QUality in Organ Donation (QUOD)

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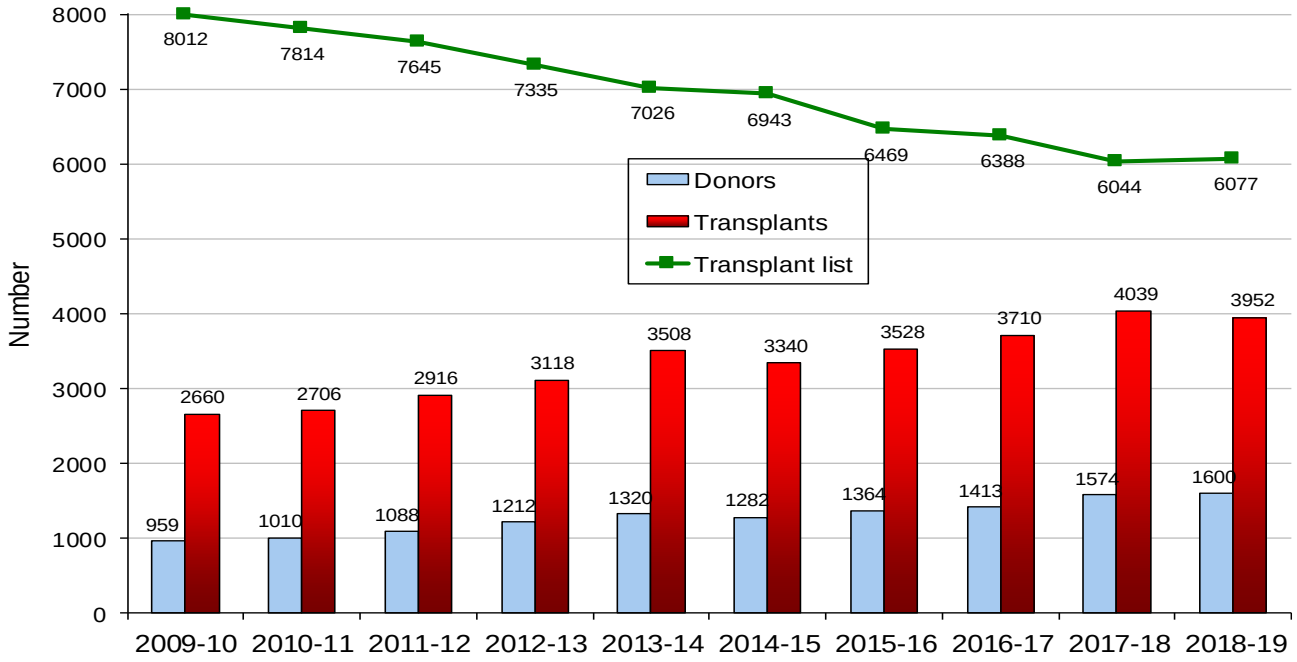
3rd International Conference on Functional Renal Imaging 2019

Overview

- Clinical challenges in Organ Donation and Transplantation
- Quality in Organ Donation (QUOD) biobank
  - An evolving biobank
  - Combining biobanking with research and development platforms
- Better donor organ assessment- A QUOD study
  - Subclinical Markers in Deceased Donor Kidneys are associated with Chronic Allograft Dysfunction- A QUOD study

NHS Blood and Transplant

Deceased donation and transplantation activity



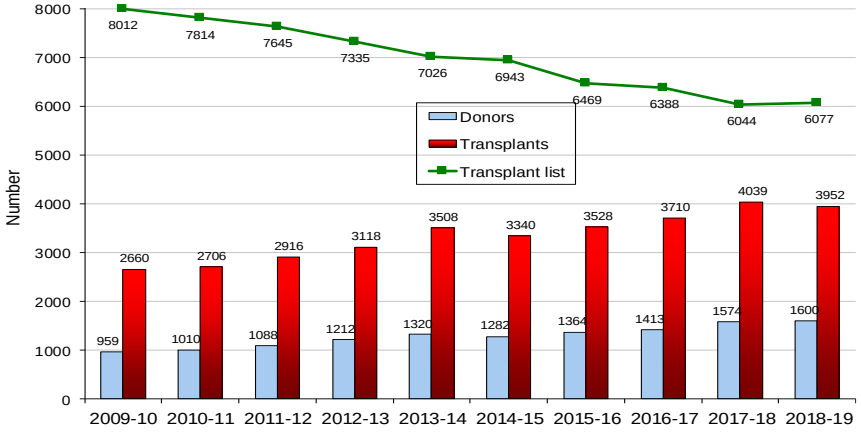
Over the last ten years

24% fall in waiting lists

49% increase in transplants (all organs)

67% increase in deceased organ donors

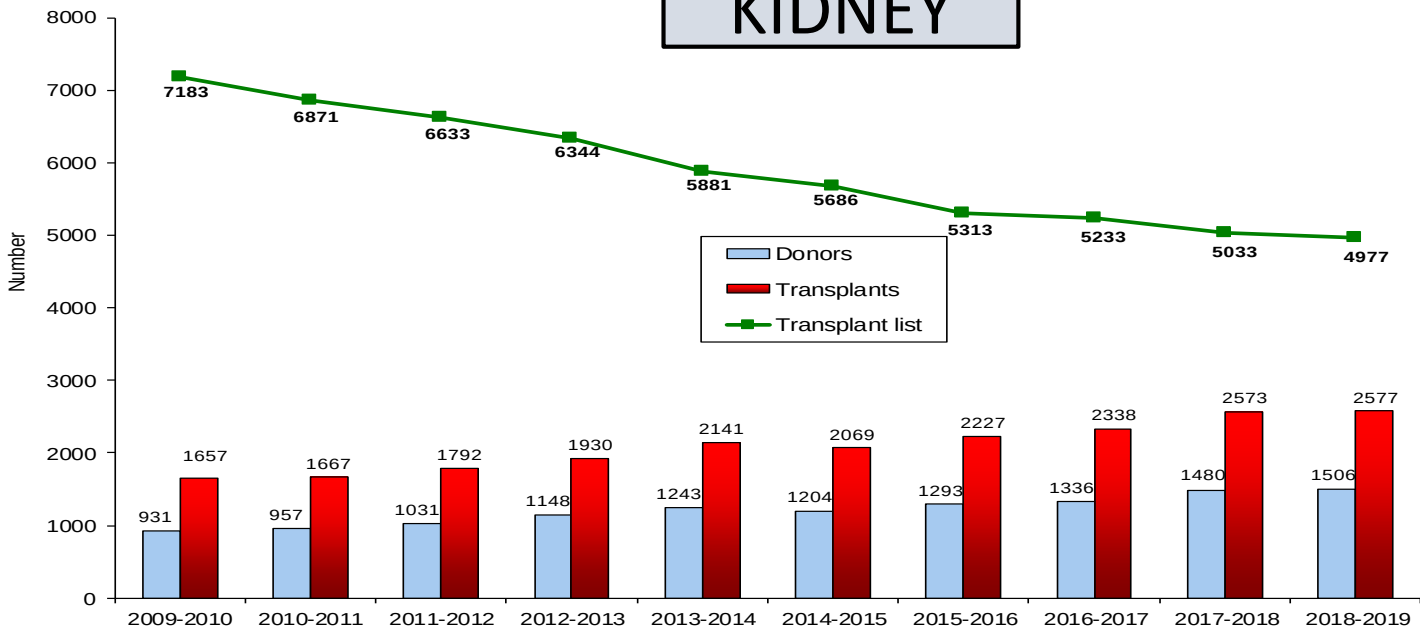
Deceased donation and transplantation activity



Over the last ten years

24% fall in waiting lists

KIDNEY



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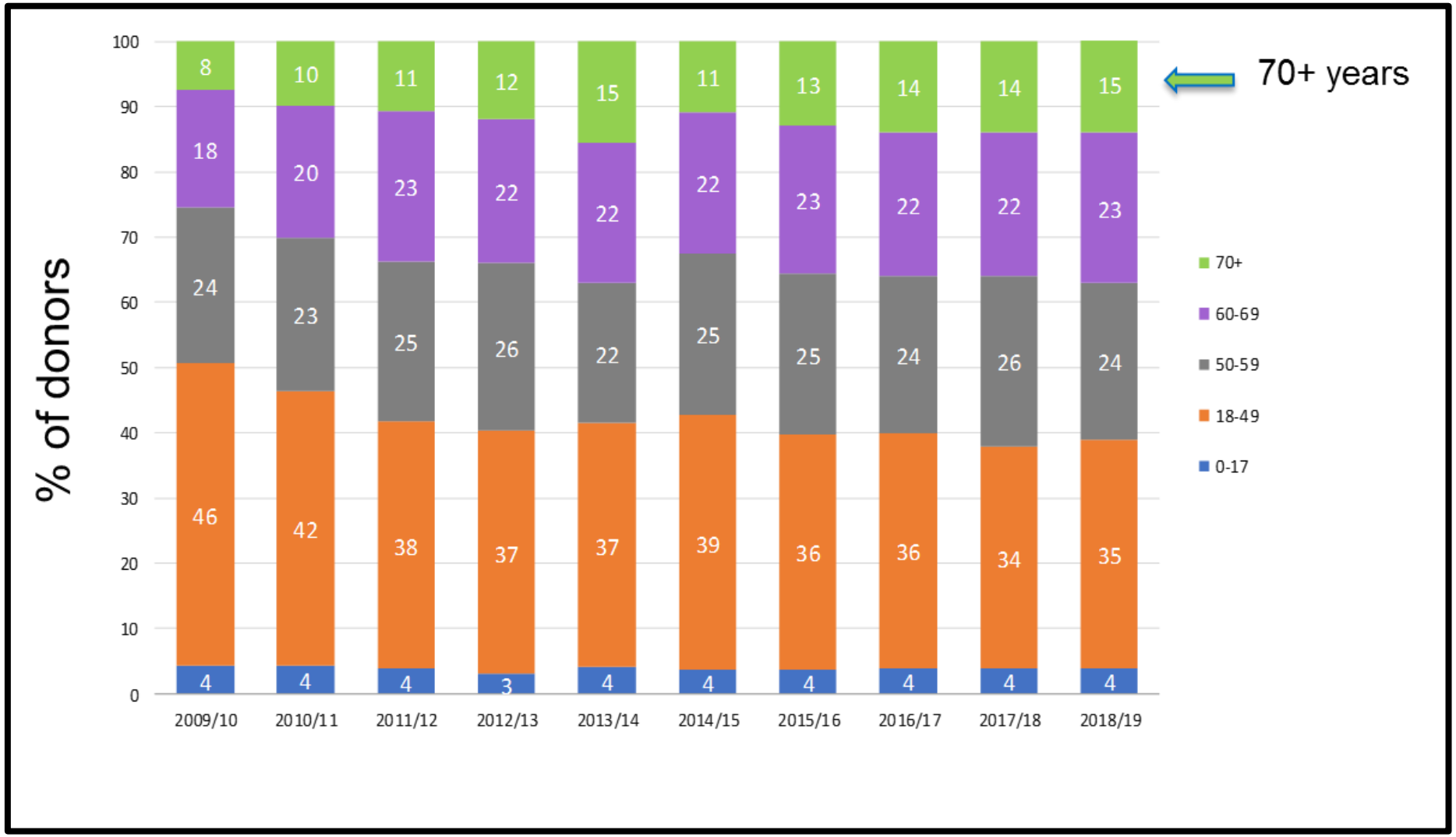
67% increase in deceased organ donors

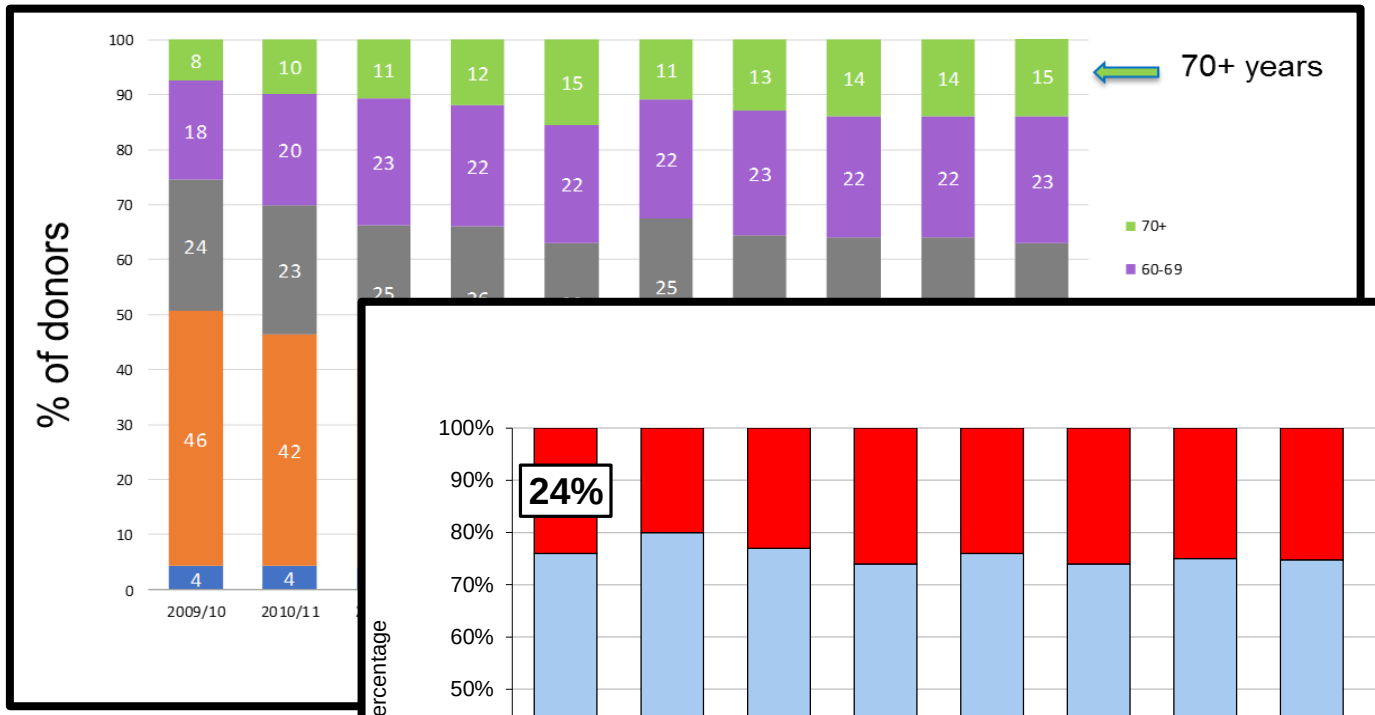
NHS Blood and Transplant

Complexity of deceased donors changes



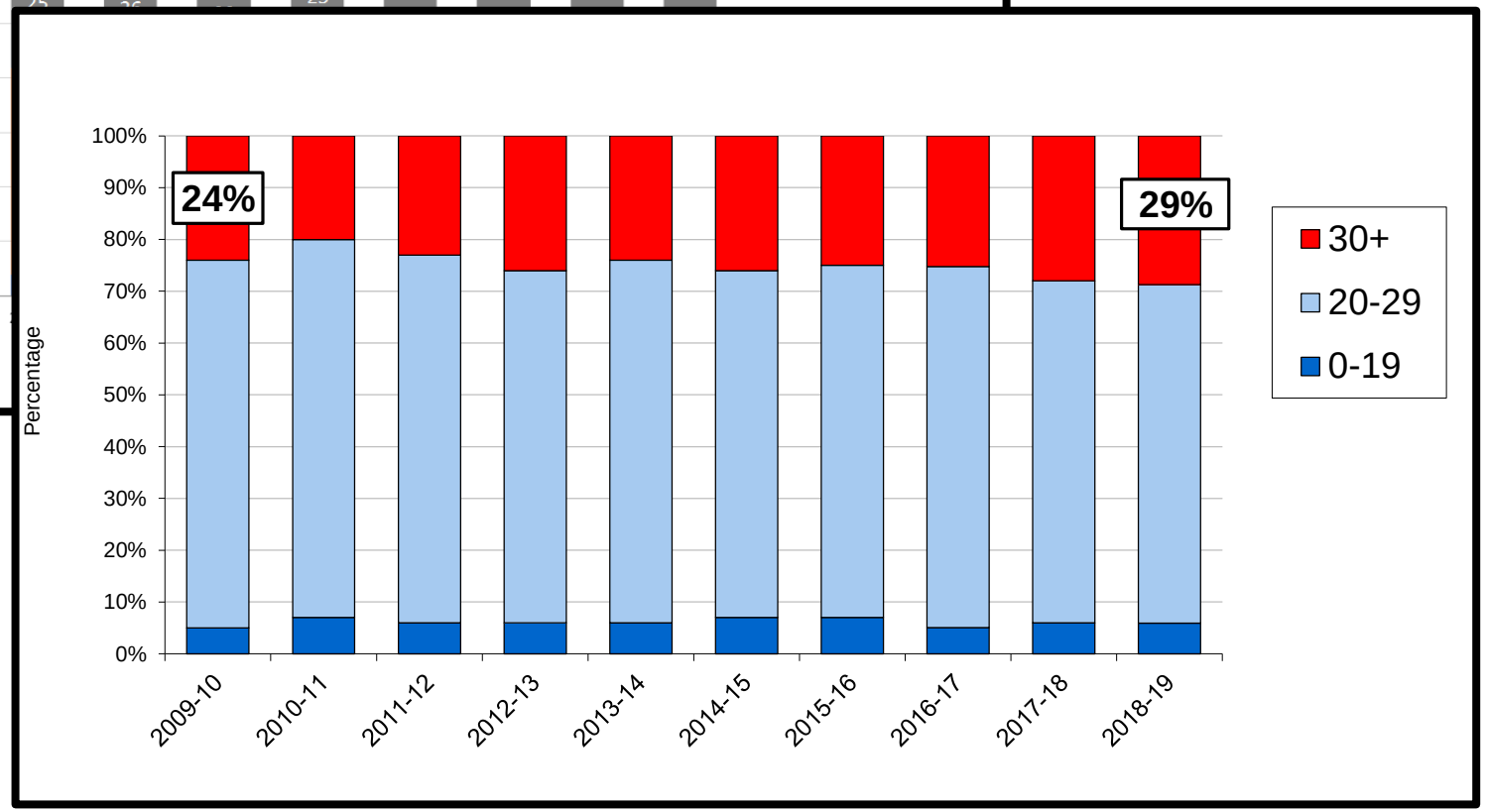
Donor age

Complexity of deceased donors changes



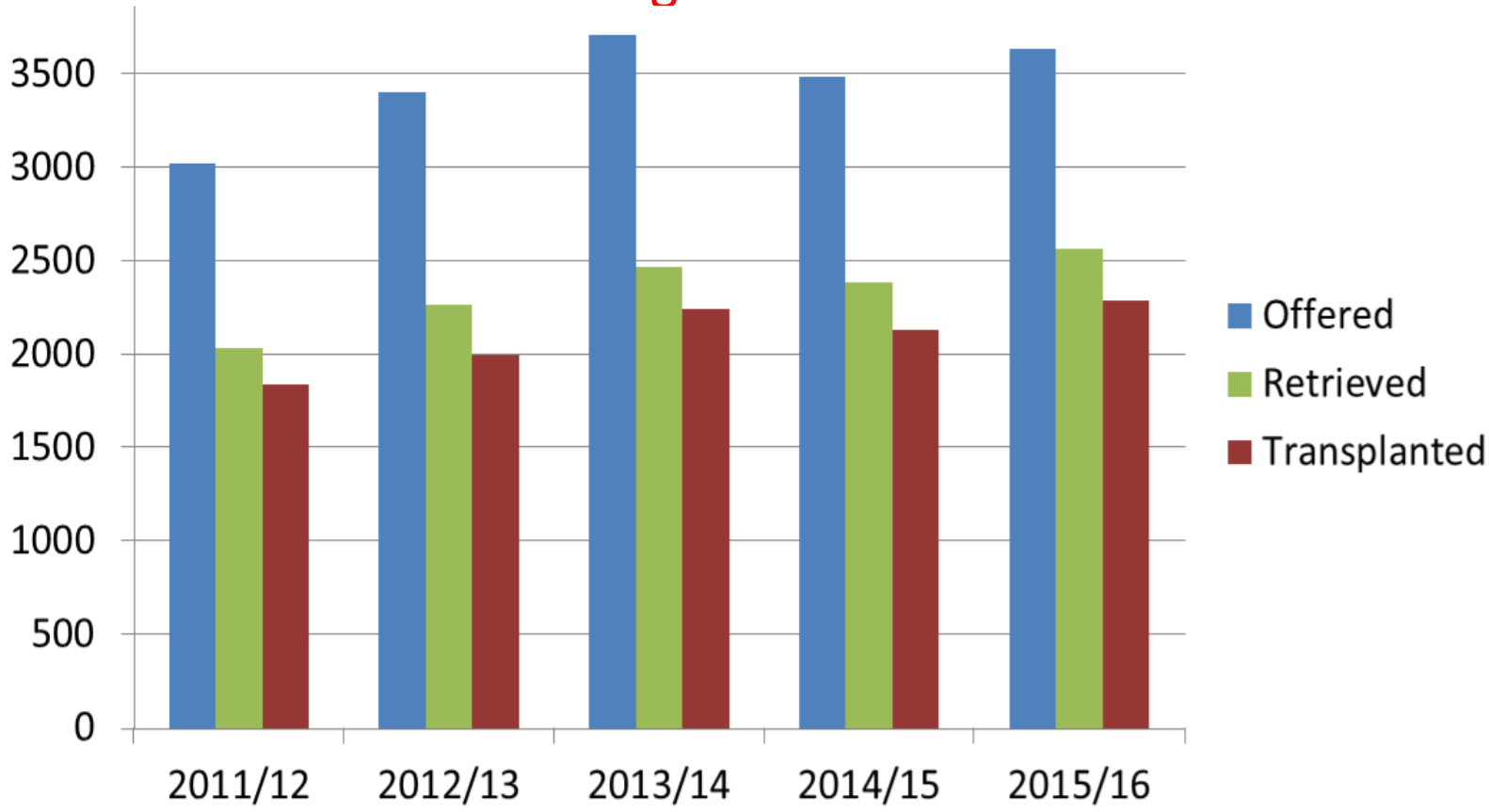
Donor age

Donor BMI



Clinical challenges in Organ Donation - Transplantation

- **Older donor kidneys are more likely to have suboptimal function in recipients and lower survival**
  - Uncertainty of the quality of donor organs
  - A high number of deceased donor organs are not utilised



Clinical challenges in Organ Donation - Transplantation

- **Shortage of donor organs**
  - **4,997 patients waiting for a kidney transplant**

Clinical challenges in Organ Donation - Transplantation

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- **Donors are older with comorbidities**
  - **High rate of unutilised organs**

Clinical challenges in Organ Donation - Transplantation

- **Shortage of donor organs**
  - **4,977 patients waiting for a kidney transplant**
- **Donors are older with comorbidities**
  - **High rate of unutilised organs**
- **Although great improvements in one year graft survival, long term allograft survival has remained unchanged**
  - **840 transplant recipients returning to dialysis each year**

Burton et al., NDT, 2019

QUOD

Quality in Organ Donation

Working in partnership with

MRC Medical Research Council

NHS Blood and Transplant

QUOD
Quality in Organ Donation

Why QUOD ?

Persistent shortage of donor organs

The increased utilisation of older and higher risk donors and the lack of accurate assessment of these organs

Improve transplant outcomes beyond the first post-transplant year

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NHS Blood and Transplant

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Developing a National Consortium

- Collaborative Programme NHSBT & Academic Centres
- The development of a national biobank
- Integration of clinical samples collected during donor management with clinical donor data & recipient outcomes

Aim of this infrastructure

- Develop national consortium & scientific platform
- Support research with special focus on injury & repair
- Identify new biomarkers and optimise donor quality
- Streamline research collaboration & facilitate service development & clinical studies

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Objectives

Authorised by HTA in permitted hospitals: capture 90% of donors

- More than 250 SNODs taking consent
- ICU teams supporting collection of samples
- 9 abdominal and 6 cardiothoracic NORS teams
- 19 H&I labs processing samples
- 8 QUOD recipient labs with technicians
- Support from NHSBT ODT staff and Stats Unit

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QUality in Organ Donation (QUOD)

- 2013: Sample collection during donor management started in UK
  - Longitudinal blood and urine samples during donor management
  - Kidney, liver, ureter & spleen biopsies at the back table
  - Samples linked to donor and recipient demographic and clinical data of the National Transplant Database UK
  - Samples collected by the Special Nurses of Organ Donation and National Organ Retrieval services
- 2018: Expansion to collection of heart, lung and islets samples & collection and storage of whole organs

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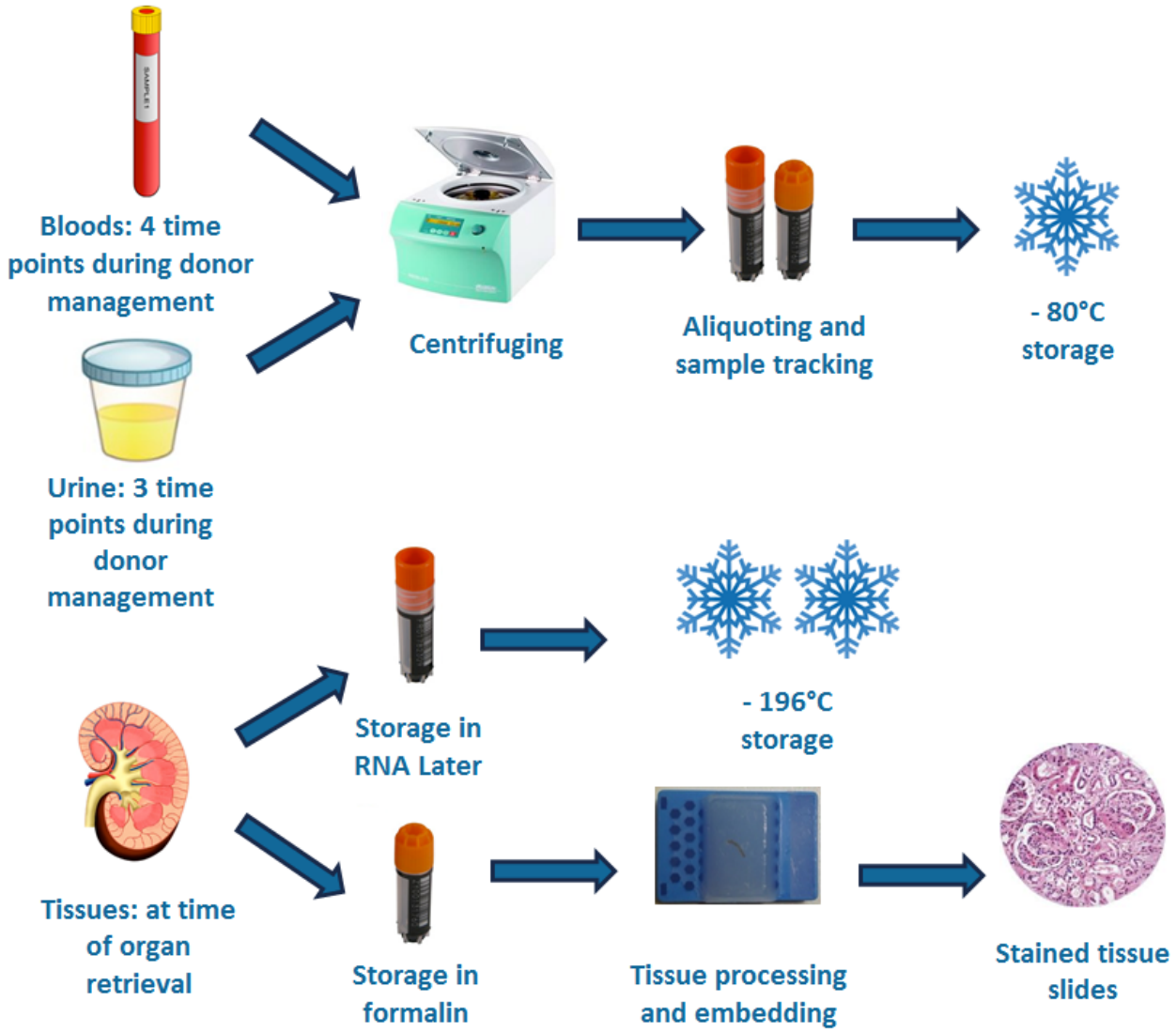
After consent for donation & research: Collection, processing and storage …



B: Blood
U: Urine
T: Tissue
- Kidney
- Liver
- Spleen
- Ureter
- Heart
- Lung (BAL)

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Sustainable userfriendly sample collection …

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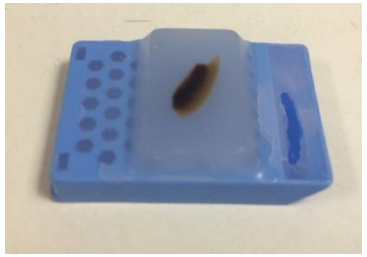
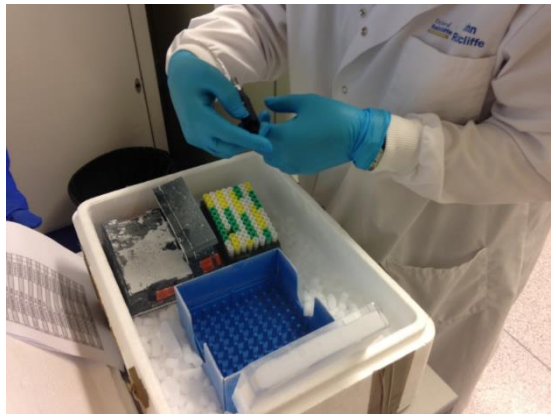
Lab tissue & aliquot preparation





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Bioresource key figures

- **Date** 1 October 2019
- **Donors** 4,400
- **Samples (biobanking items)** 70,100 in total, including:
- **Blood** 40,905 samples
- **Urine** 9,507 samples
- **Kidney** 10,925 samples (5,515 biopsies)
- **Liver** 5,750 samples (2,889 biopsies)
- **Ureter** 6,316 samples (3,183 biopsies)
- **Spleen** 3,217 samples (3,217 biopsies)
- **BAL** 69 samples
- **Heart** 844 samples (423 biopsies)

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Quality in Organ Donation

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Research applications supported by QUOD samples

> 70 projects with request of > 15,000 samples

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Pre analytical variability considerations

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Evaluating confounding factors in handling of biobanking specimens

- The clinical setting during donor management and organ transplantation provides additional challenges in the implementation of standard protocols in sample collection and processing prior to sample storage
    - Variability in sample procurement during donor management
    - Temperature variation during short term storage and sample processing
    - Variability on sample processing e.g speed of whole blood centrifugation
    - Freeze thaw cycles

Evaluating confounding factors in handling of biobanking specimens

Kaisar *et al. Clin Proteom (2016) 13:26*
DOI 10.1186/s12014-016-9126-9

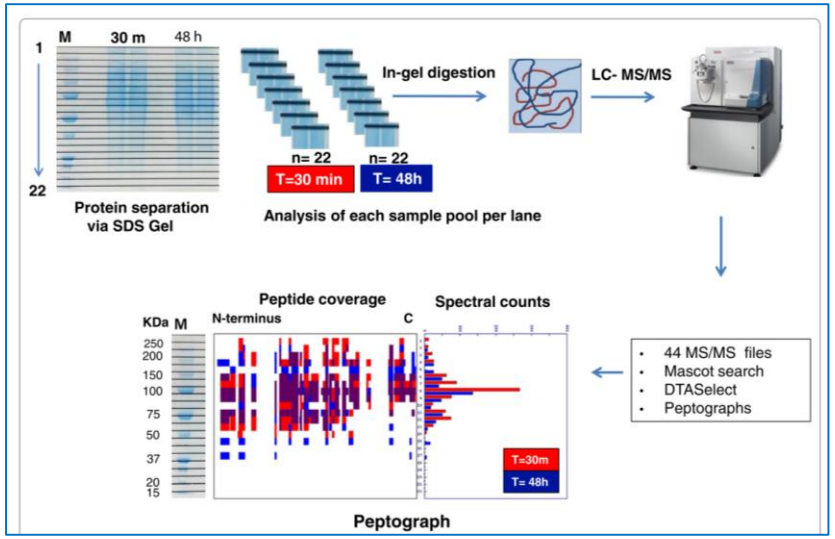
Clinical Proteomics

RESEARCH Open Access

Plasma degradome affected by variable storage of human blood

Maria Kaisar[1,2,4], Leon F. A. van Dullemen[3†], Marie-Laëtitia Thézénas[4†], M. Zeeshan Akhtar[1], Honglei Huang[1,4], Sandrine Rendel[1], Philip D. Charles[4], Roman Fischer[4], Rutger J. Ploeg[1,2‡] and Benedikt M. Kessler[4*‡]

Assessing the extent of plasma protein degradation while whole blood samples remain at RT after sample collection and prior to processing



Kaisar et al., Clinical Proteomics, 2016

Plasma Biomarker Profile Alterations during Variable Blood Storage

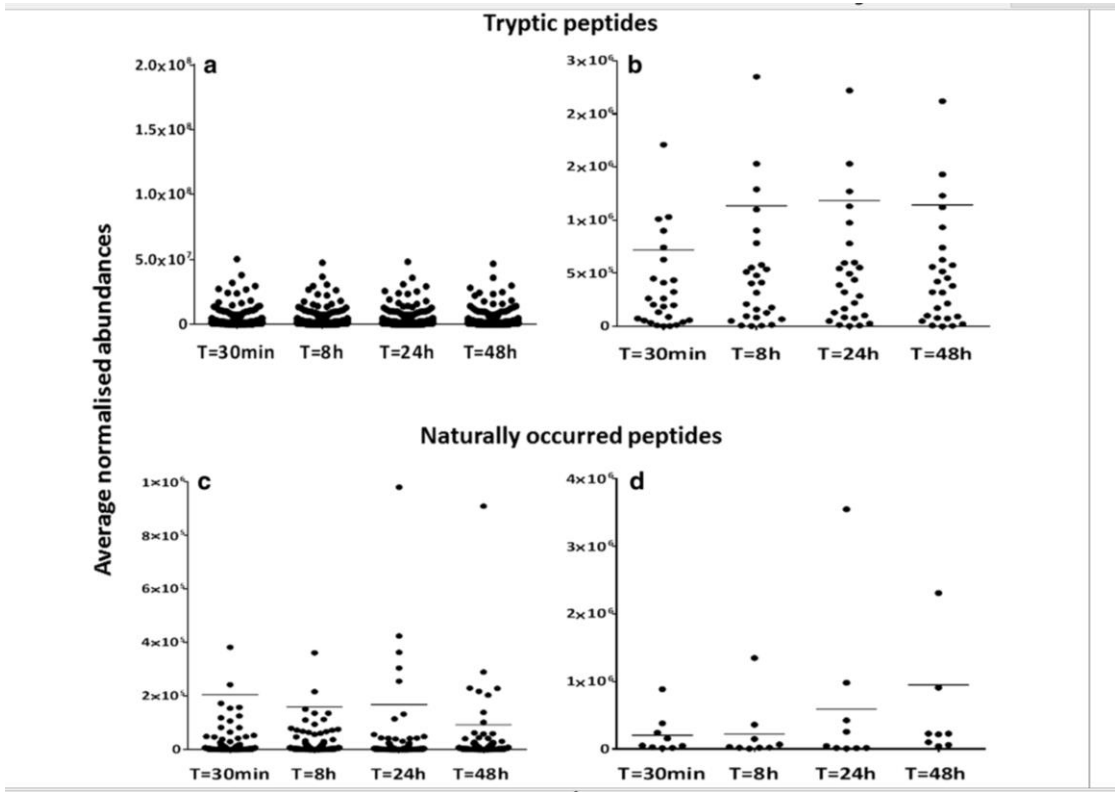


Table 1. Preanalytical effects on plasma proteome and degradome.

Protein description	LFQ LC-MS/MS Fold change[a] T = 8 h vs T = 30 min	LFQ LC-MS/MS Fold change[a] T = 24 h vs T = 30 min	LFQ LC-MS/MS Fold change[a] T = 48 h vs T = 30 min	PROTOMAP analysis T = 48 h vs T = 30 min
Fibrinogen gamma chain	1.4	1.3	1.2	No degradation
Apolipoprotein A-I	1.3	1.3	1.3	No degradation
Profilin-1	1.1	2.0	7.1	No degradation
DNA polymerase epsilon catalytic subunit A	1.2	1.2	1.2	No degradation
Coiled-coil domain-containing protein 11	1.2	1.3	1.3	No degradation
Coagulation factor XIII B chain	1.2	1.2	1.2	No degradation
Heat shock protein 70 kDa	1.3	1.3	1.2	No degradation
Dedicator of cytokinesis protein 7	1.5	1.5	1.4	No degradation
Cystatin-C	1.3	1.3	1.3	No degradation
Uncharacterized protein C2orf53	1.8	1.9	1.7	No degradation
Complement C1q subcomponent subunit B	1.3	1.3	1.3	No degradation
Leukocyte immunoglobulin-like receptor	1.2	1.4	1.4	No degradation
MCM domain-containing protein 2	1.6	1.7	1.7	No degradation
Ankyrin repeat domain-containing protein 54	2.2	2.3	2.2	No degradation
Thrombospondin-1[b]	1.2	1.3	1.4	Partially degraded
Coagulation factor XI[c]		N/E[d]		Partially degraded
Complement C1r[c]		N/E		Partially degraded
Actin[c]		N/E		Partially degraded
Complement C3[c]		N/E		Partially degraded

Kaisar et al., Clinical Chemistry, 2016

An evolving biobank;
expanding to heart, lung, islets and collection, storage of whole organs

Integration with research platforms

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NHS Blood and Transplant

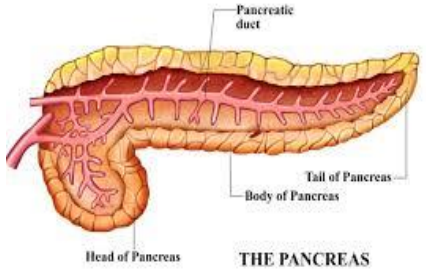
Newcastle University

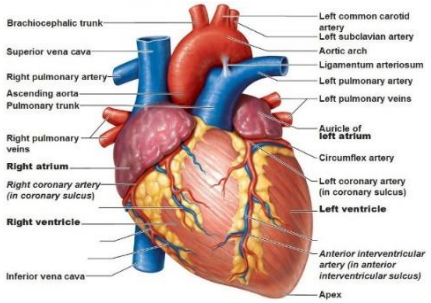
UNIVERSITY OF OXFORD

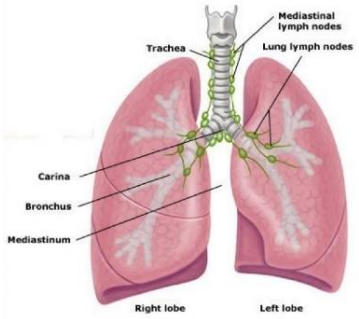
QUOD expansion to heart, lungs, islets & whole organs (pancreases, hearts)

- Characterisation of normal and chronic disease-associated pathological changes in pancreas, heart and lungs
- Study the impact of acute stress on individual tissues towards; improving our understanding of early pathological changes
- Creation of tissue atlas and study of different single-cell populations

QUOD Expansion







- Collection of **whole organs** in addition to samples
- To determine **transcriptome and proteome** of donor organs
- Creating **organ atlas** with state-of-the art pathology & imaging
- Delivering a **searchable data library**

- ➢ Better understanding of **normal vs diseased** & causes of cellular stress
- ➢ Optimise transplant success, but also help prevent or reverse chronic diseases

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Understanding the biology of organ injury

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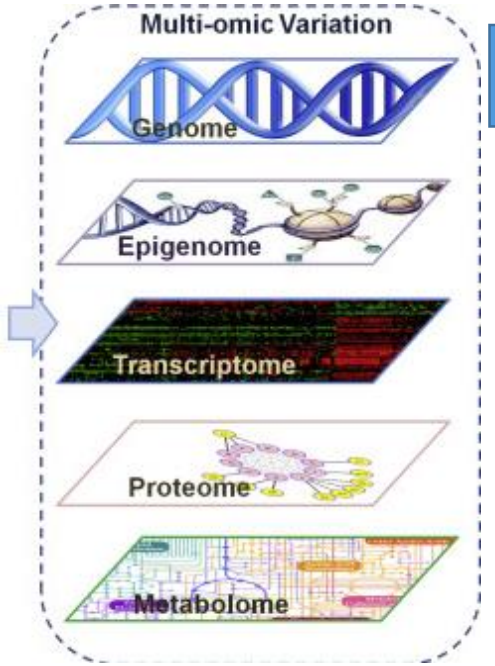
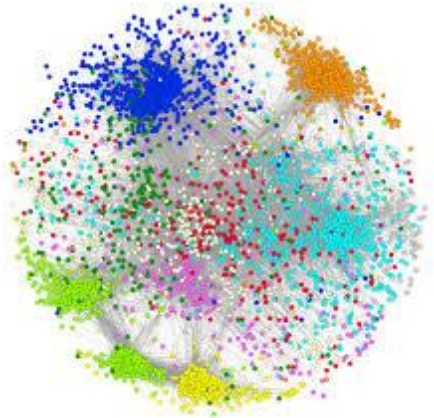
Advanced molecular and histological imaging experimental techniques

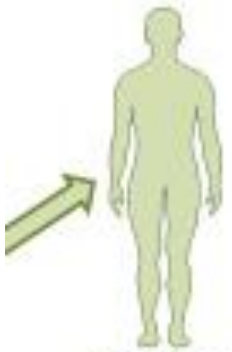


-Omics library



Biological pathways

Stratification of risk



Organs transplanted with good outcomes

Organs transplanted with suboptimal outcomes

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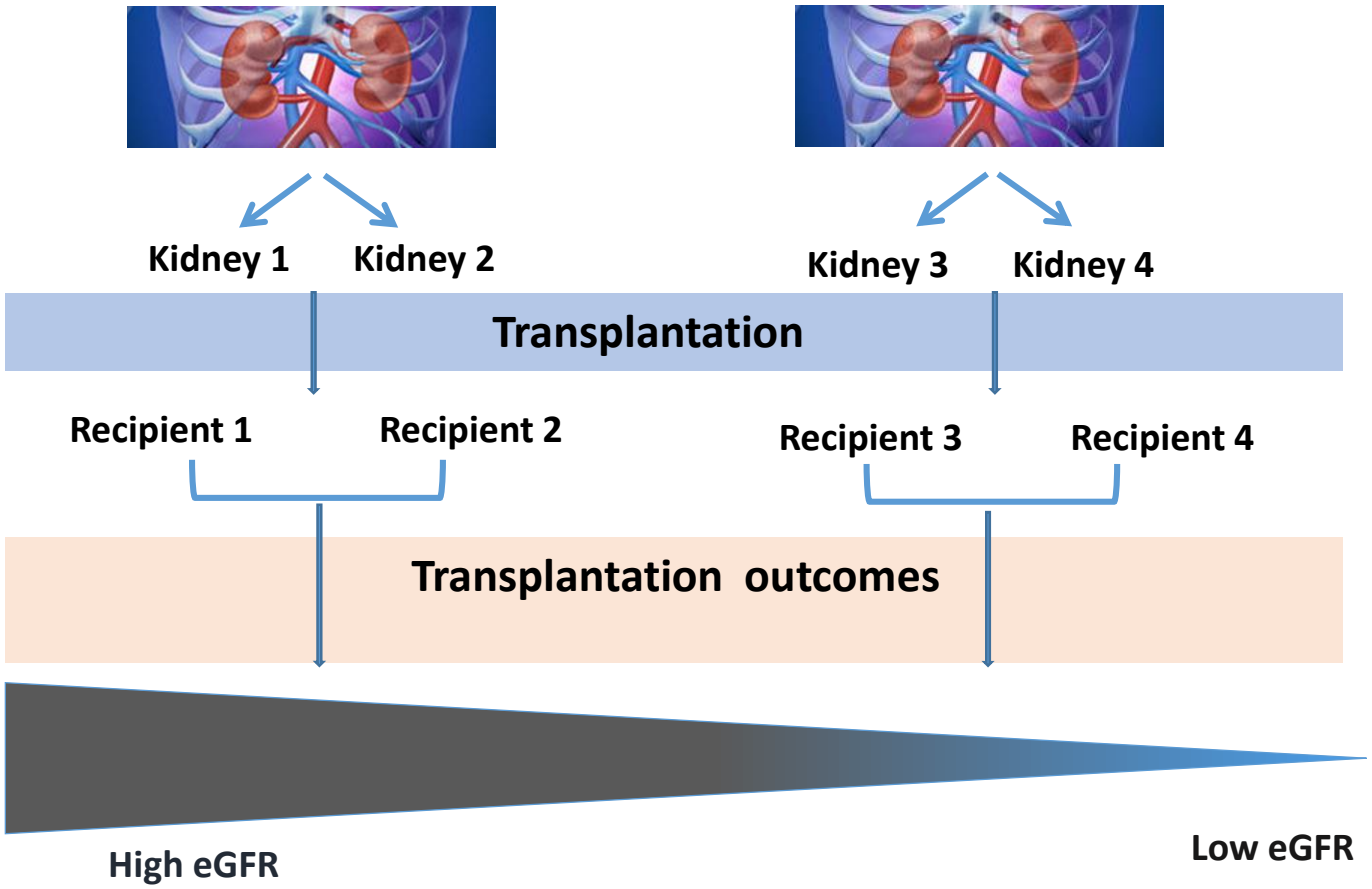
Better assessment of deceased donors and donor kidneys

Investigating the donor kidney proteome and the association with chronic allograft dysfunction

Kidney biopsies selected on the basis of transplantation outcomes



Suboptimal vs. Good transplantation outcomes

Suboptimal transplantation outcomes

Onset of delayed graft function

&

mean eGFR = 30 ml/min @ 3 & 12-month follow up

Good transplantation outcomes

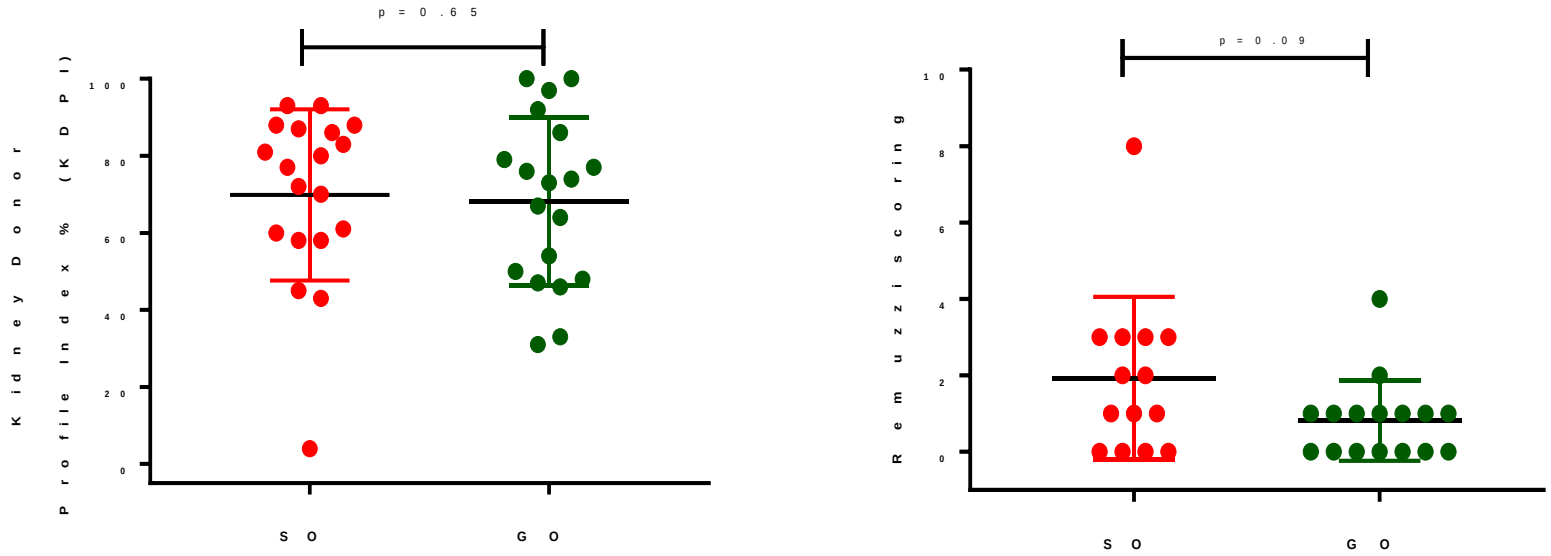
Immediate kidney function

&

mean eGFR = 65 ml/min @ 3 & 12- month follow up

	Suboptimal Outcome (n=19)	Good Outcome (n=19)	*P* Value
Donor characteristics			
Age (yr)*	56 ± 13	54 ± 11	0.5
Gender (%)			
Male	10 (53)	7 (37)	0.5
Race (%)			
White	18 (95)	16 (84)	0.6
Other	1 (5)	3 (16)	
Cause of death (%)			0.6
Intracranial heamorhage	10 (53)	10 (53)	
Hypoxic brain injury	4 (21)	2 (10)	
Other	5 (26)	7 (37)	
AKIN classification (%)			0.5
No AKIN	16 (85)	15 (79)	
1	1 (5)	3 (16)	
2	1 (5)	1 (5)	
3	1 (5)	0	
Remuzzi score[a] (%)			0.5
0- 3	13 (68)	15 (79)	
4-8	1 (5)	1 (5)	
Recipient characteristics			
Age (yr)*	50.1 ± 13.5	48.4 ± 13.6	0.5
Gender (%)			
Male	13 (68)	13 (68)	1
Race (%)			
White	15 (79)	10 (53)	0.17
Other	4 (21)	9 (47)	
HLA mismatches (%)			0.22
1	3 (16)	3 (16)	
2	5 (26)	7 (37)	
3	11 (58)	7 (37)	
4		2 (10)	
CIT (h)			1
0- 12	6 (31)	6 (31)	

Current clinical tools could not discriminate between donor kidneys with opposing extremes in post-transplantation outcomes



KDPI provides the probability of graft failure after transplantation, taking into account the following donor factors : age, ethnicity, donor type, height, weight, history of hypertension and diabetes.
KDPI of 80% indicates that the risk of graft failure is higher than for 80% of the donor kidneys for any given population

Remuzzi scoring is a histological assessment of chronic kidney disease of pre-implantation grading morphological changes in kidney tissue to a cumulative score (interstitial fibrosis, glomerulosclerosis, arherosclerosis)

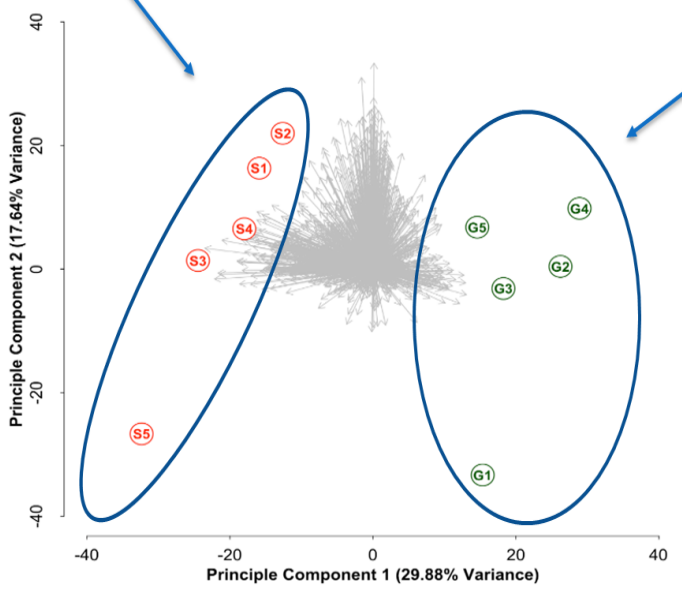
Kaisar et al., Transplantation 2019

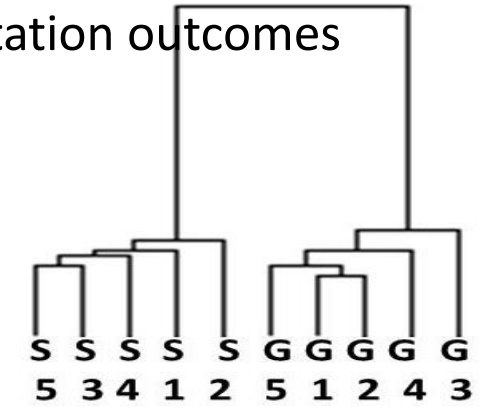
Subclinical proteomic changes in donor kidneys correlate with transplantation outcomes

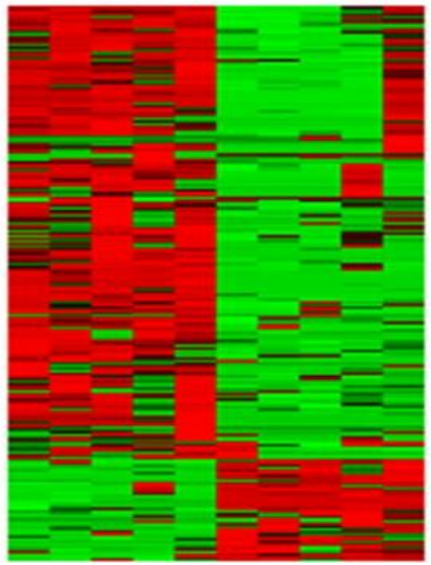
Proteomic profiling of donor kidney biopsies could distinguish the donor kidneys with good from those with suboptimal post-transplantation outcomes

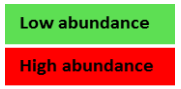
Donor kidneys with suboptimal allograft function

Donor kidneys with good allograft function









S: Suboptimal outcome
G: Good outcome

Kaisar et al., Transplantation, 2019

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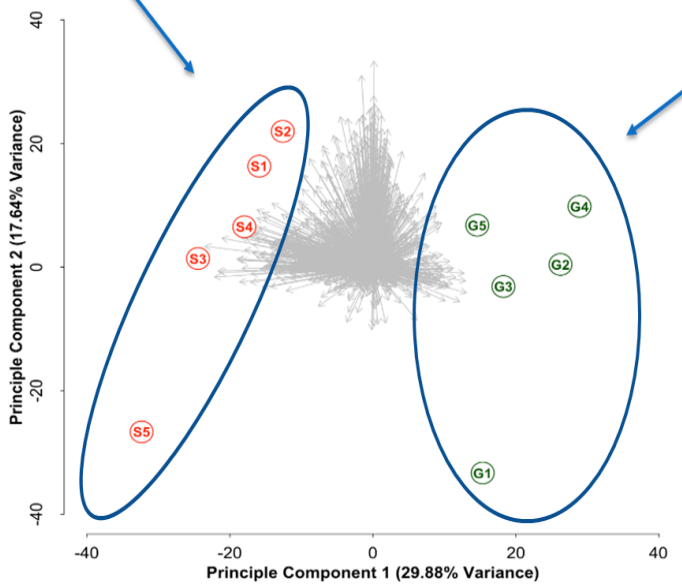
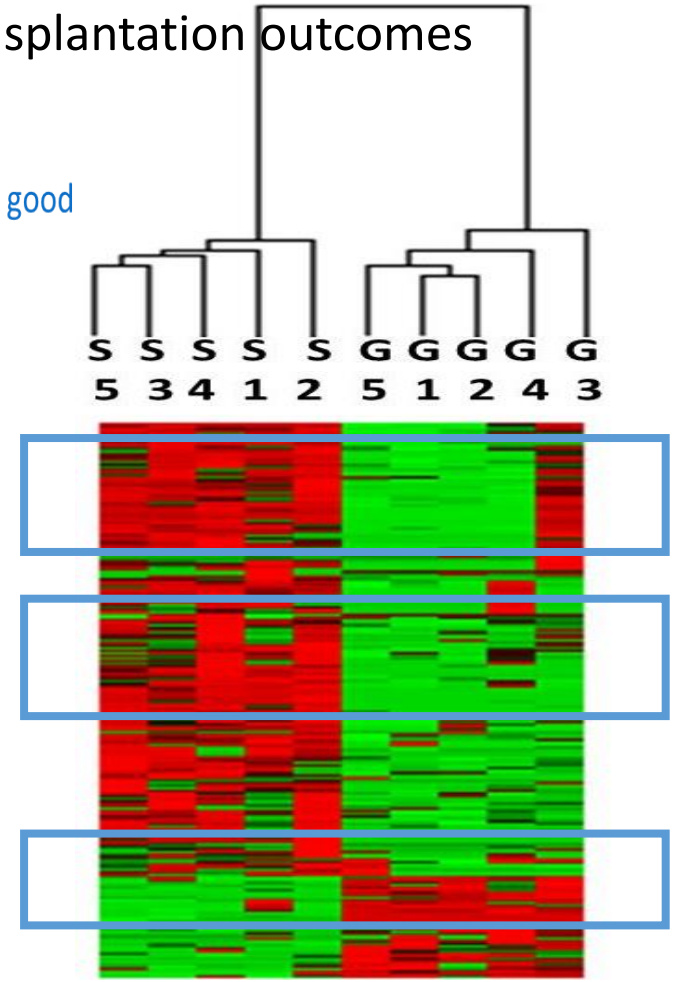
Donor kidneys with suboptimal allograft function

Donor kidneys with good allograft function





Markers of apoptosis & Kidney fibrosis

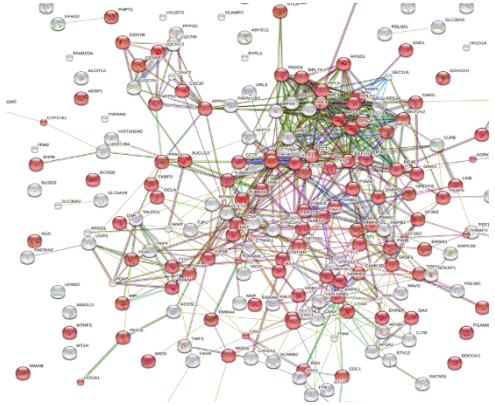
Cytoskeletal proteins

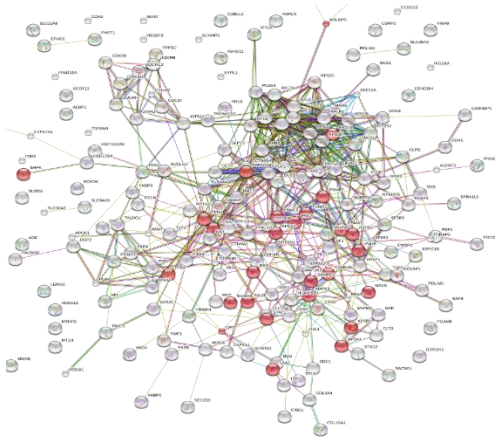
Cytoprotective proteins

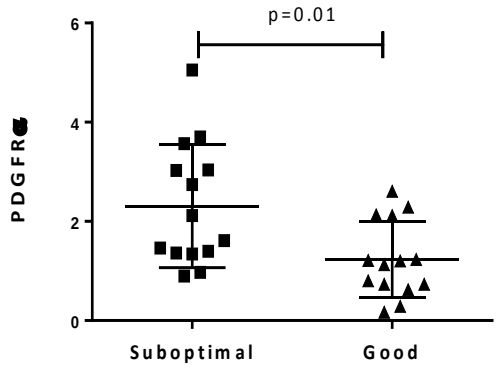
Kaisar et al., Transplantation, 2019

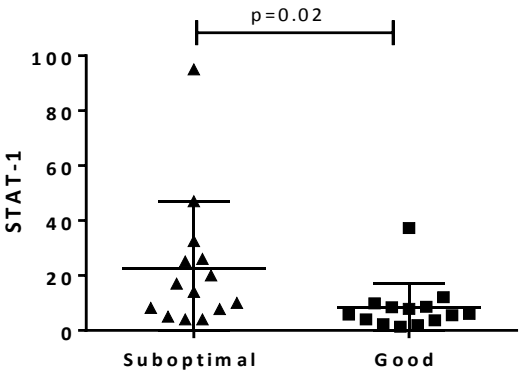
Subclinical proteomic changes in donor kidneys correlate with transplantation outcomes

Enrichment of proteins associated with apoptosis, cellular stress and fibrosis in donor kidneys with suboptimal outcomes

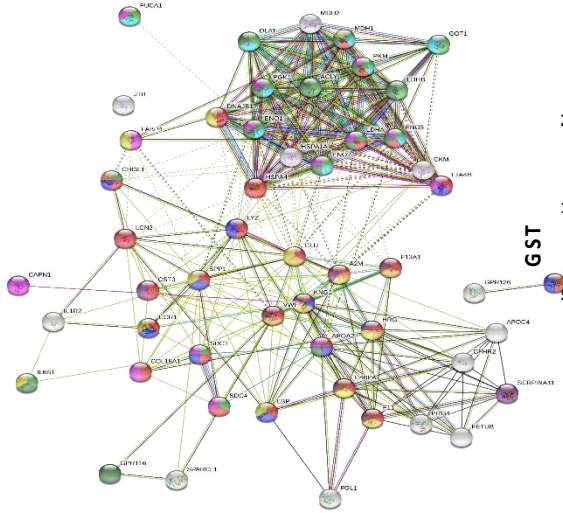


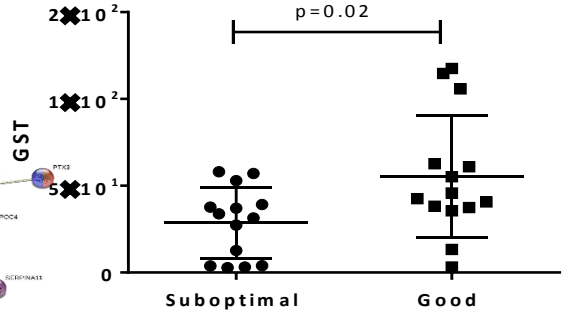


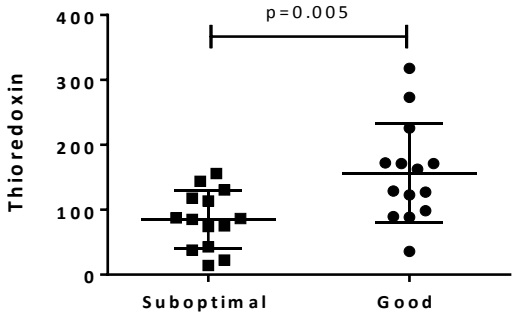


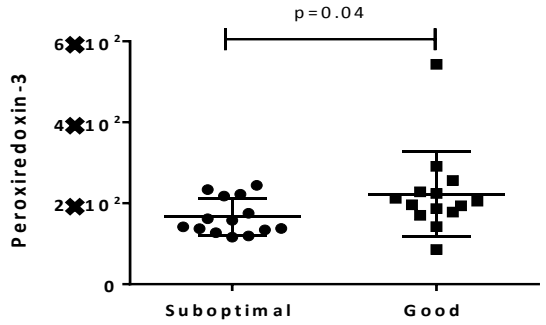


Pathway analysis shows enrichment of proteins associated with cytoprotection in donor kidneys with good outcomes



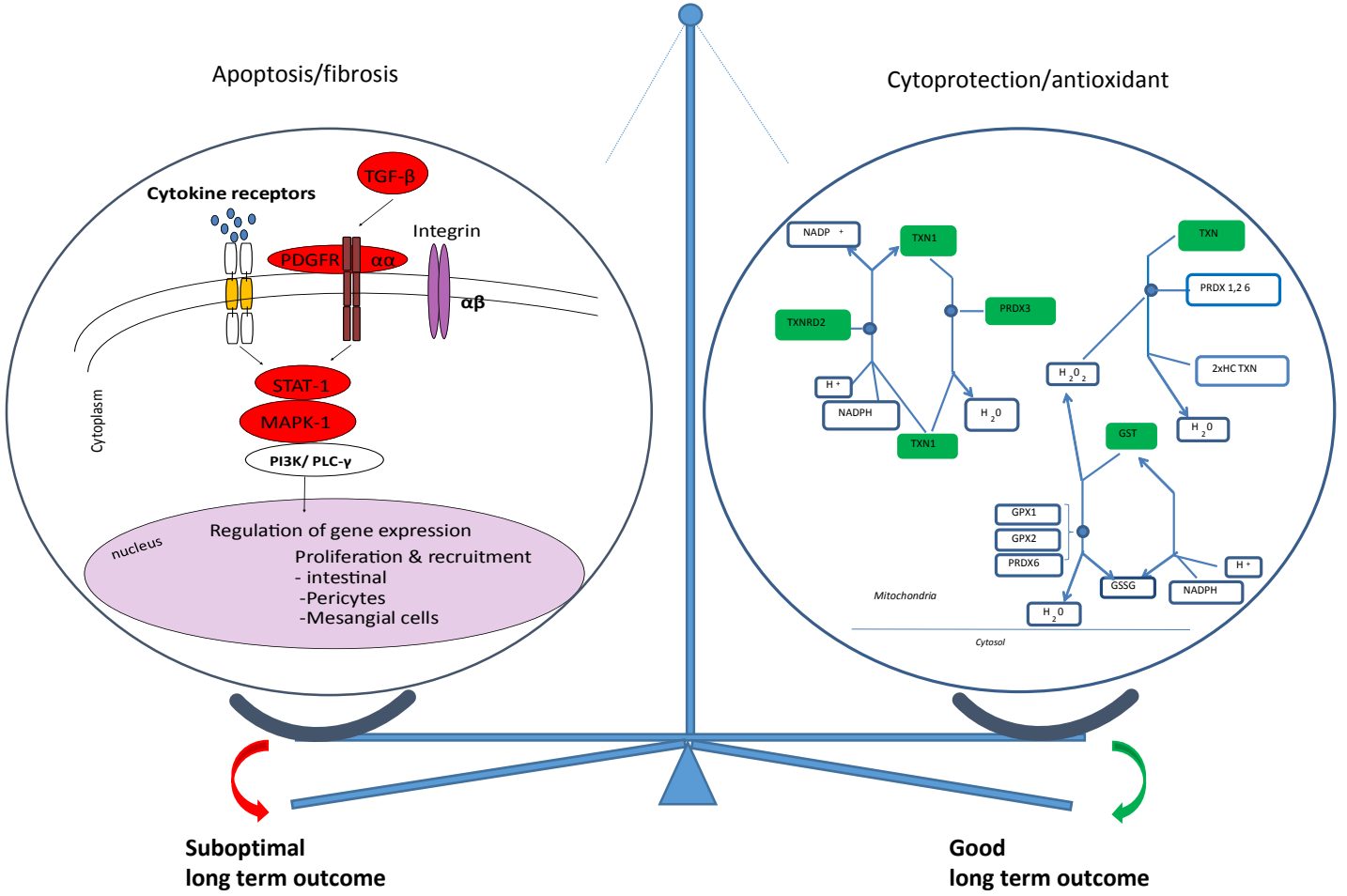






Kaisar et al., Transplantation, 2019

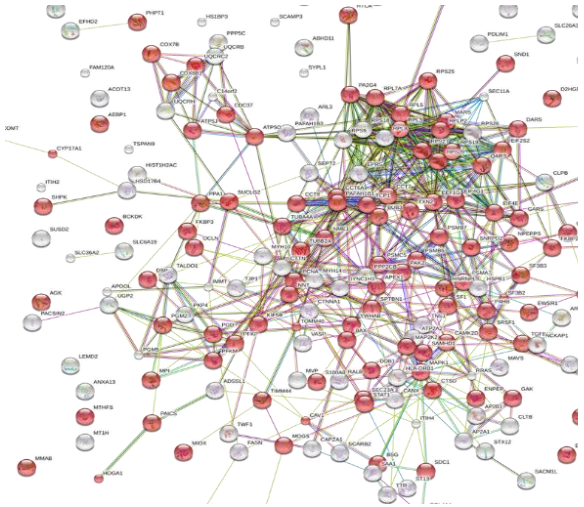
Subclinical proteomic changes in donor kidneys correlate with transplantation outcomes

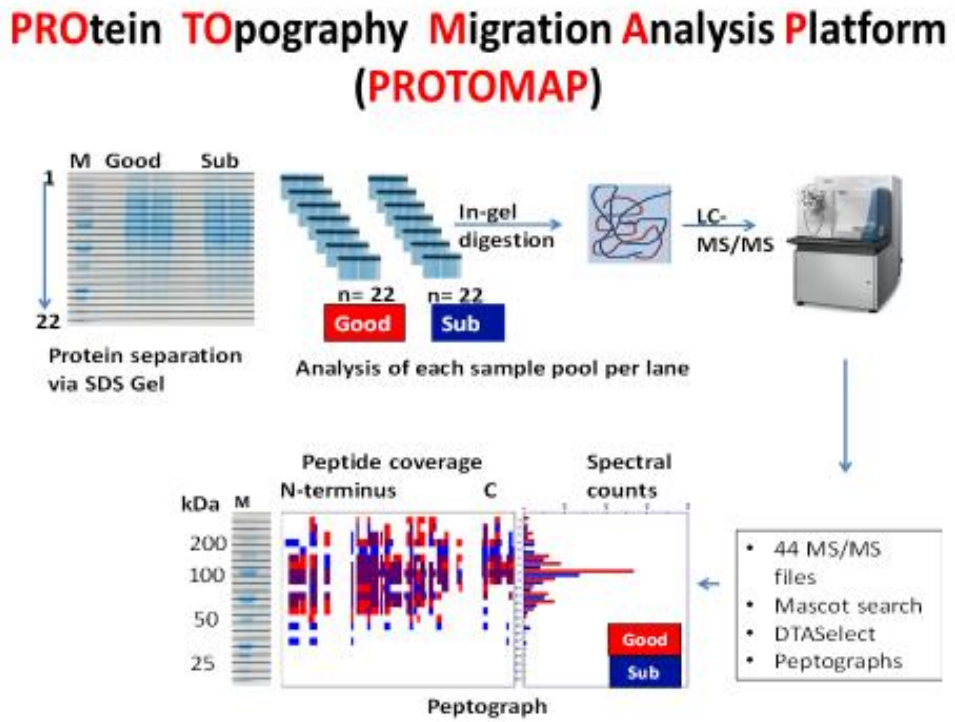


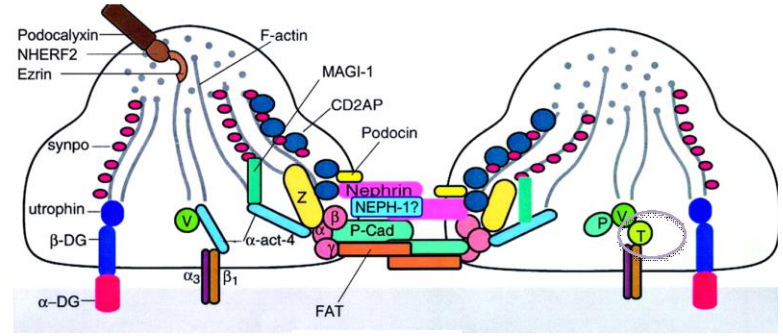
Pre-transplant interventions should aim to reduce the apoptotic / fibrotic activation and enhance a state of cytoprotection in deceased donor kidneys

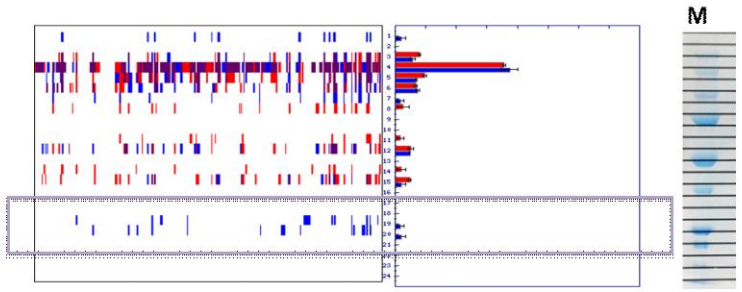
Mapping changes of cytoskeletal proteins that are associated to the development of allograft dysfunction

Pathway analysis shows enrichment of proteins associated with catabolic pathways in kidneys with suboptimal outcomes









Enrichment of catabolic pathways in deceased donor kidneys

Integrating mass spectrometry and computational analysis to further understand proteolytic events impact kidney quality

Generation of protein fragments associated to kidney function 12-month post transplant

Vaughan & Kaisar, manuscript in preparation

Acknowledgements

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