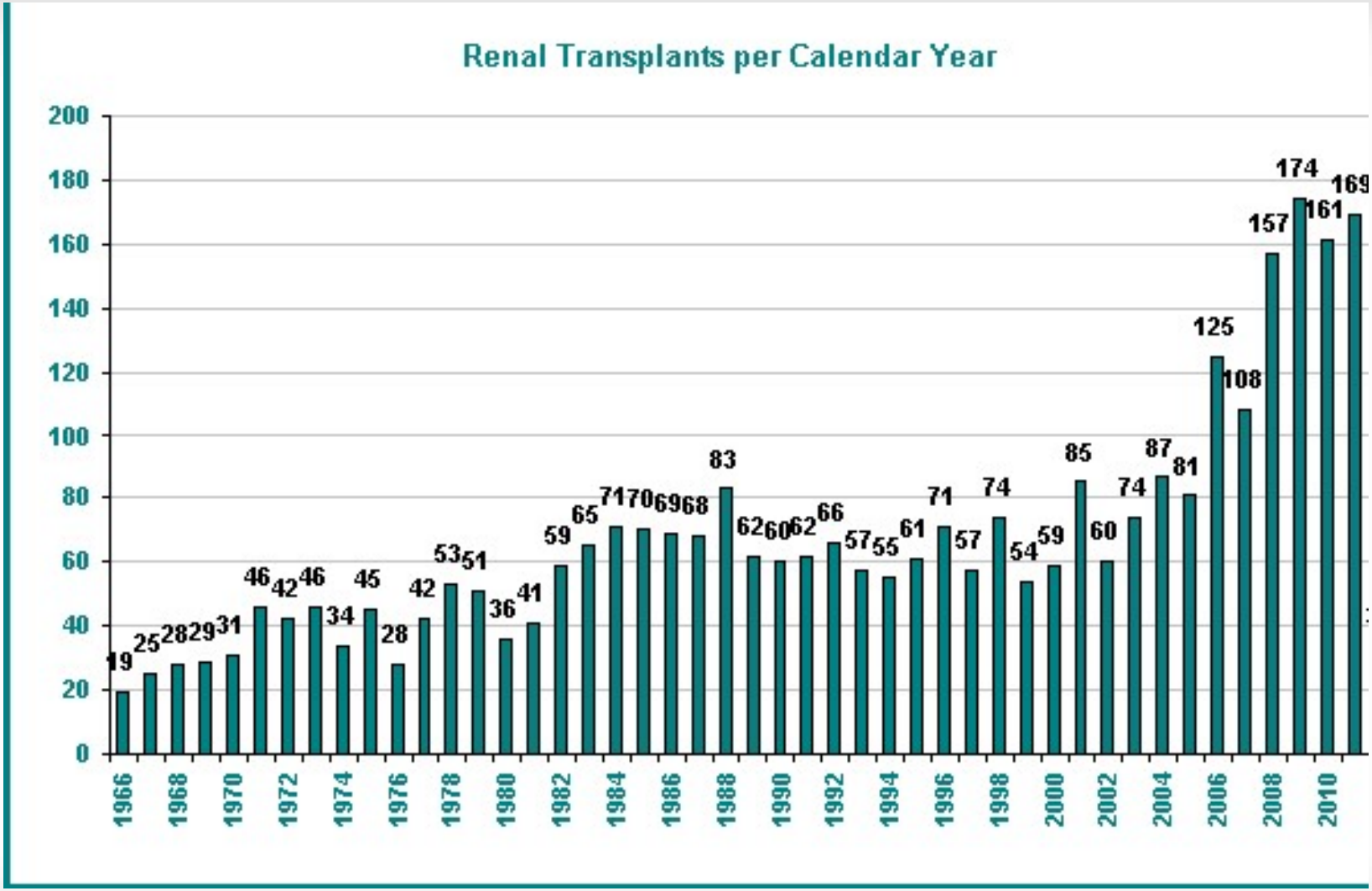
7 8
9 10
11 12

Discard

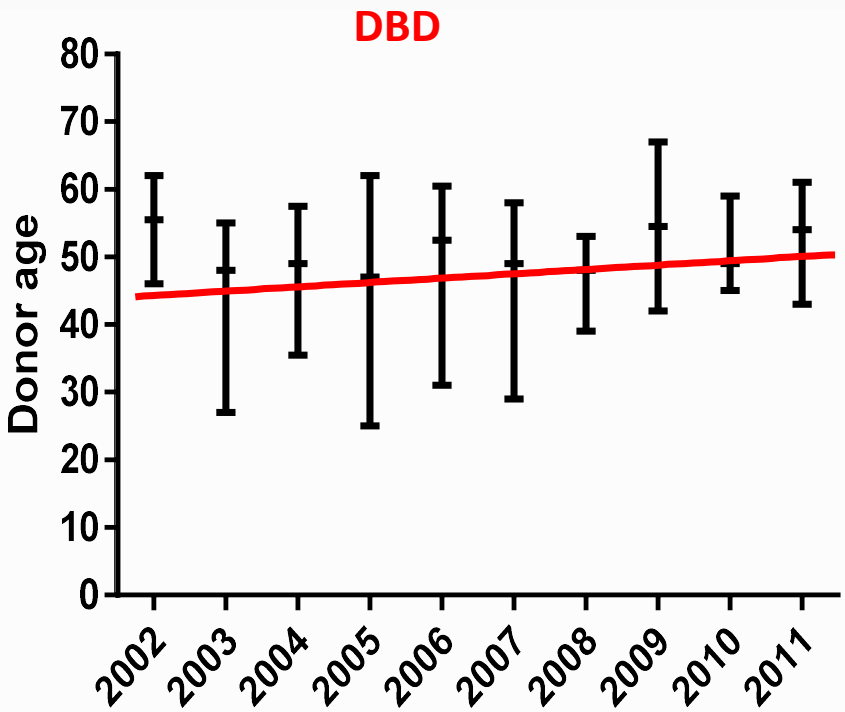


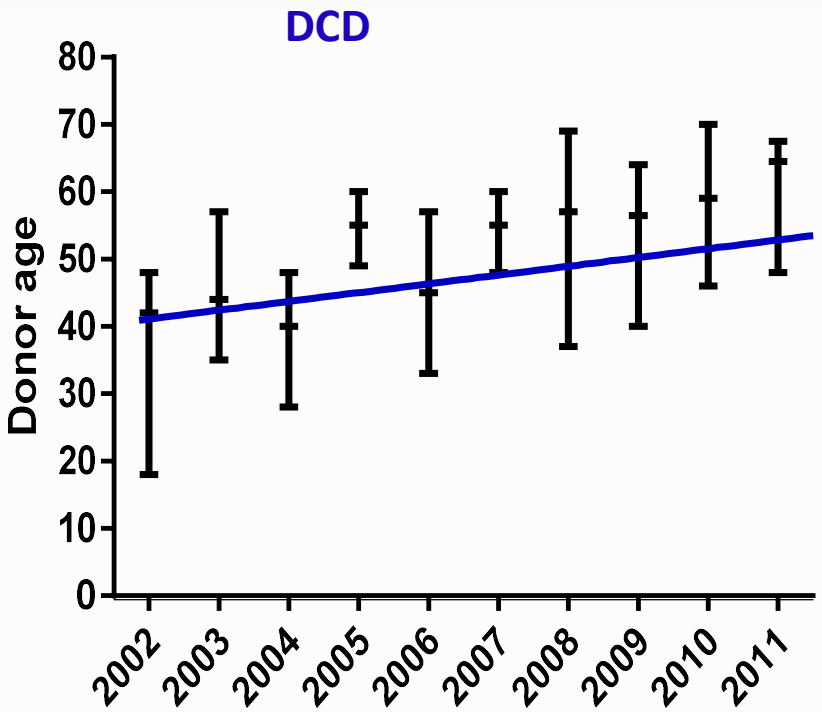
Kosmoliaptsis et al AJT 2015

Cambridge DCD transplant activity



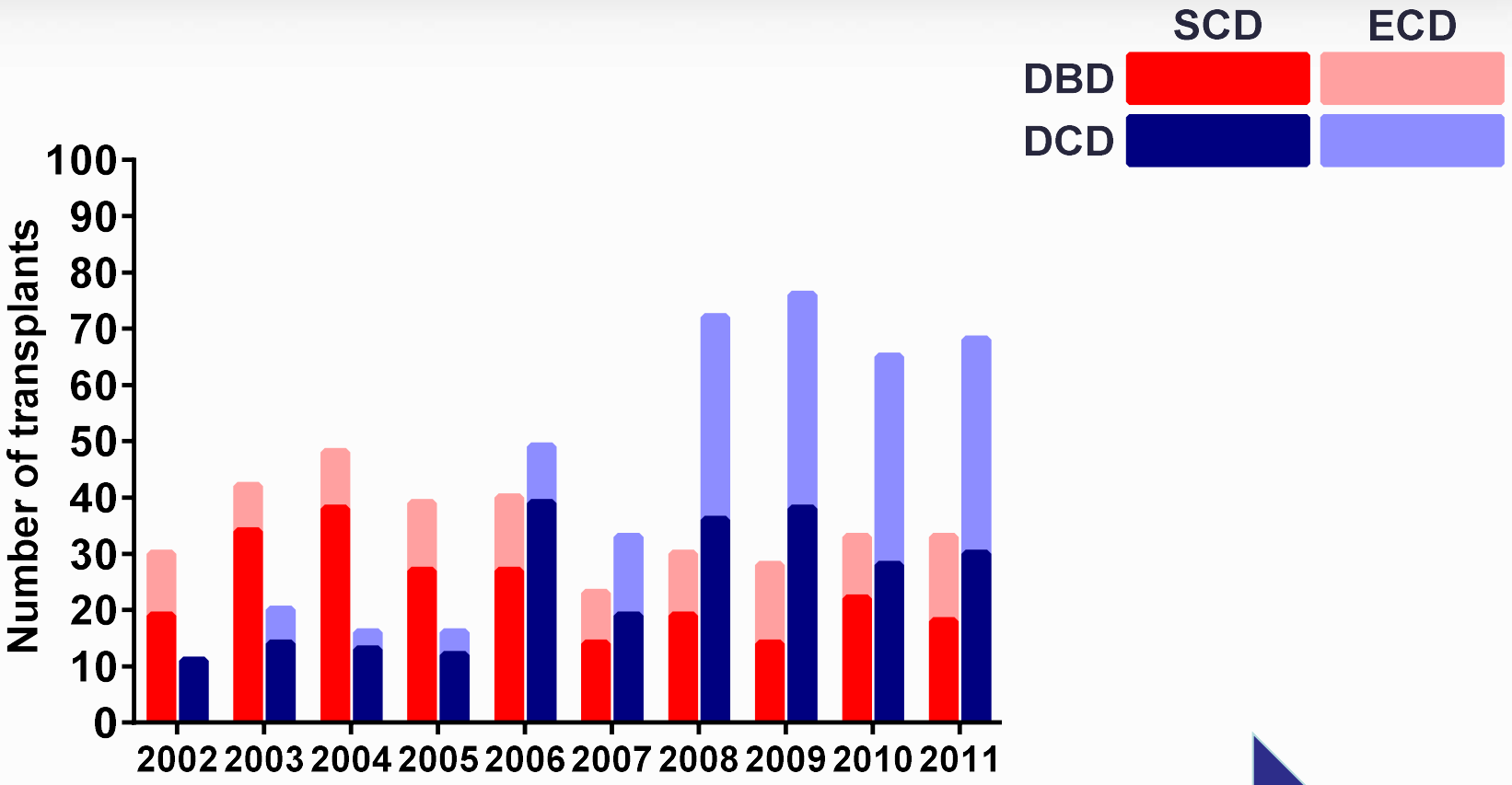
Evolution of a DCD programme





Age of donors has progressively increased

A Evolution of a DCD programme



Age of donors has progressively increased

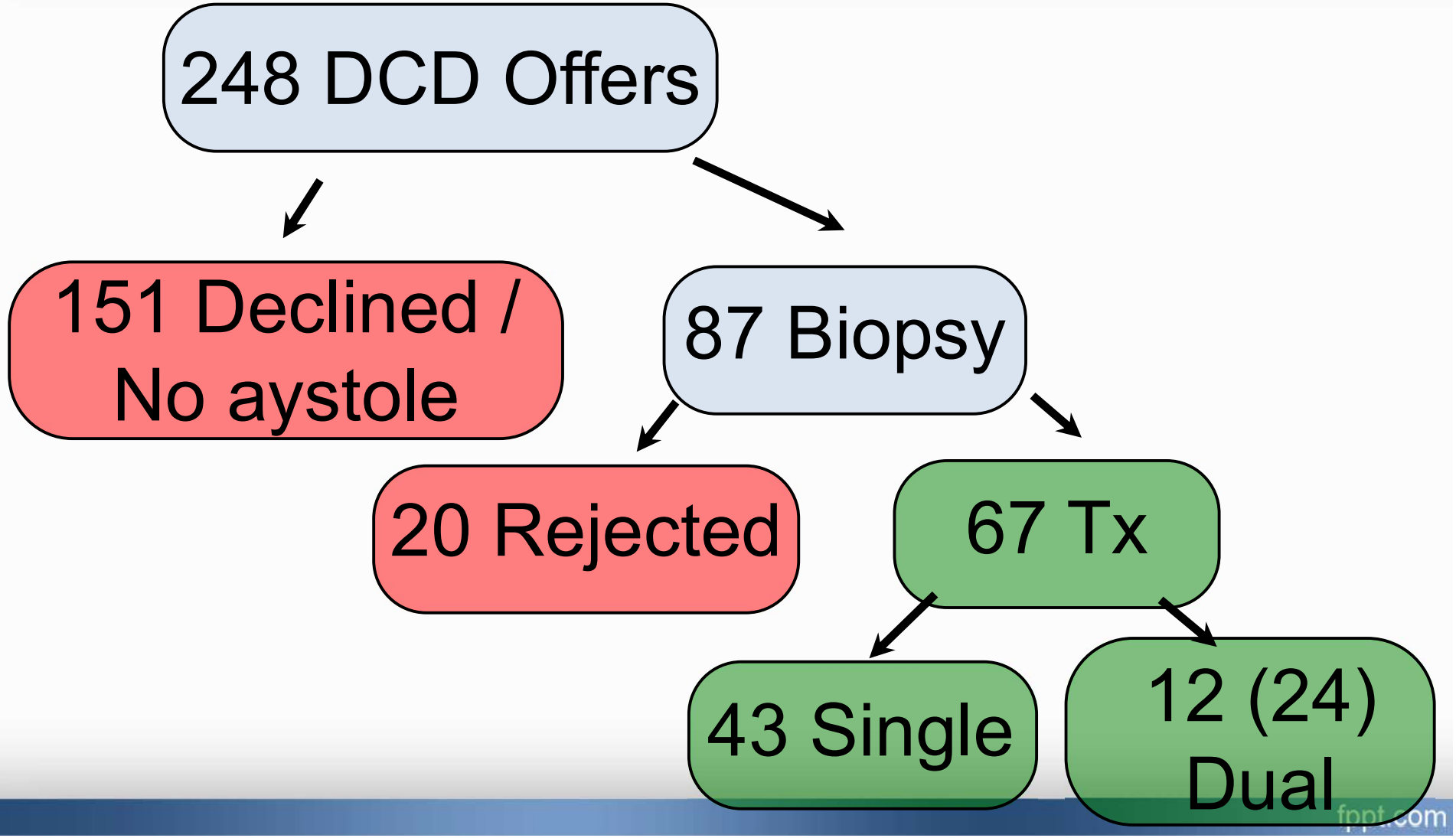
Utilise DCD donors over 70?

American Journal of Transplantation 2015; 15: 2931–2939
Wiley Periodicals Inc.

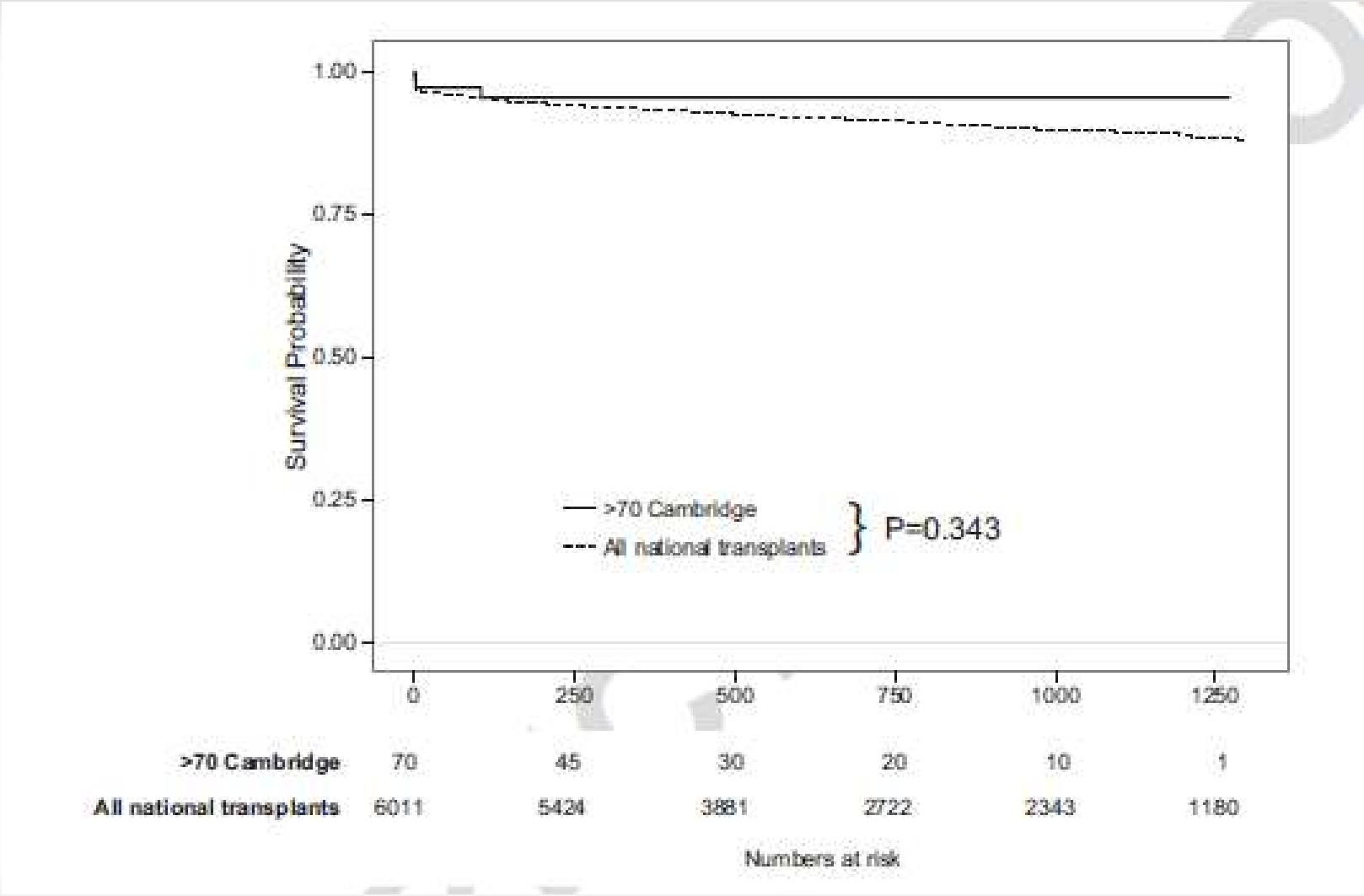
doi: 10.1111/ajt.13349

Successful Transplantation of Kidneys From Elderly Circulatory Death Donors by Using Microscopic and Macroscopic Characteristics to Guide Single or Dual Implantation

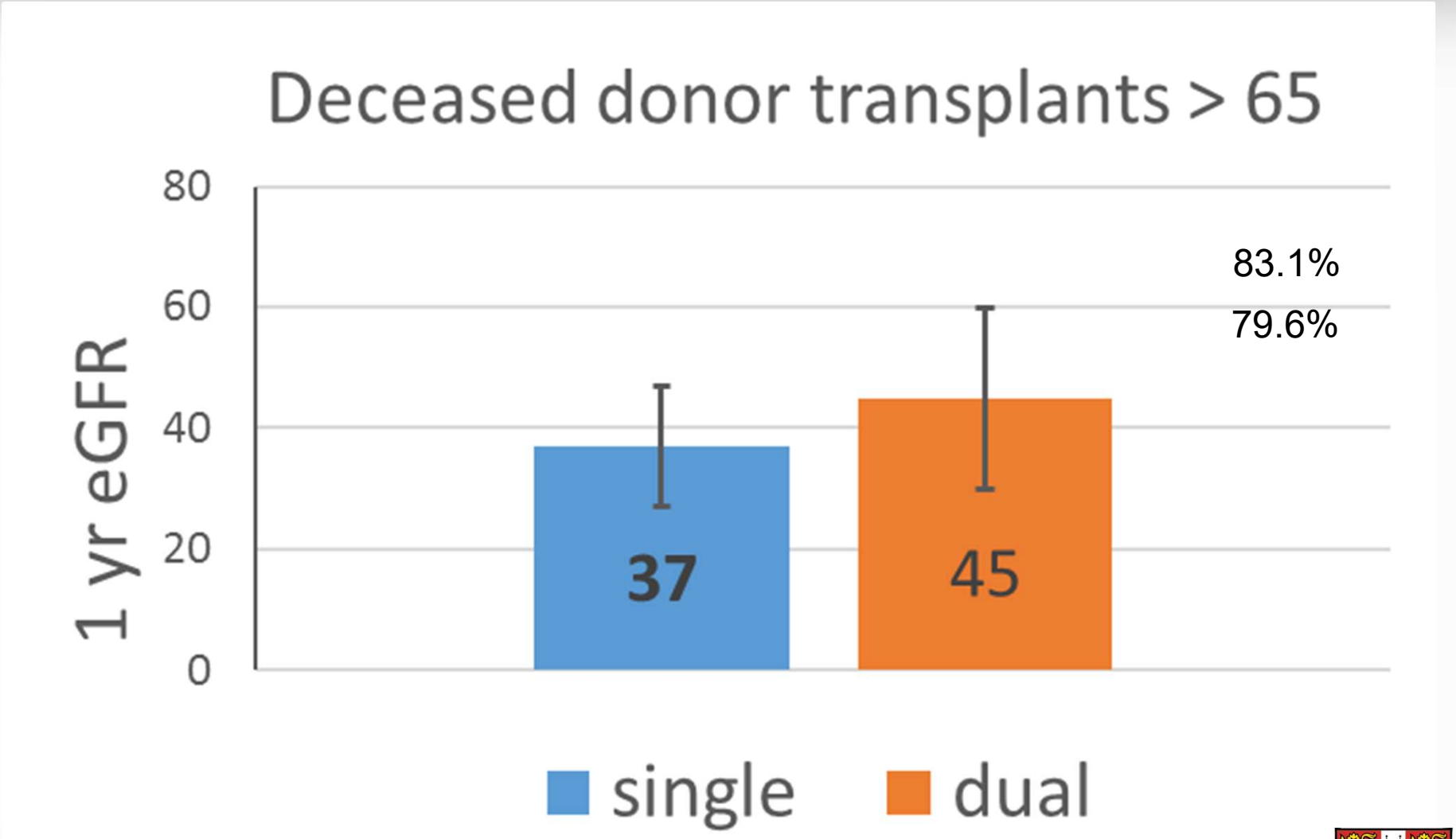
Utilise DCD donors over 70?



Transplant survival (vs national)



National Outcomes for dual transplants from donors aged over 65 years

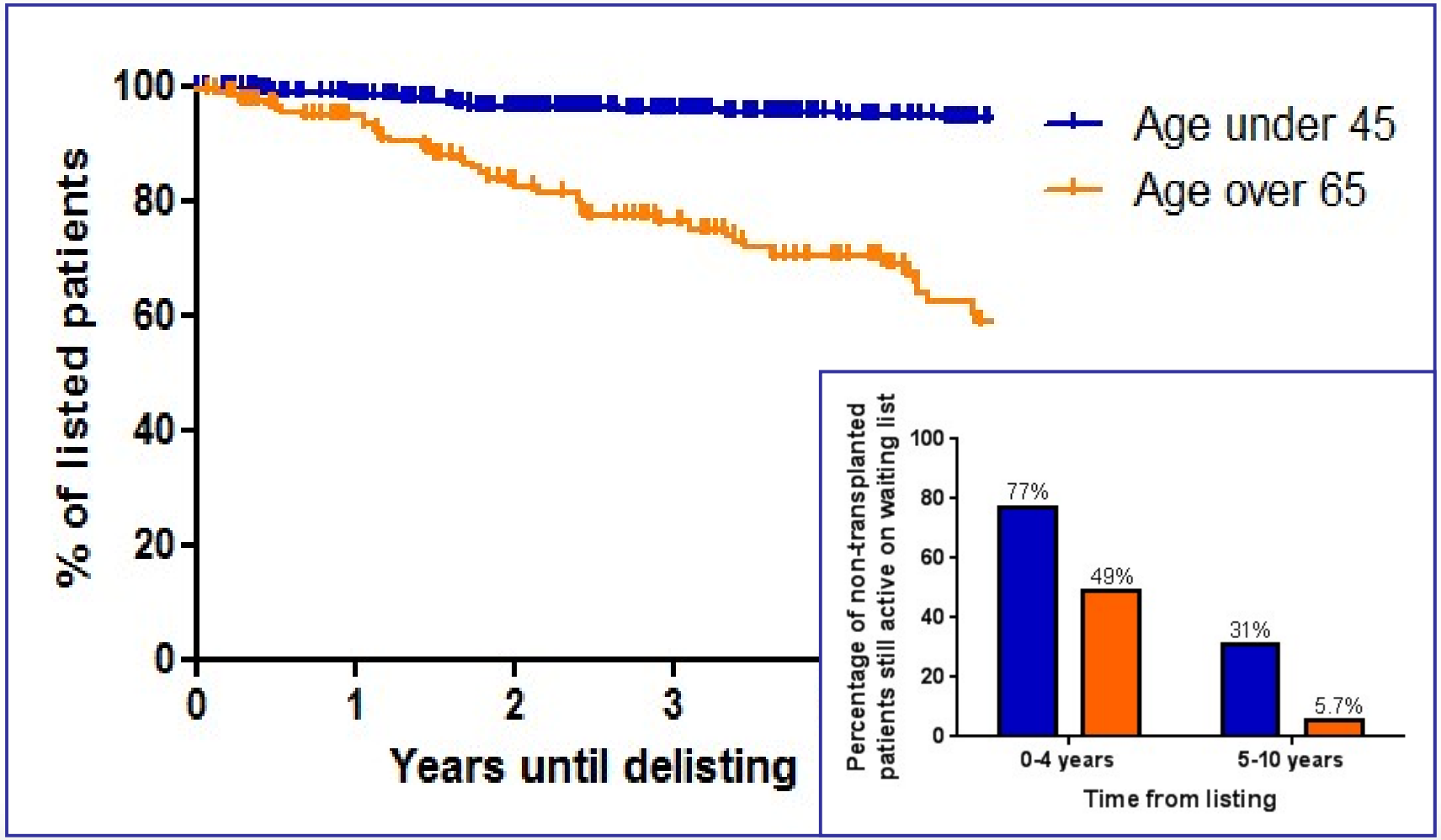


Recipient Selection

Local Expansion of Donation After Circulatory Death Kidney Transplant Activity Improves Waitlisted Outcomes and Addresses Inequities of Access to Transplantation

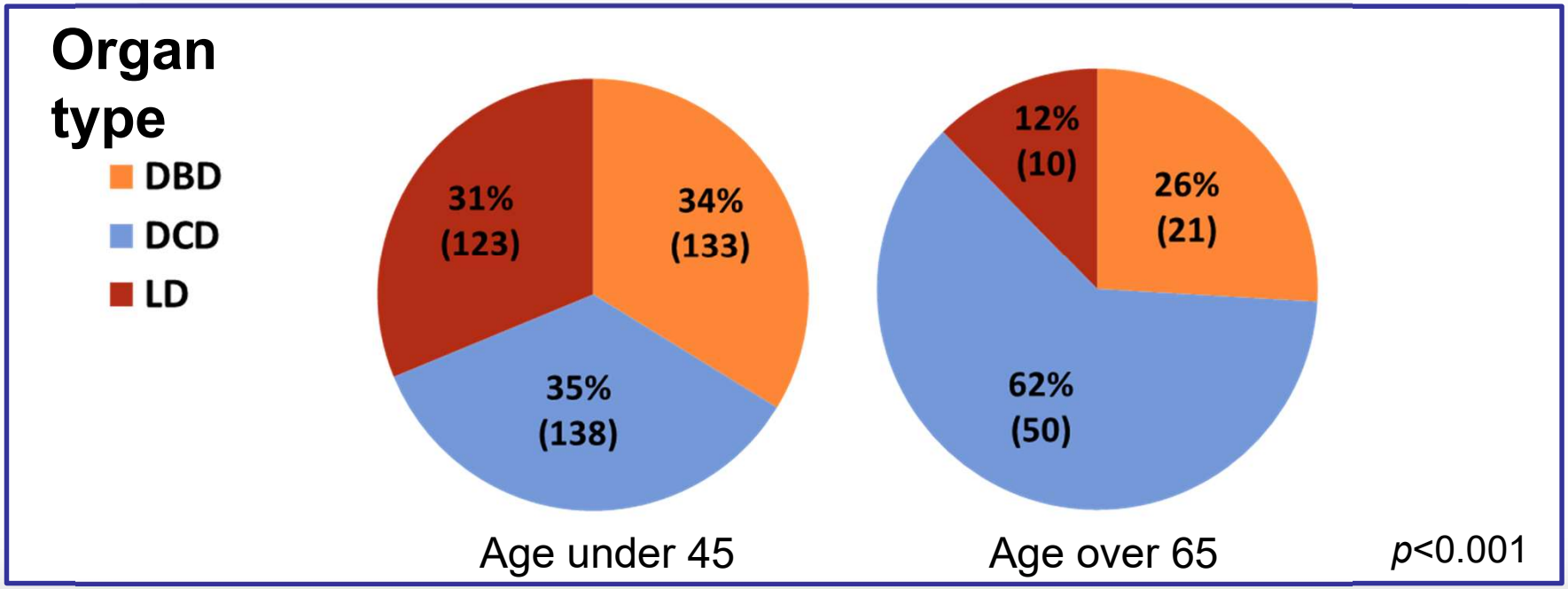
B. Mirshekar-Syahkal[1], D. Summers[1],
L. L. Bradbury[2], M. Aly[1], V. Bardsley[3], M. Berry[4],
J. M. Norris[1], N. Torpey[4], M. R. Clatworthy[4],
J. A. Bradley[1] and G. J. Pettigrew[1,*]

Elderly recipients have narrow window for transplantation

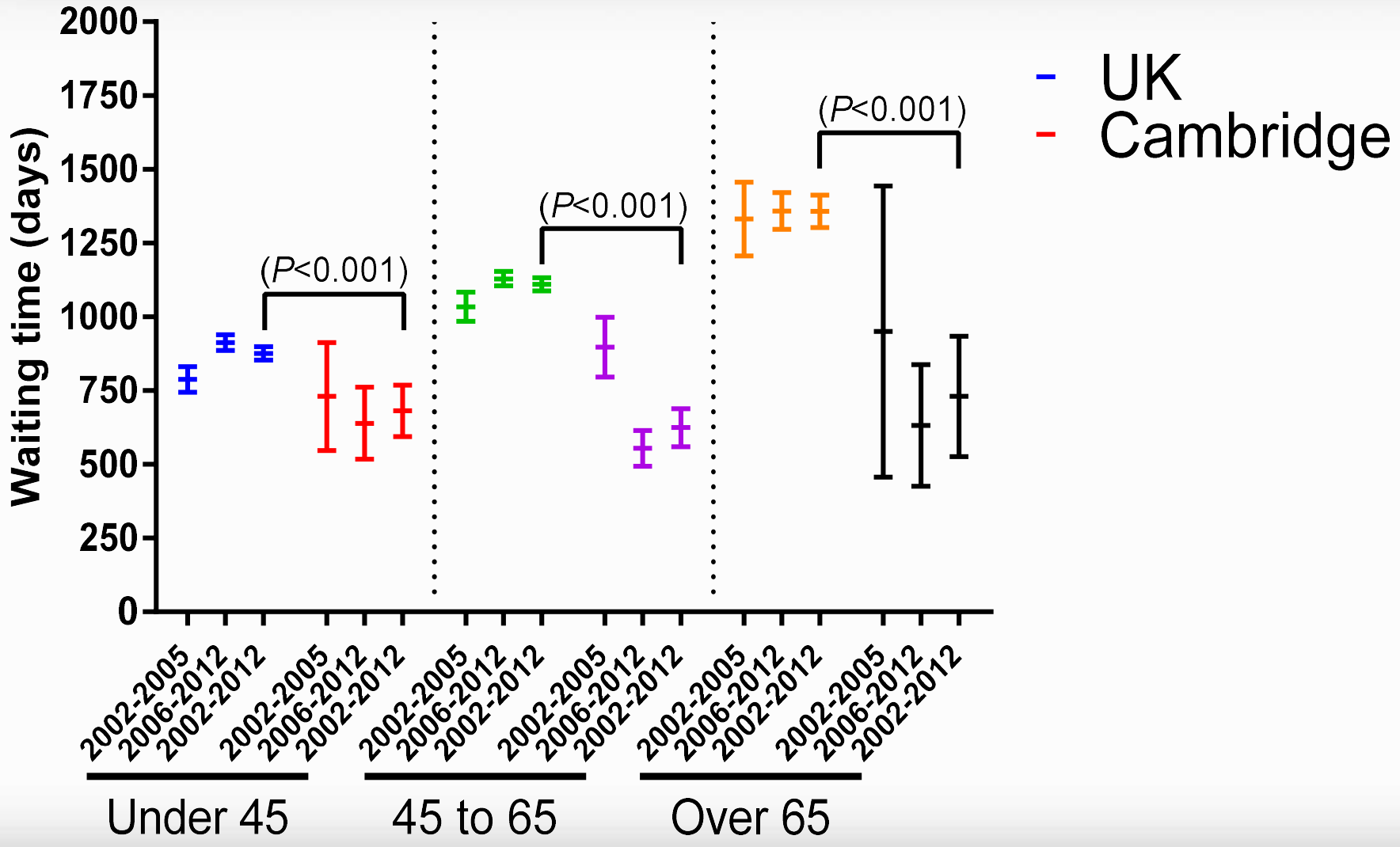


Different recipient cohorts receive different kidneys

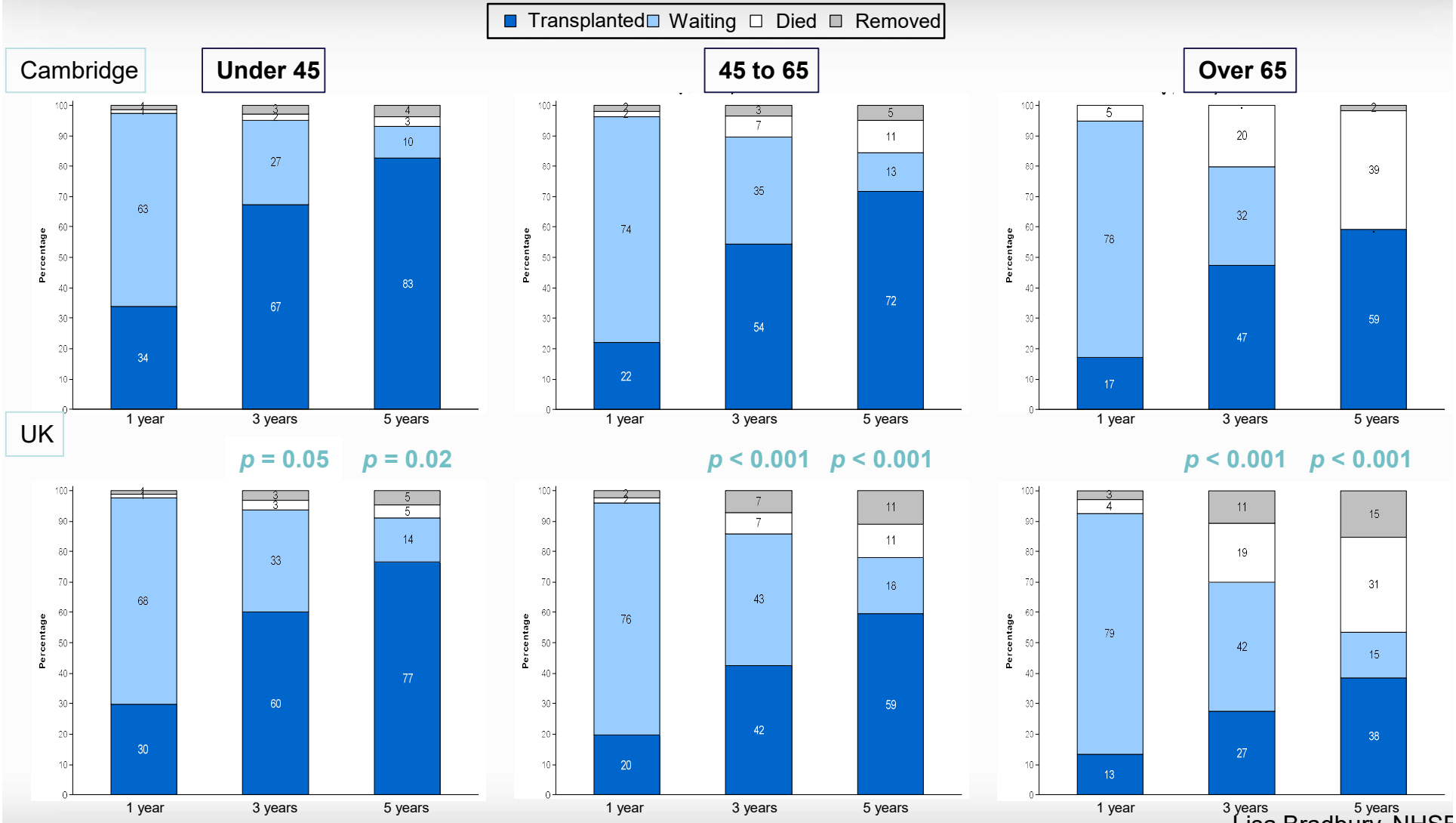
	Age under 45	Age over 65	p-value
Cold ischaemic time (hours)	14.4 (6.5-26.7)	14.4 (5.9-21.5)	ns
Donor age	43 (1-69)	61 (23-79)	<0.001
ECD donors	12%	63%	<0.001



Waiting times by recipient age

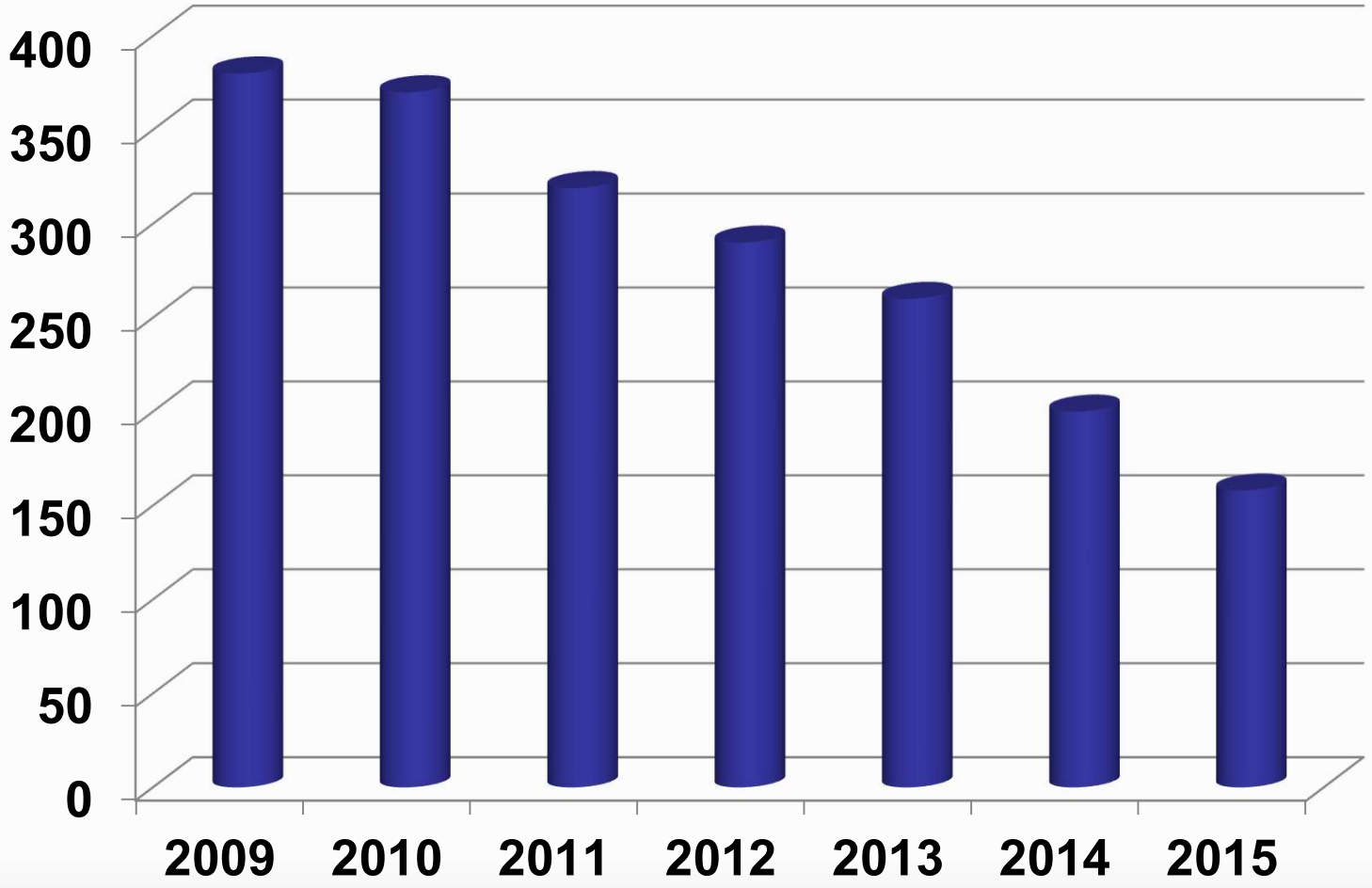


Patient outcomes from listing



Lisa Bradbury, NHSE

How has the waiting list been influenced?



National Digital Pathology Service – Potential Drawbacks

- ***Increase in cold ischaemic times?***
- ***Complications of biopsy?***
- ***Does it perhaps lead to excess kidney discard?***
- ***Remains controversial in the US***

Remuzzi - Controversies

The Donor Kidney Biopsy and Its Implications in Predicting Graft Outcomes: A Systematic Review

Received 27 June 2014, revised 06 Januar
accepted for publication 07 January 2015

C. J. Wang[1,*], J. B. Wetmore[1], G. S. Crary[2] and B. L. Kasiske[1]

Determinants of Discard of Expanded Criteria Do
Impact of Biopsy and Machine Perfusion

Pre-Implant Biopsy Predicts Outcome of Single-Kidney Transplantation Independent of Clinical Donor Variables

Johannes Hofer,[1,2] Heinz Regele,[1] Georg A. Böhmig,[3] Georg Gutjahr,[4] Željko Kikić,[3] Ferdinand Mühlbacher,[5] and Josef Kletzmayr[6,7]

Histopathological evaluation of pretransplant donor biopsies in expanded criteria donors with high kidney donor profile index: a retrospective observational cohort study

Ana Sánchez-Escuredo, Amaia Sagasta, Ignacio Revuelta, Lida M. Rodas, David Parede, Mireia Musquera, Fritz Diekmann, Josep M. Campistol, Manel Solé, Federic

RESEARCH

OPEN ACCESS

Long term outcomes of transplantation using expanded criteria donors: prospective, popula cohort study

Olivier Aubert,[1] Nassim Kamar,[2,3,4,5] Dewi Vernerey,[1] Denis Viglietti,[1,6] F Jean-Paul Duong-Van-Huyen,[1,8] Dominique Eladari,[1,9] Jean-Philippe Em Jerome Verine,[10] Lionel Rostaing,[2,3,4,5] Nicolas Congy,[4,11,12] Céline Guilb Georges Mourad,[5,14] Valérie Garrigue,[5,14] Emmanuel Morelon [5,15,1 Michèle Kessler,[5,16,18] Marc Ladrière,[5,16,18] Michel D Christophe Legendre,[1,5,7,16] Xavie

Long-term outcome of renal transplantation from octogenarian donors: A multicenter controlled study

Piero Ruggenenti, Cristina Silvestre, Luigino Boschiero, Giovanni Rota, Lucrezia Furian, Annalisa Perna Giuseppe Rossini, Giuseppe Remuzzi, Paolo Rigotti

The reproducibility and predictive value on outcome of renal biopsies from expanded criteria donors

M. Antonieta Azancot[1], Francesc Moreso[1], Maite Salcedo[2], Carme Cantarell[1], Manel Perello[1], Irina B. Torres[1], Angeles Montero[2], Enric Trilla[3], Joana Sellarés[1], Joan Morote[3] and Daniel Seron[1]

Excess Kidney Discard?

Table 3: Comparison with national DCD kidney transplant activity

	Cambridge	Rest of UK	Cambridge/total (%)
A			
>70	55	113	32.7%
<70	180	1445	11.1%
Proportion donors >70	23.4%	7.3%	

	Cambridge	Rest of UK	Cambridge/total (%)
B			
Single >70	43	77	35.8%
Double >70	12	36	25.0%
Proportion donors >70	21.8%	31.9%	

DCD, donation after circulatory death.

The Devil is in the Detail

How to accurately assess the impact of a national histopathology service?

- ***Just how many extra kidney transplants are performed?***
- ***What is their outcome?***

Would a prospective randomised trial work?

Randomly allocate kidneys from donors over 60 years to biopsy access or not

- ***Clearly un-blinded***
- ***Likely that simply offering biopsy would alter practice – the serum rhubarb effect.***
- ***Pre-Implantion Trial of Histopathology In renal Allografts - the PITHIA trial***

Who was PITHIA

- The Pythia – Delphic oracle
- Priestess of the temple of Apollo
- 8th Century BC – around 390 AD

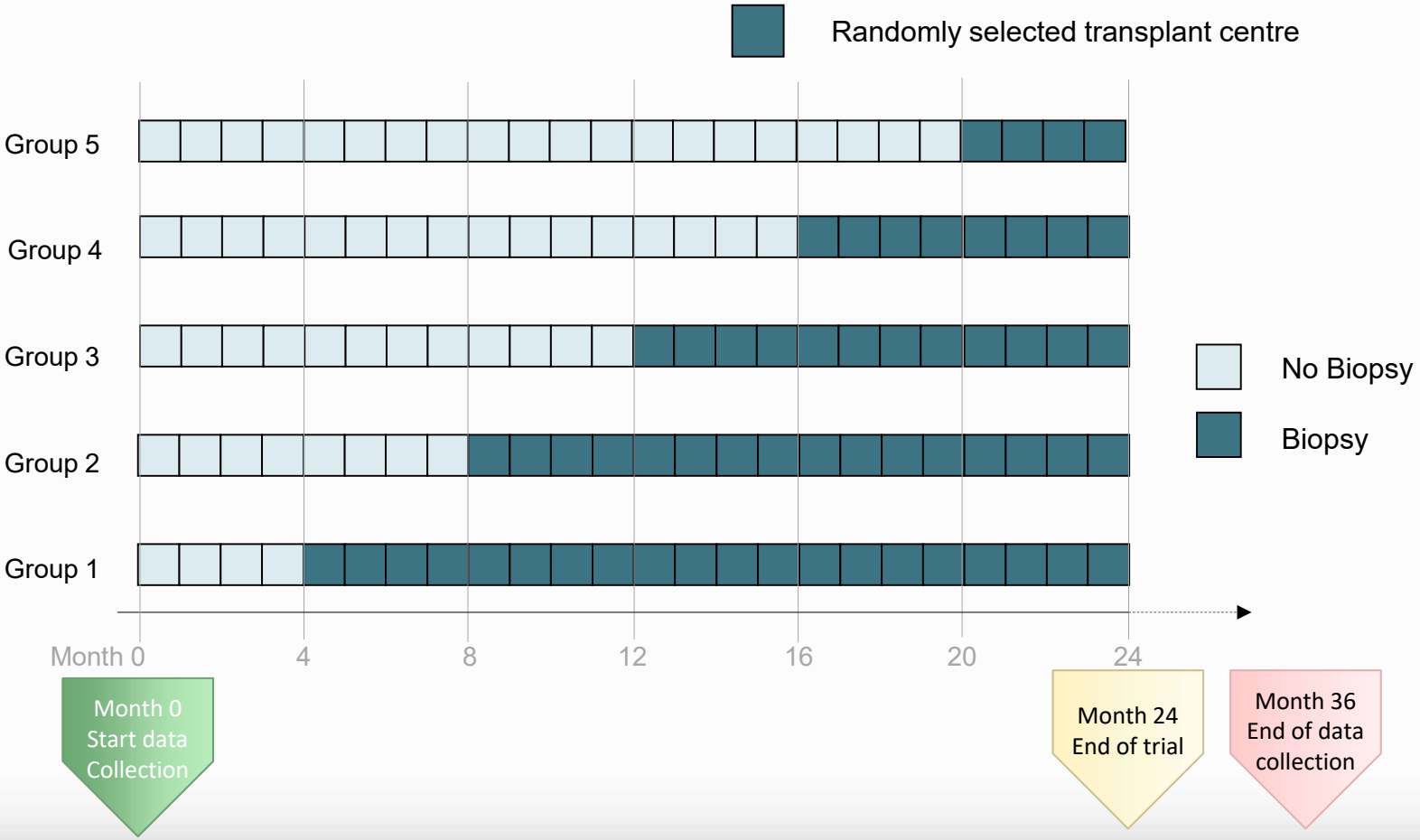
- King Croesus of Lydia 5th Century BC

- ‘If Croesus goes to war, he will destroy a great empire’

www.pithia.org.uk
@PITHIA_trial (Twitter)

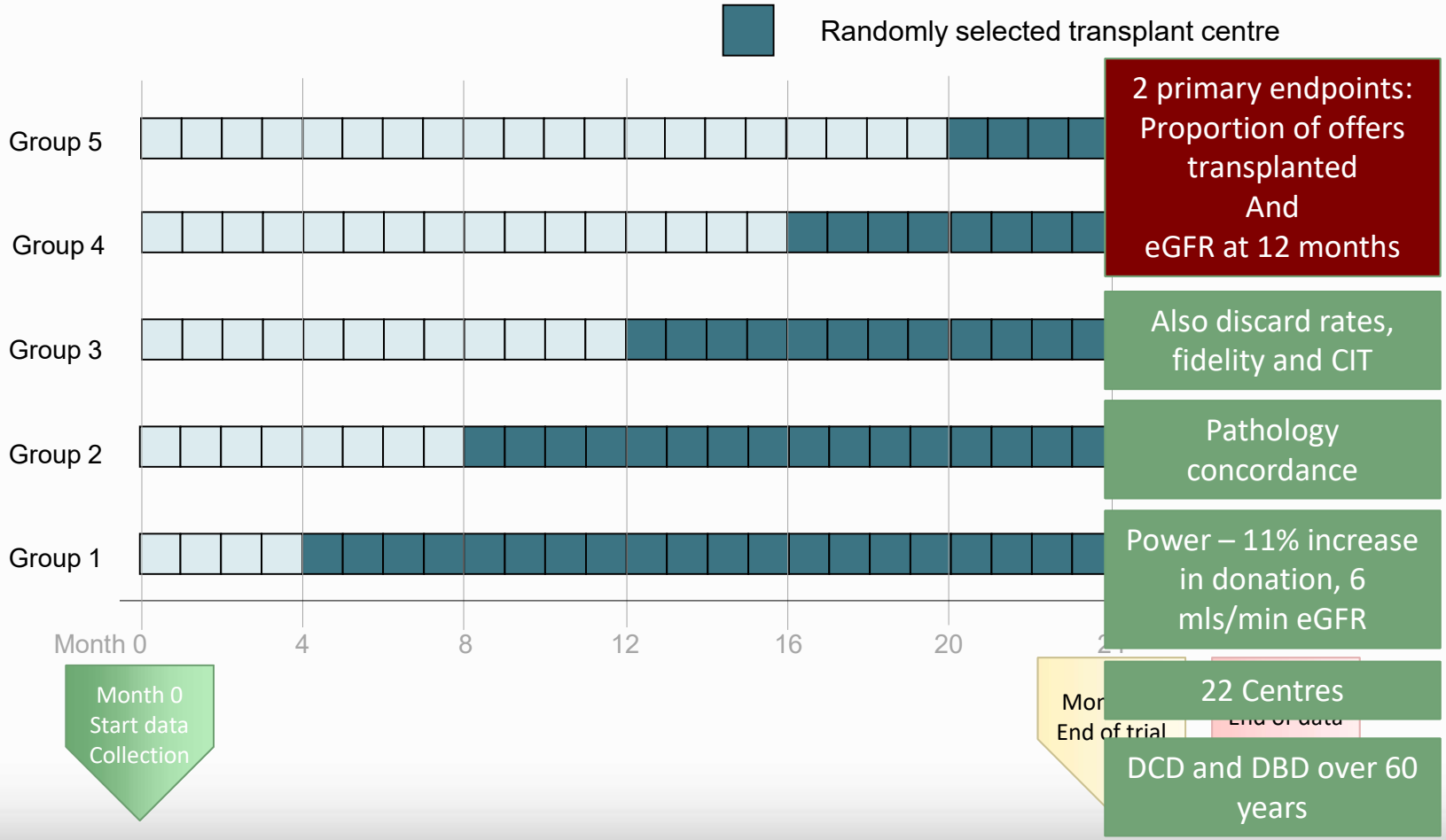
The PITHIA trial

Does having access to a biopsy result increase the number and quality of kidneys for transplantation?



The PITHIA trial

Does having access to a biopsy result increase the number and quality of kidneys for transplantation?



2 primary endpoints:
Proportion of offers transplanted
And
eGFR at 12 months

Also discard rates, fidelity and CIT

Pathology concordance

Power – 11% increase in donation, 6 mls/min eGFR

22 Centres

DCD and DBD over 60 years

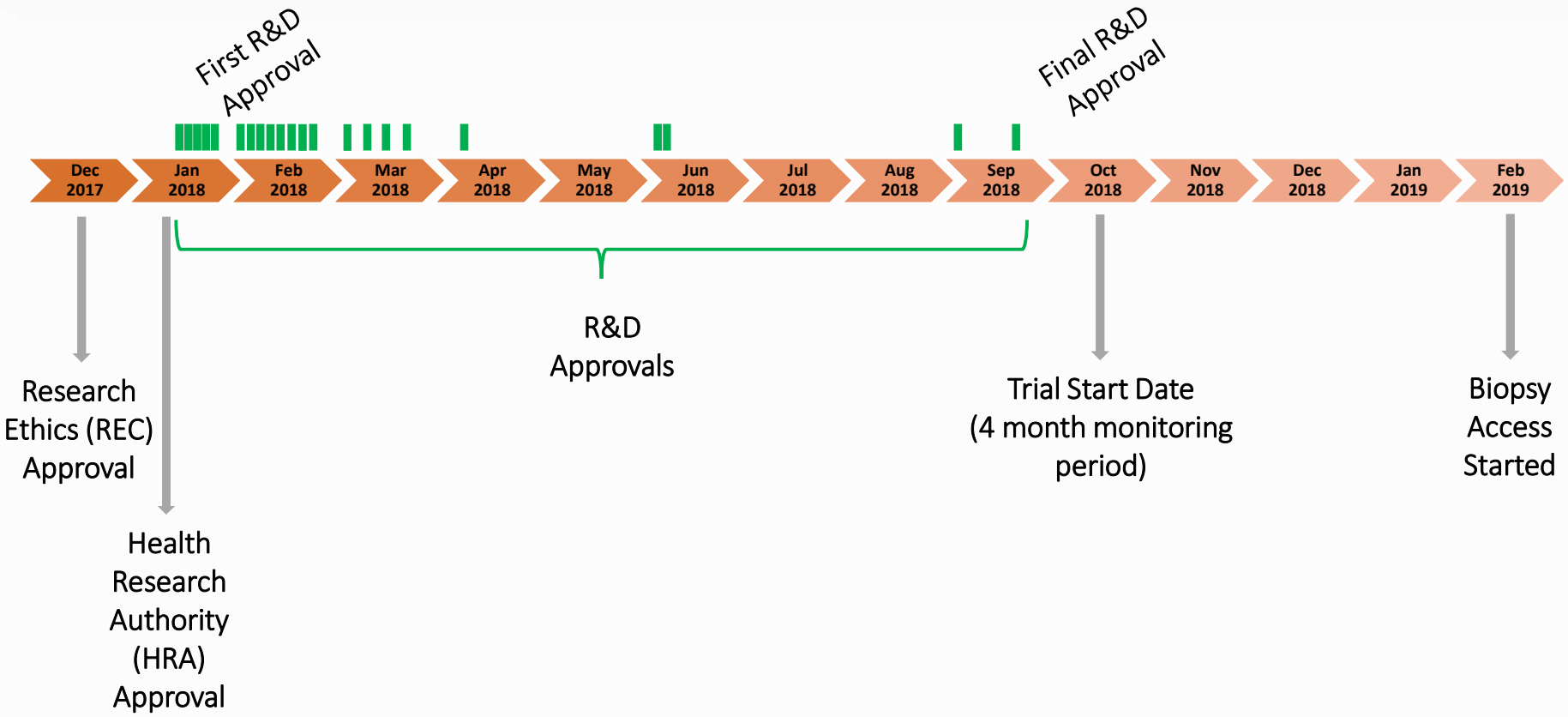
The PITHIA trial

- Pre-Implantation Trial of Histopathology In renal transplant Allografts – PITHIA
- Trial will demonstrate the value of pre-implantation histopathology in increasing number and quality of transplants.
- Powered for an additional 150 kidney transplants.
- Stepped-wedge cluster design.
- The first randomised registry trial in transplantation – relatively low cost trial design.

FUNDED BY
NIHR | National Institute for Health Research

Timelines

NHS Blood and Transplant



Trial Process

Participating centre requests PITHIA sample → NORS team takes biopsy → Biopsy processed, scanned and uploaded → Histo-pathologist reviews and completes Remuzzi score → Report sent to transplant centre

sysmex

Logistics

Organ Recovery

Donor aged over 60 years

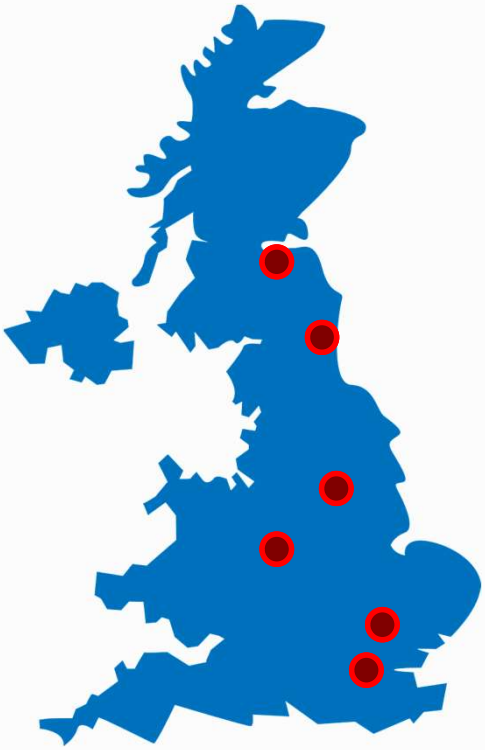
Transport

Sample accompanies NORS team to base

Sample accompanies an organ

Sample travels separately

Biopsy Processing



Logistics

Biopsy Technique

-
-

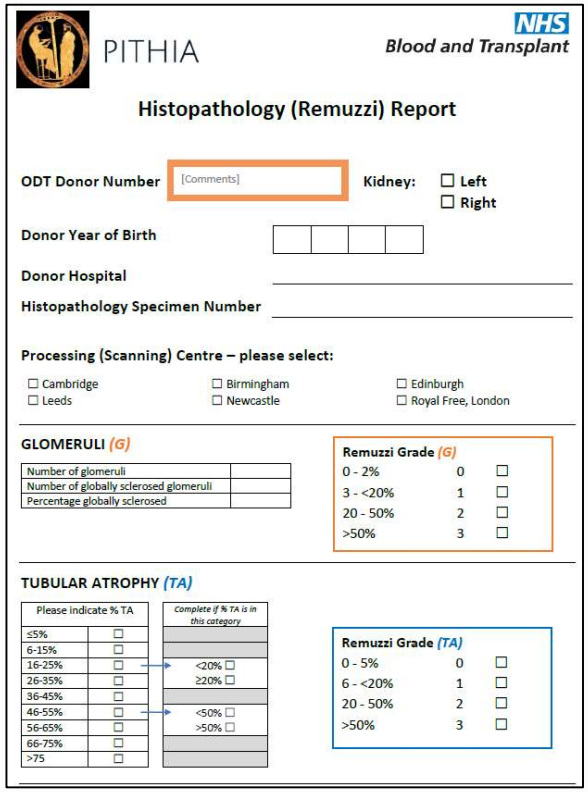
Biopsy Technique

PITHIA

Pre-Implantation Trial of
Histopathology In renal Allografts

BETTER **QUALITY**
ASSESSMENT IN
TRANSPLANTATION

Histopathology Report



PITHIA

NHS Blood and Transplant

Histopathology (Remuzzi) Report

ODT Donor Number [Comments] **Kidney:** ☐ Left ☐ Right

Donor Year of Birth ☐☐☐☐

Donor Hospital _____

Histopathology Specimen Number _____

Processing (Scanning) Centre – please select:

☐ Cambridge ☐ Birmingham ☐ Edinburgh
☐ Leeds ☐ Newcastle ☐ Royal Free, London

GLOMERULI *(G)*

Number of glomeruli	
Number of globally sclerosed glomeruli	
Percentage globally sclerosed	

Remuzzi Grade *(G)*

0 - 2%	0	☐
3 - <20%	1	☐
20 - 50%	2	☐
>50%	3	☐

TUBULAR ATROPHY *(TA)*

Please indicate % TA		*Complete if % TA is in this category*
≤5%	☐	
6-15%	☐	
16-25%	☐	<20% ☐ ≥20% ☐
26-35%	☐	
36-45%	☐	
46-55%	☐	<50% ☐ >50% ☐
56-65%	☐	
66-75%	☐	
>75	☐	

Remuzzi Grade *(TA)*

0 - 5%	0	☐
6 - <20%	1	☐
20 - 50%	2	☐
>50%	3	☐

INTERSTITIAL FIBROSIS *(IF)*

Please indicate % IF		*Complete if % IF is in this category*
≤5%	☐	
6-15%	☐	
16-25%	☐	<20% ☐ ≥20% ☐
26-35%	☐	
36-45%	☐	
46-55%	☐	<50% ☐ >50% ☐
56-65%	☐	
66-75%	☐	
>75	☐	

Remuzzi Grade *(IF)*

0 - 5%	0	☐
6 - <20%	1	☐
20 - 50%	2	☐
>50%	3	☐

ARTERIES *(A)*

Number of arteries	

NOTE: Score based on arteries only. If severe arteriolar changes then mention as other adverse feature in comments.

Remuzzi Grade *(A)*

Normal	0	☐
Wall thickness less than (<) lumen diameter	1	☐
Wall thickness equal or slightly greater than (>) lumen diameter	2	☐
Wall thickness much greater than (>) lumen diameter	3	☐

REMUZZI SCORE (*G* + *TA* + *IF* + *A*) = / 12

ADEQUACY

Is the biopsy adequate (≥ 25 glomeruli AND > 1 artery)?

☐ Yes

☐ No

You will also be given the contact number for the Histopathologist, who you can contact for additional information or queries.

GCP Compliance...

A few key points:

- Make patients on the waiting list aware of the trial
- Discuss the biopsy and its implications with the potential recipient, before they consent to the transplant
- Audits may be carried out during the trial

Link to online Good Clinical Practice Training: https://learn.nihr.ac.uk

Safety

- A reminder to report any incident occurring during the organ donation and transplantation process to NHSBT
- All safety events related to the trial will be reported to the Data Monitoring Committee in real-time

www.safe.nhsbt.nhs.uk/IncidentSubmission

Practical Aspects

- Once a centre is enrolled – request biopsy as clinically indicated
- No mandatory component
- Biopsy result available in 4-5 hours – discussion with on-call pathologist
- Trial will run for next two years
- Around 2500 kidneys will be included in the trial
- Review meeting four weeks after access to Histopathology Service

Pre-implantation Biopsy Service

- Two primary end-points
- Several positive outcomes:

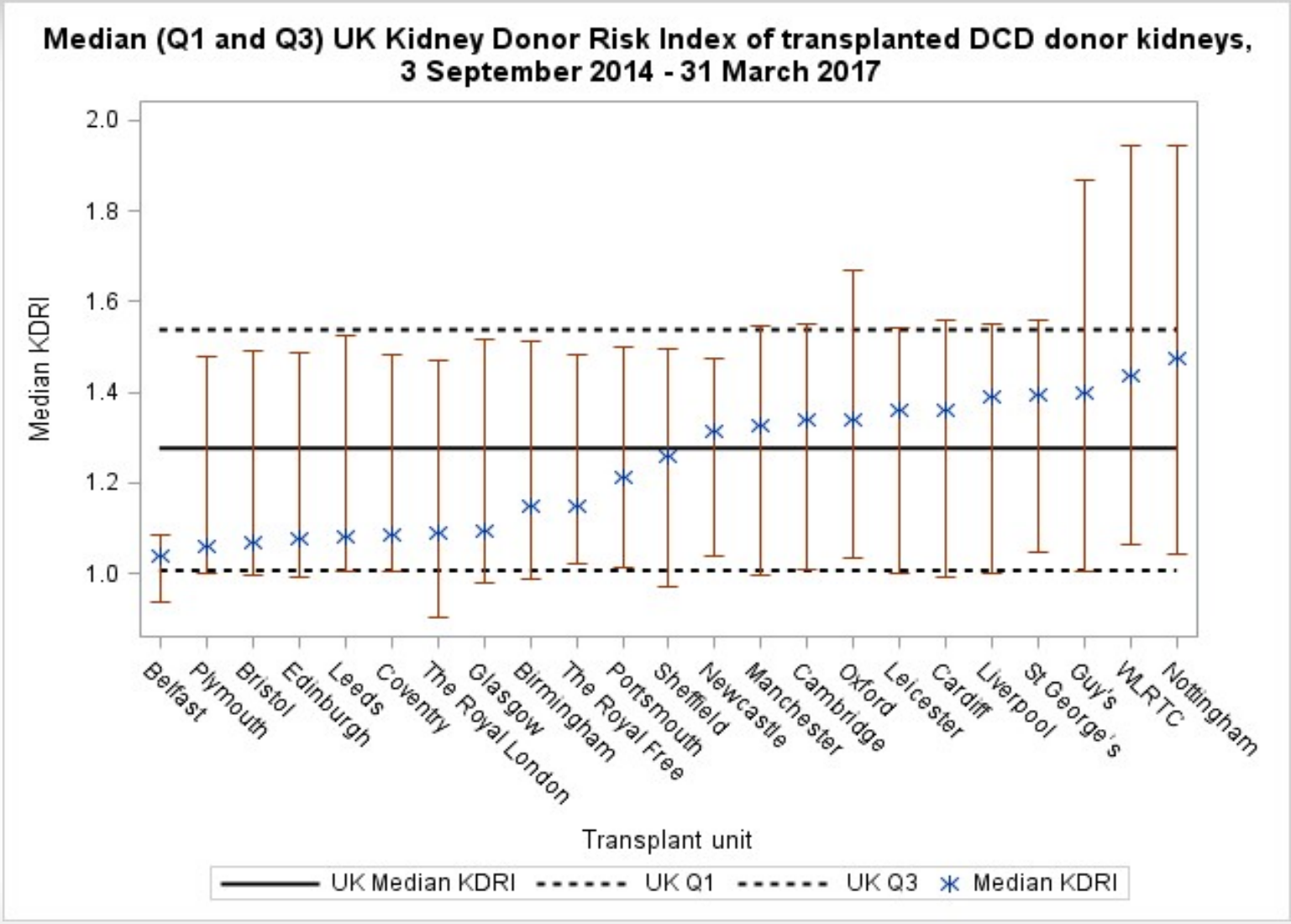
  a) Numbers of transplants increased, with better outcomes

  b) Numbers of transplants increased, outcomes unchanged

  c) Numbers unchanged, but outcomes better.
- Transplant numbers probably most important?
- If so, then for the trial to be successful:

Availability of biopsy service needs to engender change in practice

Pre-implantation Biopsy Service



Pre-implantation Biopsy Service

- Provide greater confidence in selection of ‘marginal’ donors
- Opportunity to further expand donor selection

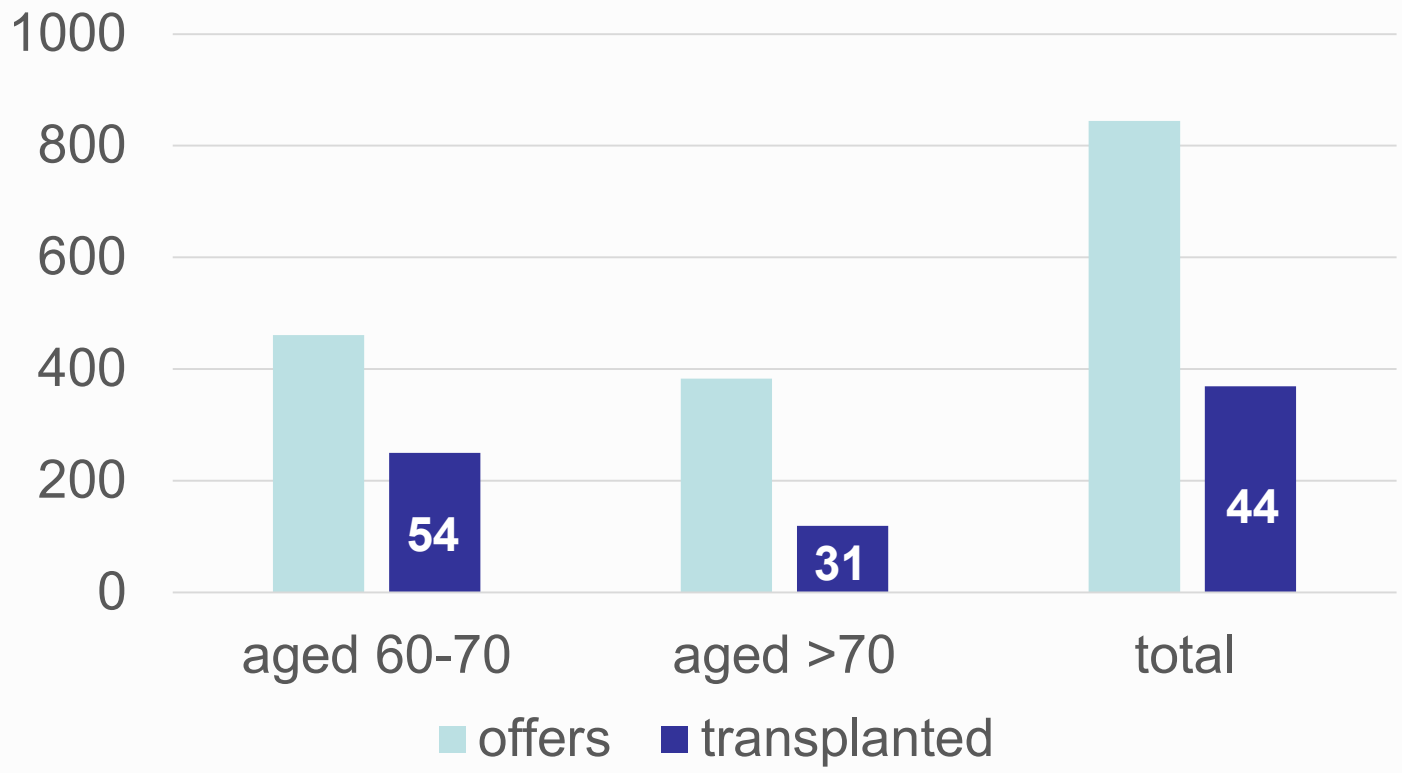
Long-term outcome of renal transplantation from octogenarian donors: A multicenter controlled study

Piero Ruggenenti, Cristina Silvestre, Luigino Boschiero, Giovanni Rota, Lucrezia Furian, Annalisa Perna, Giuseppe Rossini, Giuseppe Remuzzi ✉, Paolo Rigotti

‘Biopsy-guided allocation of kidneys from octogenarian donors permits further expansion of the donor organ pool and faster access to a kidney transplant, without increasing the risk of premature graft failure’.

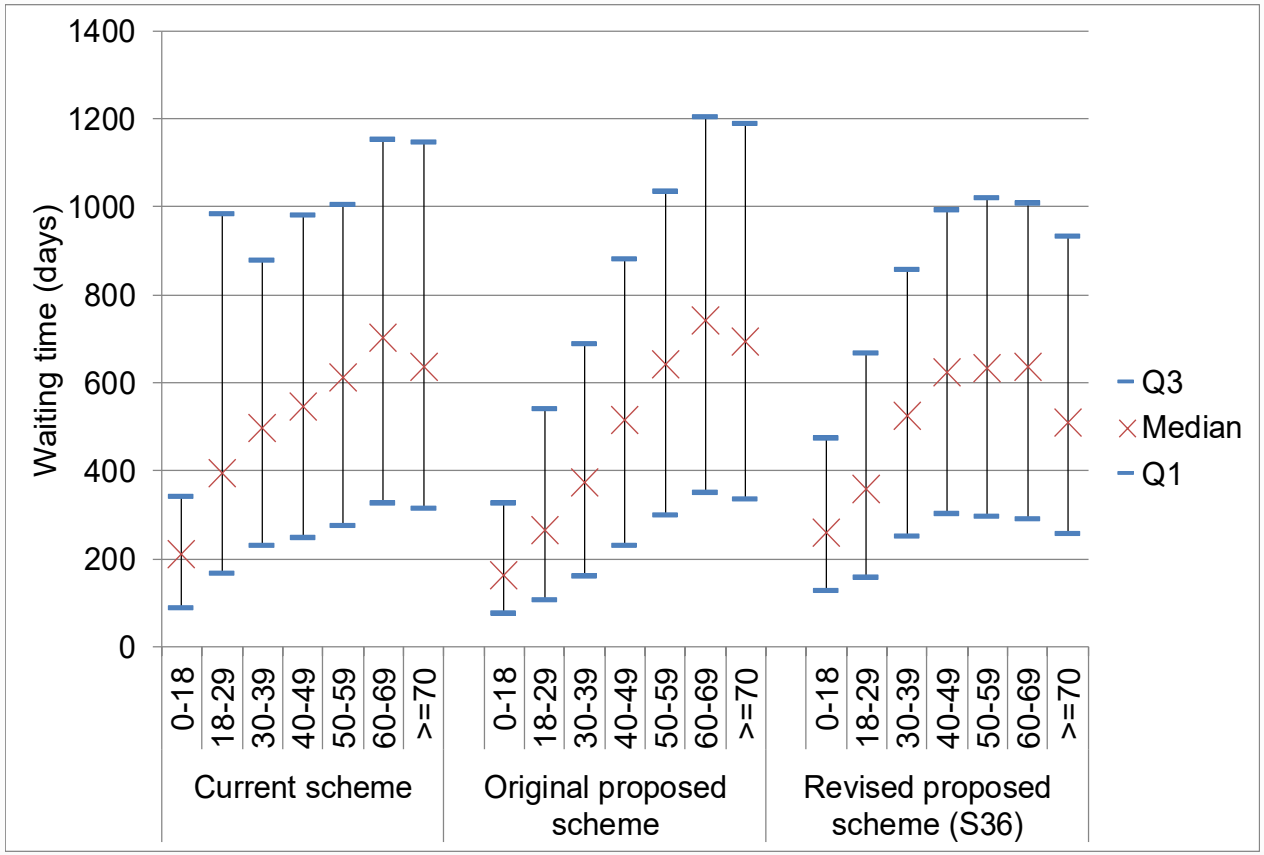
- Address the inequity of transplant for elderly listed patients.
- Particularly useful in conjunction with new KAS

Transplants from elderly deceased donors
1st May to 31st October 2019



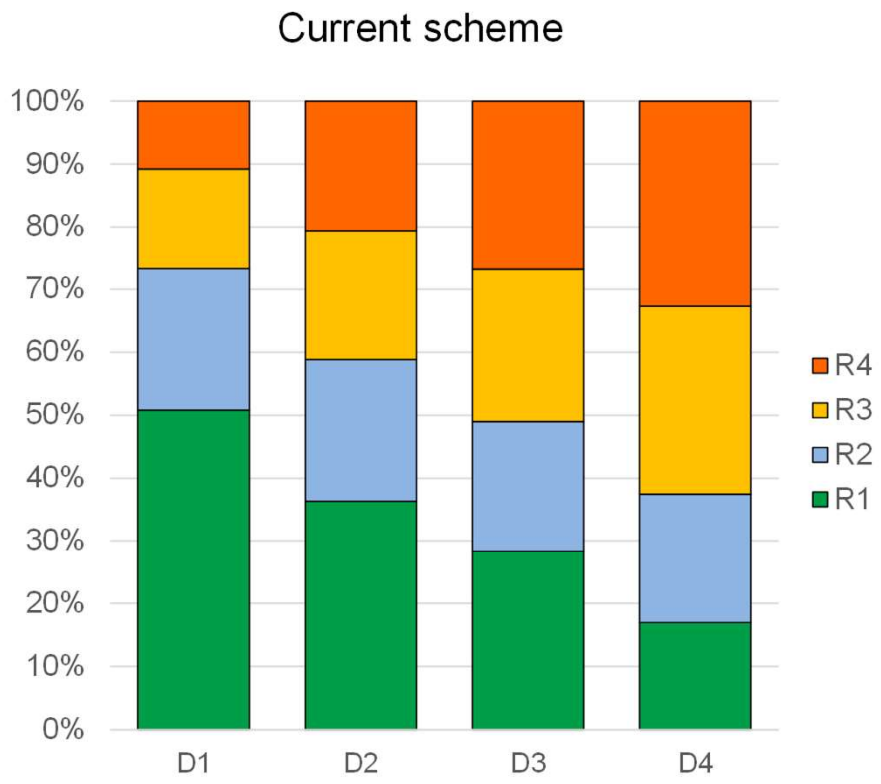
Proposed Kidney Allocation Scheme

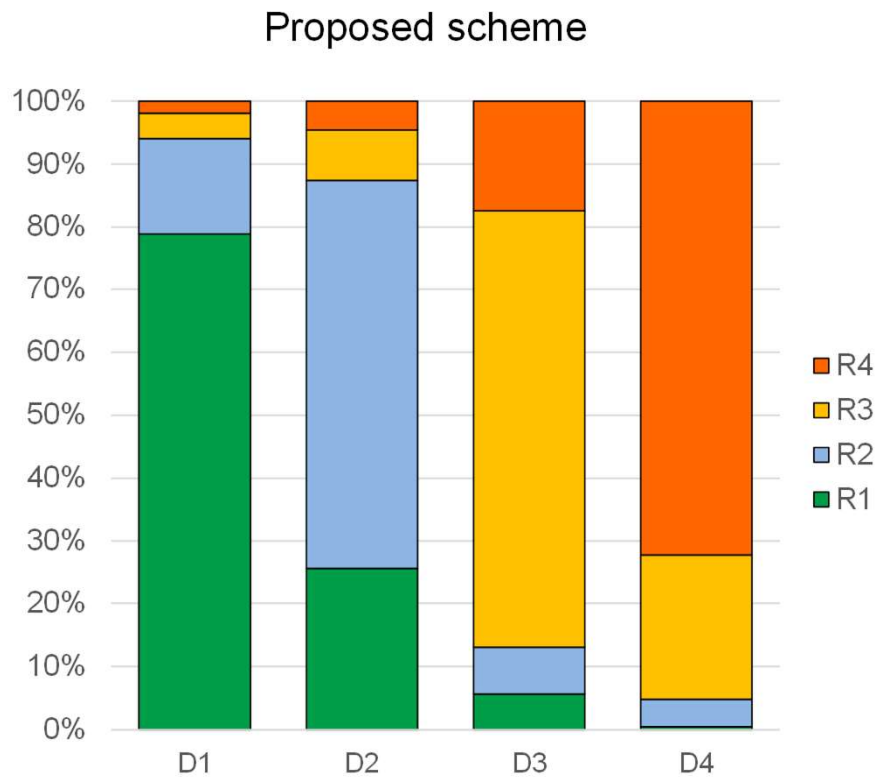
NHS Blood and Transplant



‘Quality’ matching donor to recipient

NHS Blood and Transplant

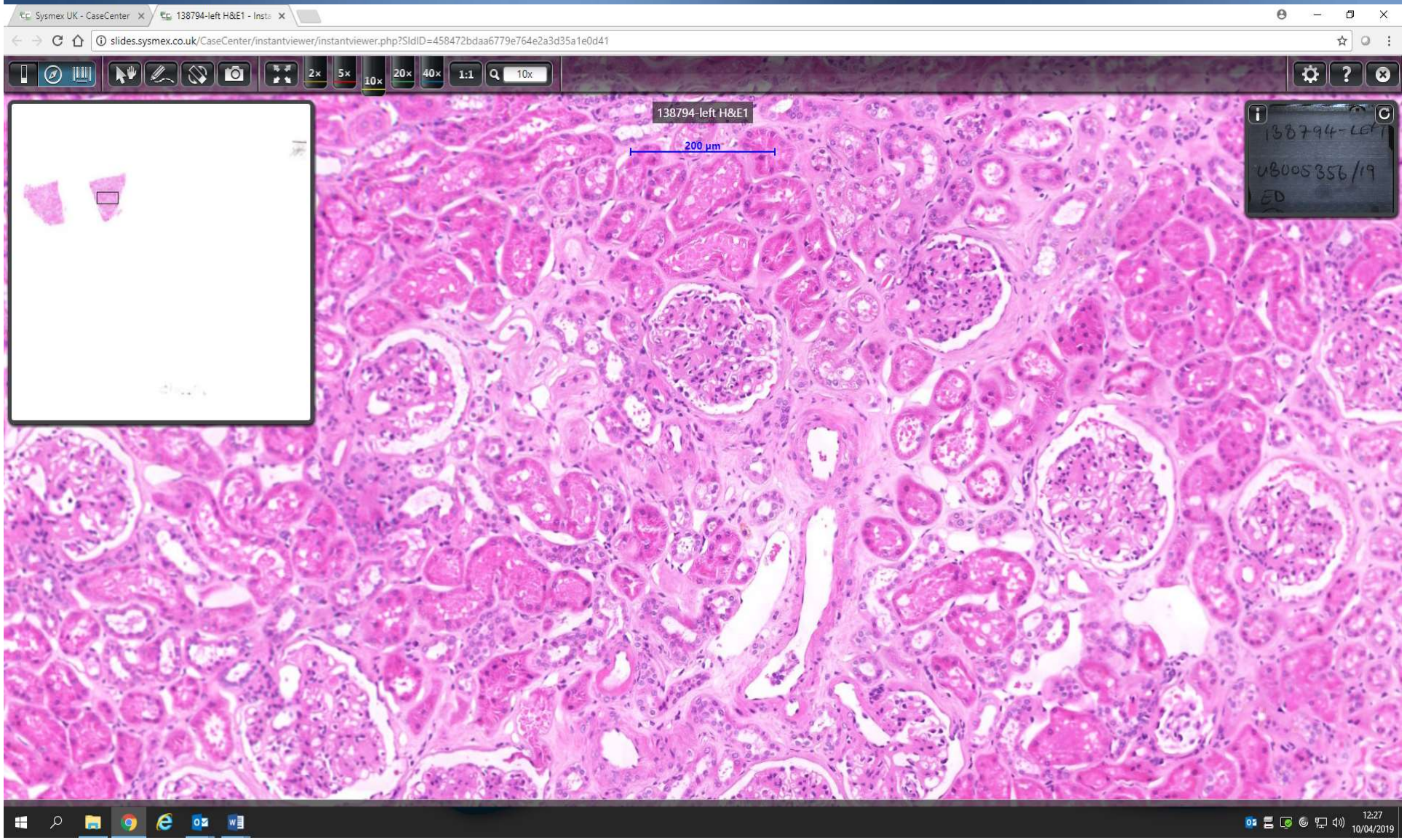




PITHIA Case Study

- 63 year old DCD donor. Scotland
- Cardiac arrest from choking on food bolus
- Parkinson's
- > 10 year of diabetes – on insulin
- HbA1c Feb 2019 – 85.
- ?Peripheral neuropathy – not confirmed.
- Creatinine 70 uM/L, eGFR of 90. 80kg, 177cm.

PITHIA Case Study



Final word…

- This is a **trial**!
- **No one** knows what to do with kidneys from **elderly** and **marginal** donors and **no one** knows whether **biopsies** will definitely help or not
- If centres don't order biopsies in the trial then we will **never know** the answer to this question
- The aim is to see whether biopsies will help you **select**, and **transplant**, kidneys that you normally have declined

@PITHIA_trial

Surgeons	Patient Reps	Nephrologists	Statisticians	Pathologists	NHSBT
• Gavin Pettigrew • Dominic Summers • Tobi Ayorinde • Roberto Cacciola • Rutger Ploeg • Simon Knight • Chris Callaghan	• Fiona Loud • Stewart Powell • Keith Pennington • Richard Jarvis	• Nick Torpey	• Karla Hemming • Laura Pankhurst • Ed Wilson • Helen Thomas	• Desley Neil • Sathia Thiru • Vicky Bardsley • Meryl Griffiths • Sandrine Rendel	• Emma Laing • Alison Deary • Anna Mora • Claire Williment • Maggie Stevens • Mick Stokes • Tanya Partridge

Principal Investgators					
Belfast	James McDaid	Hammersmith Hospital	Frank Dor	Oxford	Simon Knight
Birmingham	Adnan Sharif	Leeds	Adam Barlow	Plymouth	Peter Rowe
Bristol	Samuel Turner	Leicester	Atul Bagul	Portsmouth	Paul Gibbs
Cardiff	Laszlo Szabo	Liverpool	Adham El-Bakry	Royal Free Hospital	Gareth Jones
Coventry	Dababrata Roy	Manchester	Titus Augustine	Royal London	Rajesh Sivaprakasam
Edinburgh	John Terrace	Newcastle	Colin Wilson	Sheffield	Badri Shrestha
Glasgow	Karen Stevenson	Nottingham	Sam Dutta	St George's Hospital	Abbas Ghazanfar
Guy's Hospital	Chris Callaghan				

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Kidney Research UK
Funding research to save lives

Kidney Research Yorkshire
Working in Yorkshire to beat kidney disease

NHS Blood and Transplant