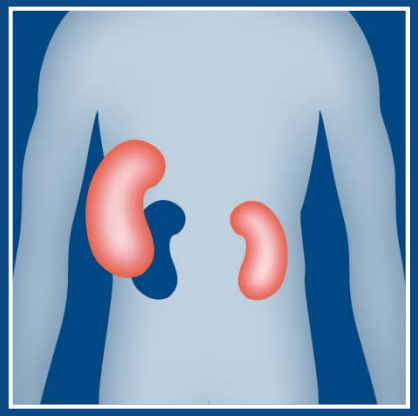
Nephro Update Europe 2018

5-6 October, Budapest

Transplantation



Rainer Oberbauer, Austria

Subtopics

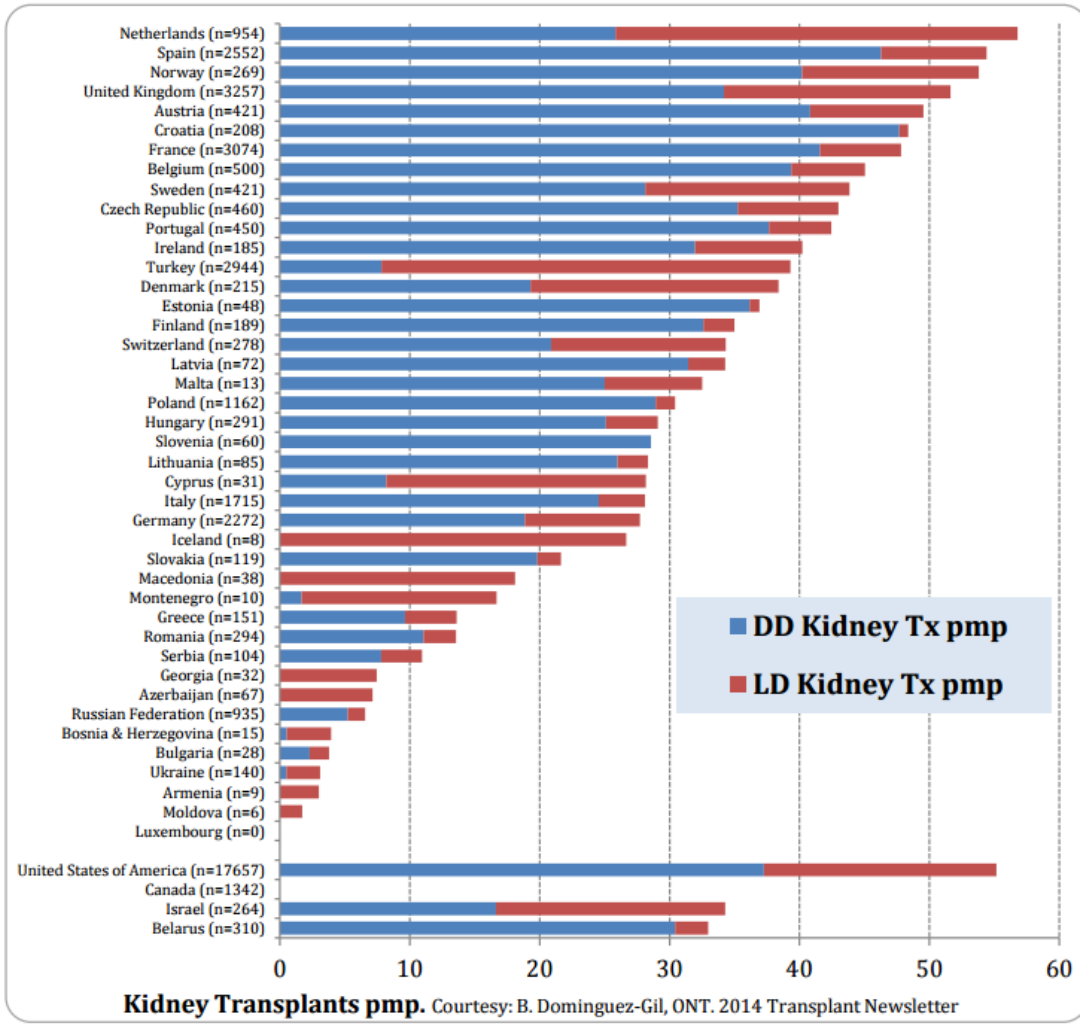
- Kidney transplantation in Europe
- Donor & recipient selection
- News on alloimmunity
- The incompatible patient
- How to improve outcomes

Kidney transplantation in Europe

State of the Art

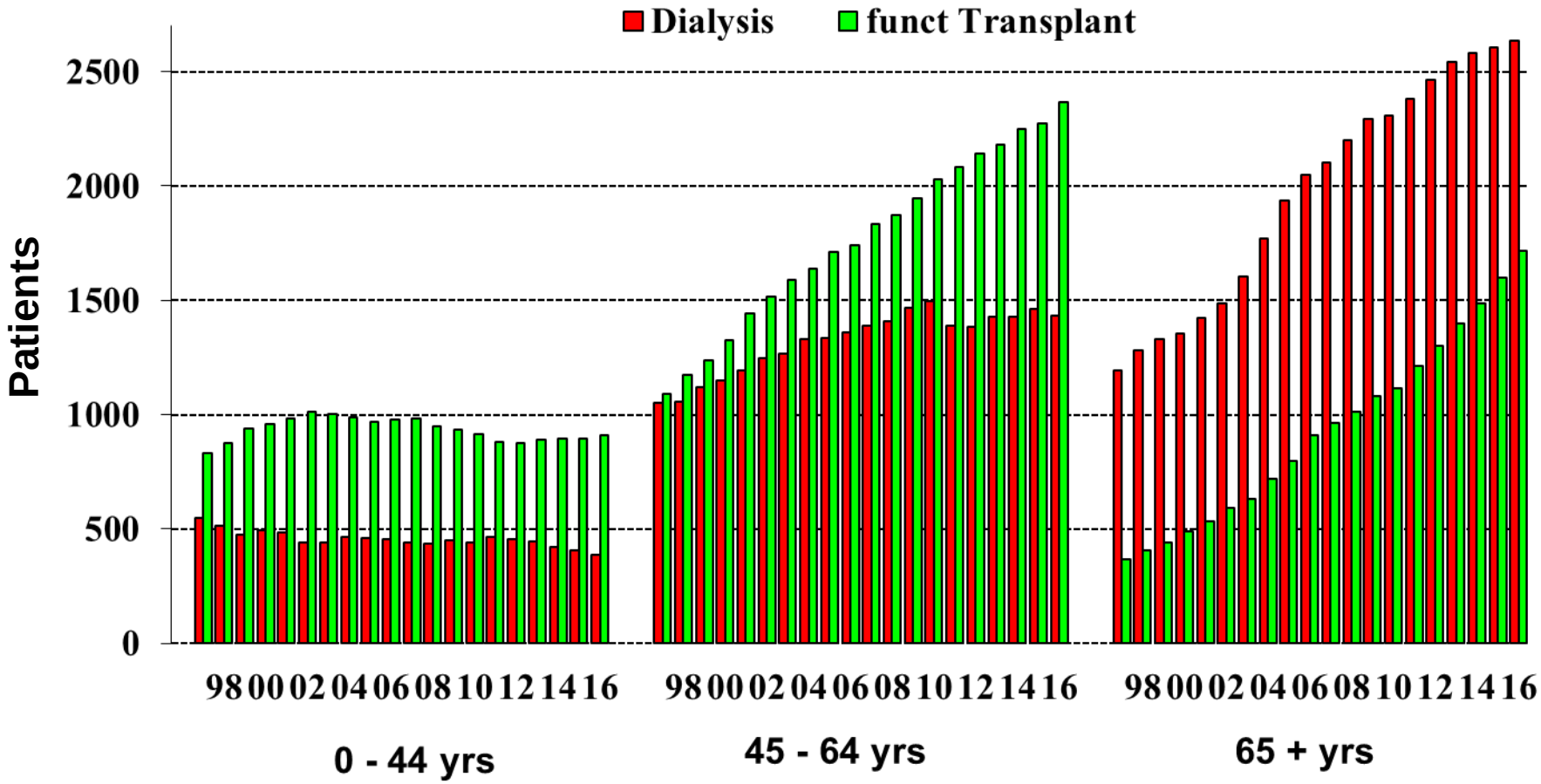
- Epidemiology of kidney transplantation in EU
- Who qualifies for kidney transplantation – pushing the envelope
- Risk prediction in live donor transplantation

Kidney Transplant in the EU 28+



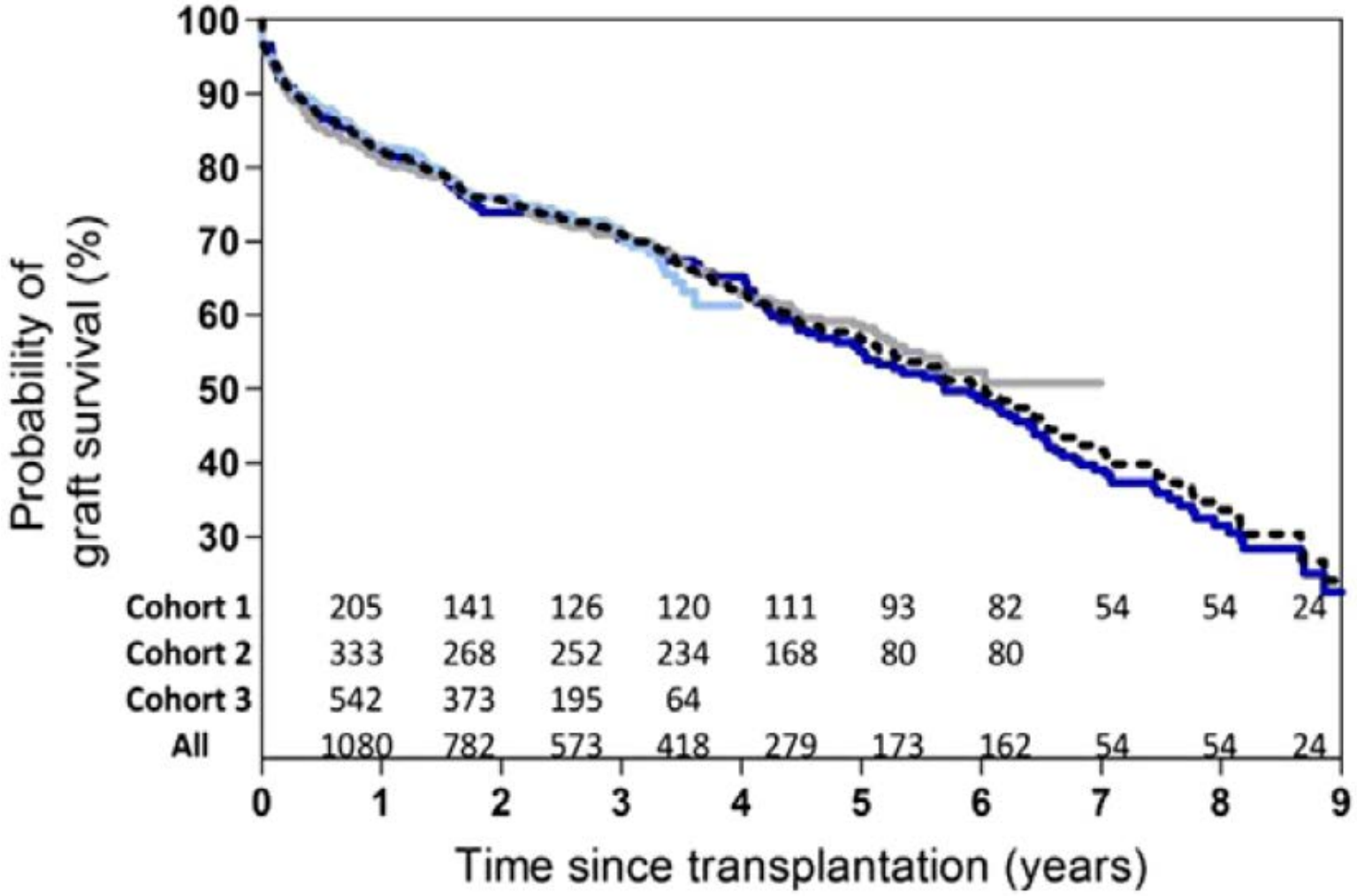
European Directorate for the Quality of Medicines & HealthCare (EDQM) Volume 21: 2016

ESRD is a disease of the elderly – Pushing the envelope in transplant



www.nephro.at Annual Report 2017

Actual graft survival in recipients >75yrs in EU



Pippias M et al. Transpl Int. 2018 May;31(5):540-553.

Take-Home Message

- Epidemiology of KTX in EU 28+ varies considerably
- Expanding the age limits of kidney transplantation
- KDIGO-Waitlisting Guidlines 2018

List of References – Kidney transplant in Europe

1. Haller MC, Kammer M, Oberbauer R. Nephrol Dial Transplant. 2018 Apr 20. doi: 10.1093/ndt/gfy099

2. Kramer A et al. Clin Kidney J. 2018 Feb;11(1):108-122.

3. Pippias M et al. Transpl Int. 2018 May;31(5):540-553.

4. Vanholder R, Annemans L, Brown E, et al. Nat Rev Nephrol 2017; 13: 393-409.

5. European Directorate for the Quality of Medicines & HealthCare (EDQM) Volume 21: 2016

6. KDIGO Guidelines on waitlisting – 2018 (pending)

Donor & recipient selection

State of the Art – Donor & recipient selection

- Risk prediction of live donors and recipients
- Donor organ quality and expected recipient survival matching
- Ex vivo repair of marginal donor kidneys

Risk prediction in live donor transplant

http://www.meduniwien.ac.at/nephrogene/index.php/data

Donor mortality model			
Predictor	Coefficient	Individual Example Value	Coefficient x Value
Donor age (years)	0,1120	48,0000	5,3752
Smoking status (yes vs no) 1=yes	0,4300	0,0000	0,0000
Total cholesterol (mmol/l)	-0,1078	6,5000	-0,7008
Serum creatinine (µmol/l)	0,0182	71,0000	1,2920
Individual LP			5,9664
Mean LP			7,2449
Baseline Survival			0,9921402
Estimated 10-year Risk			0,002195

Haller M et al. AJT 2018 (pending)

Risk prediction in live donor transplant

http://www.meduniwien.ac.at/nephrogene/index.php/data

	Performance measure		
Model	Optimism corrected C-statistic	Explained variation	Global shrinkage factor
Donor mortality model	0.81	48.1%	0.97
Recipient mortality model	0.77	25.4%	0.94
Graft loss model	0.66	10.2%	0.88

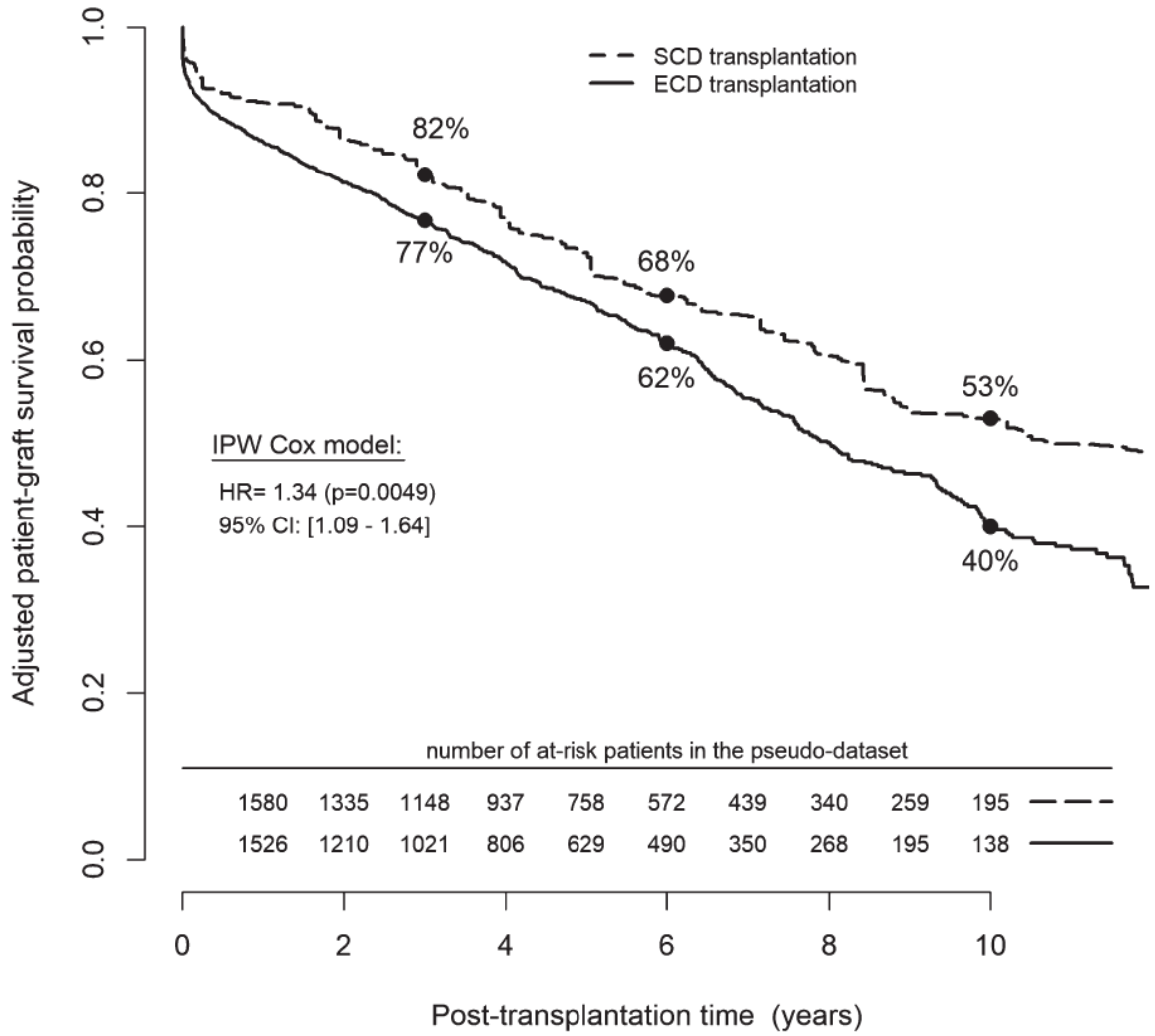
Haller M et al. AJT 2018 (pending)

Risk based allocation – KDRI/EPTS

Conclusions: Risk-based matching engendered a moderate, overall increase in graft and patient survival, accrued through benefits for recipients aged ≤ 45 years but disadvantage to recipients aged > 60 years

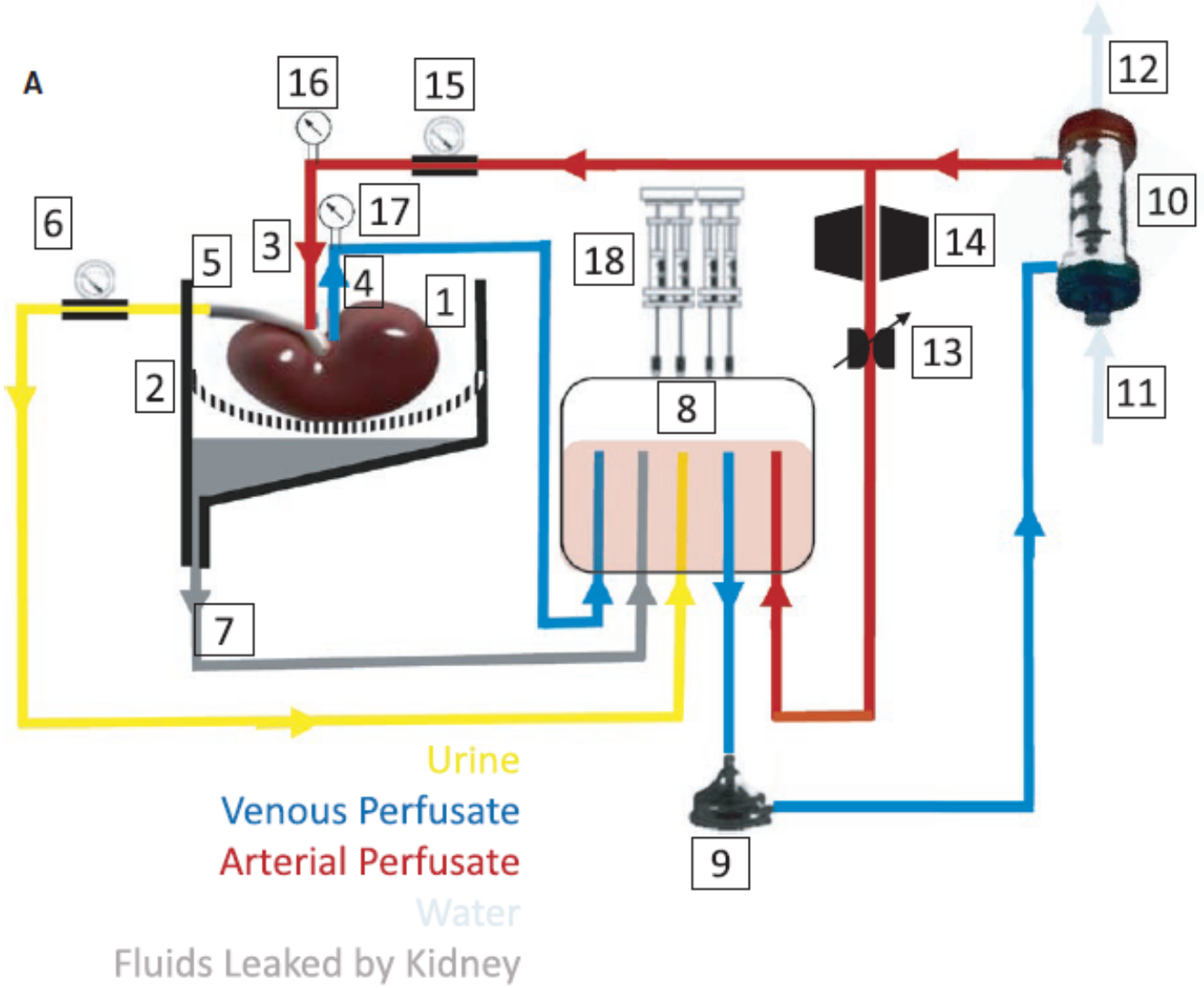
Calisa V et al. Transplantation 2018, Feb 26. doi: 10.1097/TP.0000000000002144.

Increasing the pool of marginal donors



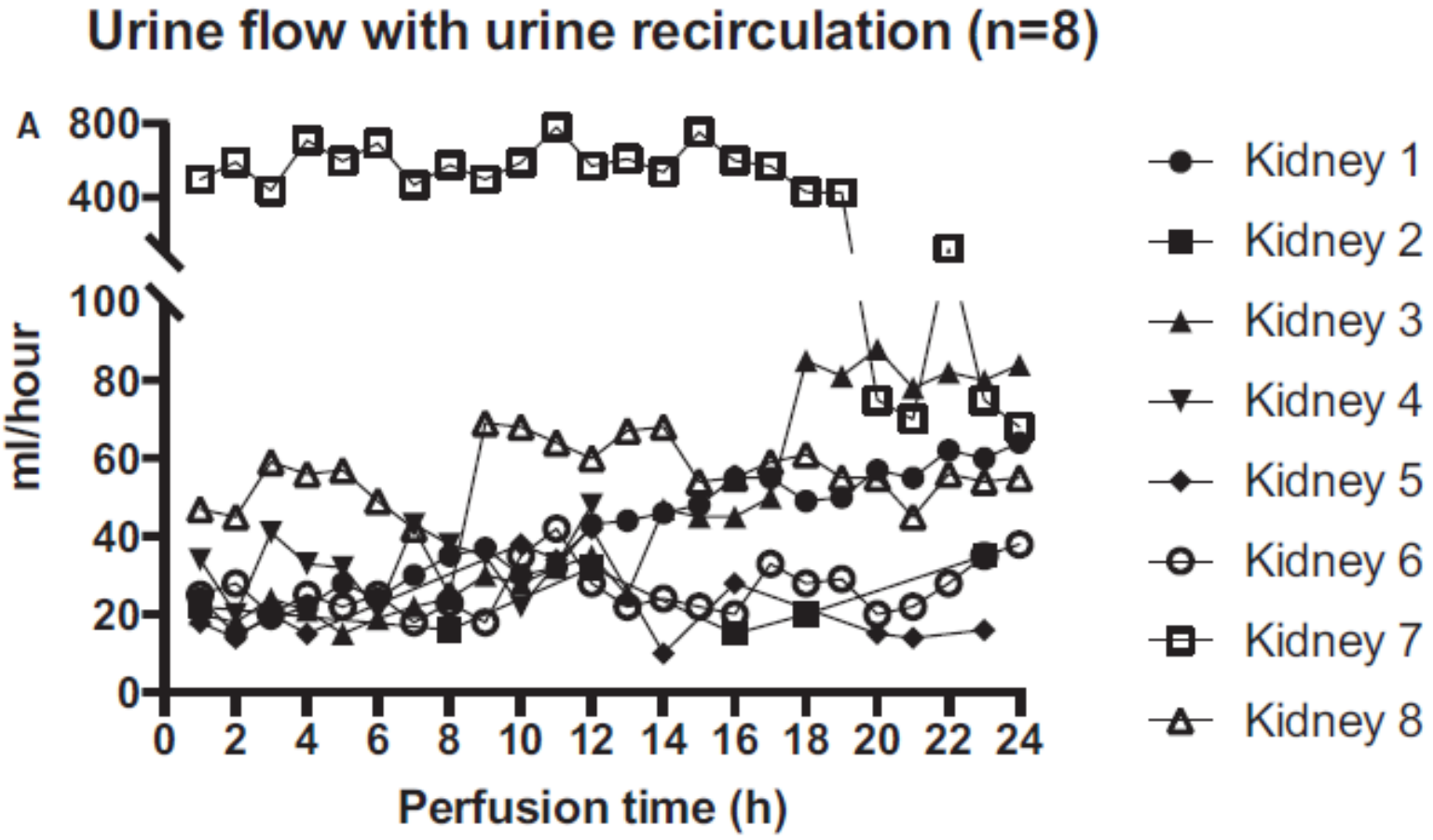
Querard AH et al. Am J Transplant. 2018 May;18(5):1151-1157.

Normothermic machine perfusion



Weissenbacher A et al. AJT 2018 May 14. doi: 10.1111/ajt.14932

Normothermic machine perfusion



Weissenbacher A et al. AJT 2018 May 14. doi: 10.1111/ajt.14932

Take-Home Message

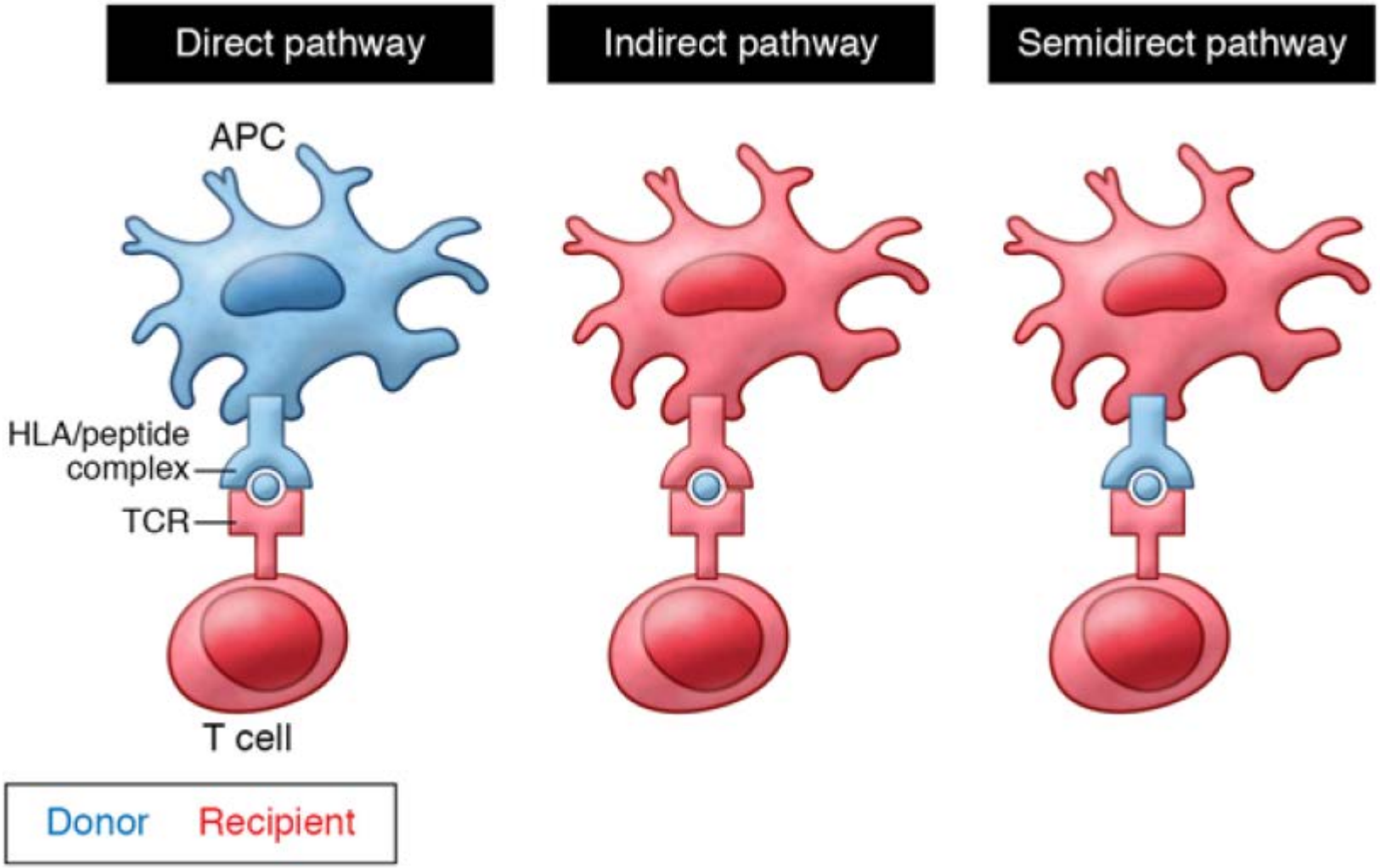
- Online risk calculator for live donor transplant
- Deceased donors: Expanding the limits
- Normothermic machine perfusion

List of References – Donor & recipient selection

1. Haller MC, Wallisch C, Mjøen G, Holdaas H, Dunkler D, Heinze G, Oberbauer R. Predicting donor, recipient and graft survival in living donor kidney transplantation to inform pre-transplant counseling: Development of a bedside risk prediction tool. AJT 2018 (pending)
2. Calisa V et al. Survival and quality of life impact of a risk-based allocation algorithm for deceased donor kidney transplantation. Transplantation 2018, Feb 26. doi: 10.1097/TP.0000000000002144.
3. Querard AH et al. Propensity score-based comparison of the graft failure risk between kidney transplant recipients of standard and expanded criteria donor grafts: Toward increasing the pool of marginal donors. Am J Transplant. 2018 May;18(5):1151-1157
4. Weissenbacher A et al. Twenty-four-hour normothermic perfusion of discarded human kidneys with urine recirculation. AJT 2018. *May 14. doi: 10.1111/ajt.14932*

News on alloimmunity

State of the Art – Indirect Allorecognition



DeWolf S & Sykes M. JCI 2017, 127:2473-81

State of the Art – nonHLA alloimmunity

	HR	Lower 95% CI	Upper 95% CI	P-value
Eplet MM (IQR) 40	**1.43**	**1.01**	**2.02**	**0.042**
Genome-wide SNP-MM (IQR) 29 Mio	1.02	0.85	1.22	0.858
Genome-wide nsSNP-MM (IQR) w/o Transmembrane 150 k	0.89	0.63	1.28	0.543
Transmembrane nsSNP-MM (IQR) 60k (2.5k MM)	**1.68**	**1.17**	**2.41**	**0.005**

Reindl-Schweighofer R et al. The Lancet 2018 (press)

State of the Art – Current Controversies

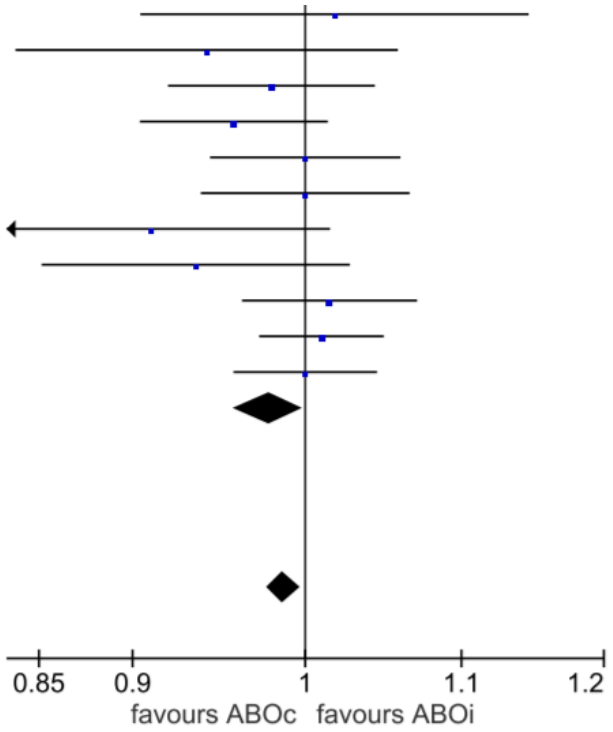
- Which subset of anti-donor HLA antibodies allows individual treatment decisions?
- What is the interrelationship of T-cell-mediated and B-cell-mediated immunity and their relative contribution to graft injury?

Wekerle T et al. The Lancet 2017 May 27;389(10084):2152-2162

The incompatible patient

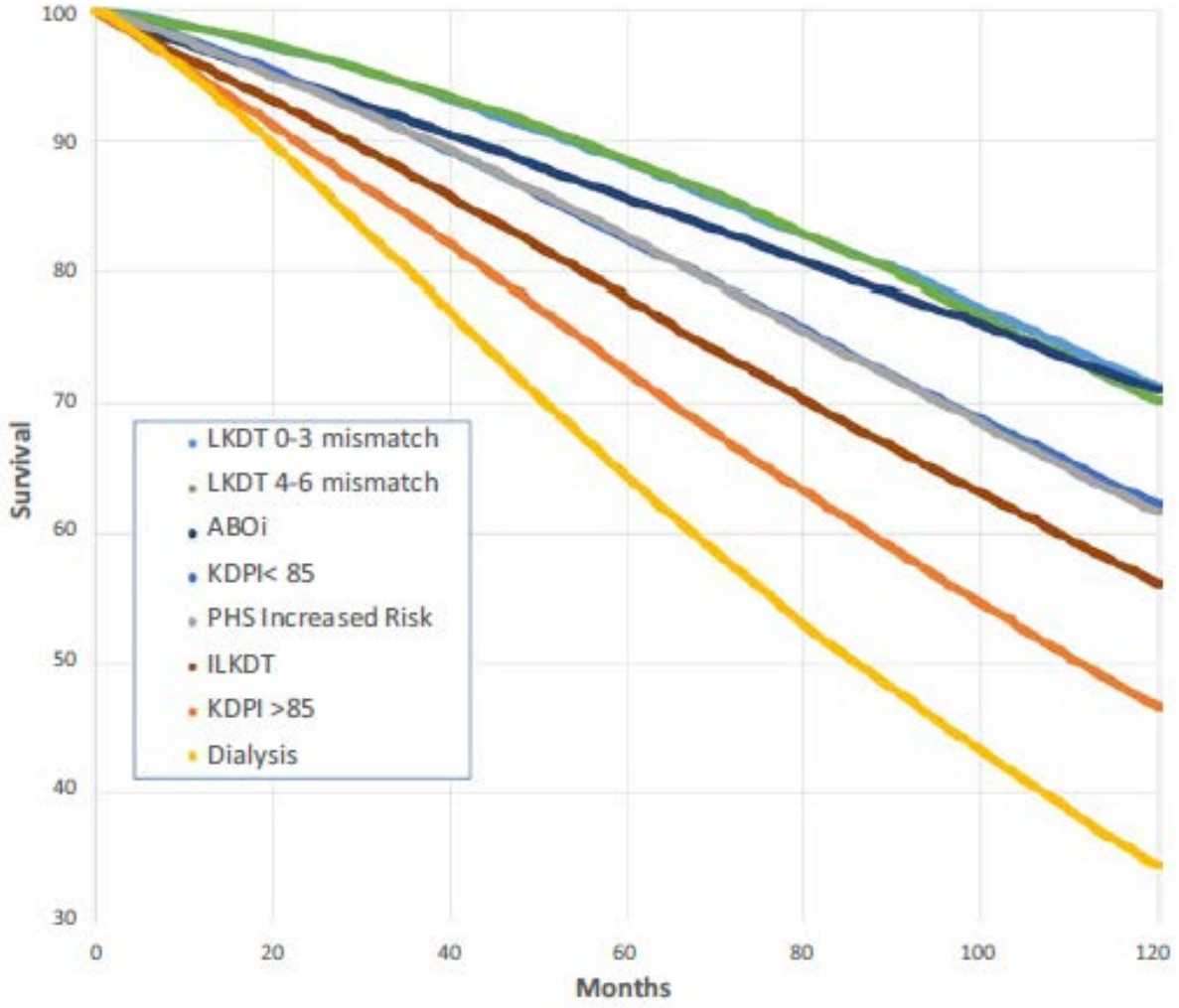
State of the Art – The AB0-incompatible patient

Genberg, 2008	15	15	29	30	1.1%	1.02 [0.90, 1.15]	2008
Habicht, 2011	20	21	47	47	1.6%	0.94 [0.84, 1.06]	2011
van Agteren, 2014	48	50	98	100	3.6%	0.98 [0.92, 1.04]	2014
Barnett, 2014	59	62	166	167	4.9%	0.96 [0.90, 1.01]	2014
Kauke, 2014	26	26	52	52	1.9%	1.00 [0.94, 1.06]	2014
Melxopoulou, 2015	30	30	30	30	1.7%	1.00 [0.94, 1.07]	2015
Schachtner, 2015	32	35	62	62	2.5%	0.91 [0.82, 1.02]	2015
Becker, 2015	32	34	68	68	2.5%	0.94 [0.85, 1.03]	2015
Sanches-Escudero, 2016	30	30	142	146	2.7%	1.01 [0.96, 1.07]	2016
Zschiedrich, 2016	84	85	91	93	4.7%	1.01 [0.97, 1.05]	2016
Bennani, 2016	44	44	44	44	2.4%	1.00 [0.96, 1.04]	2016
Subtotal (95% CI)		**432**		**839**	**29.6%**	**0.98 [0.96, 1.00]**	
Total events	420		829				
Heterogeneity: Chi² = 10.56, df = 10 (P = 0.39); I² = 5%							
Test for overall effect: Z = 2.07 (P = 0.04)							
Total (95% CI)		**1306**		**4401**	**100.0%**	**0.99 [0.98, 1.00]**	
Total events	1279		4346				
Heterogeneity: Chi² = 21.58, df = 25 (P = 0.66); I² = 0%							
Test for overall effect: Z = 2.62 (P = 0.009)							
Test for subgroup differences: Chi² = 1.06, df = 1 (P = 0.30), I² = 5.2%							



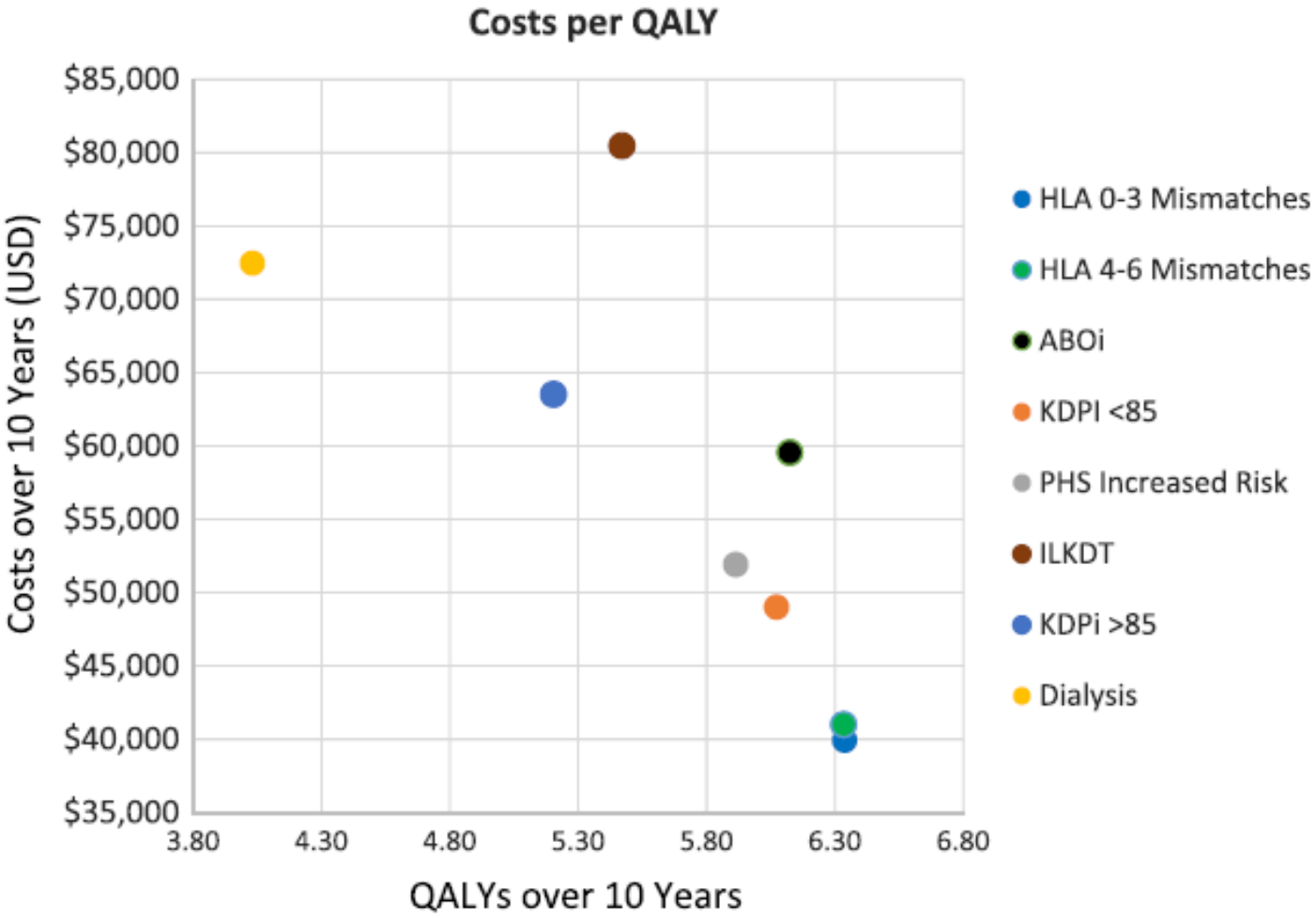
De Weerd AE, Betjes MGH. Clin J Am Soc Nephrol. 2018 Jul 16. pii: CJN.00540118.

State of the Art – Transplant is Cost Effective



Axelrod DA et al. Am J Transplant. 2018 May;18(5):1168-1176.

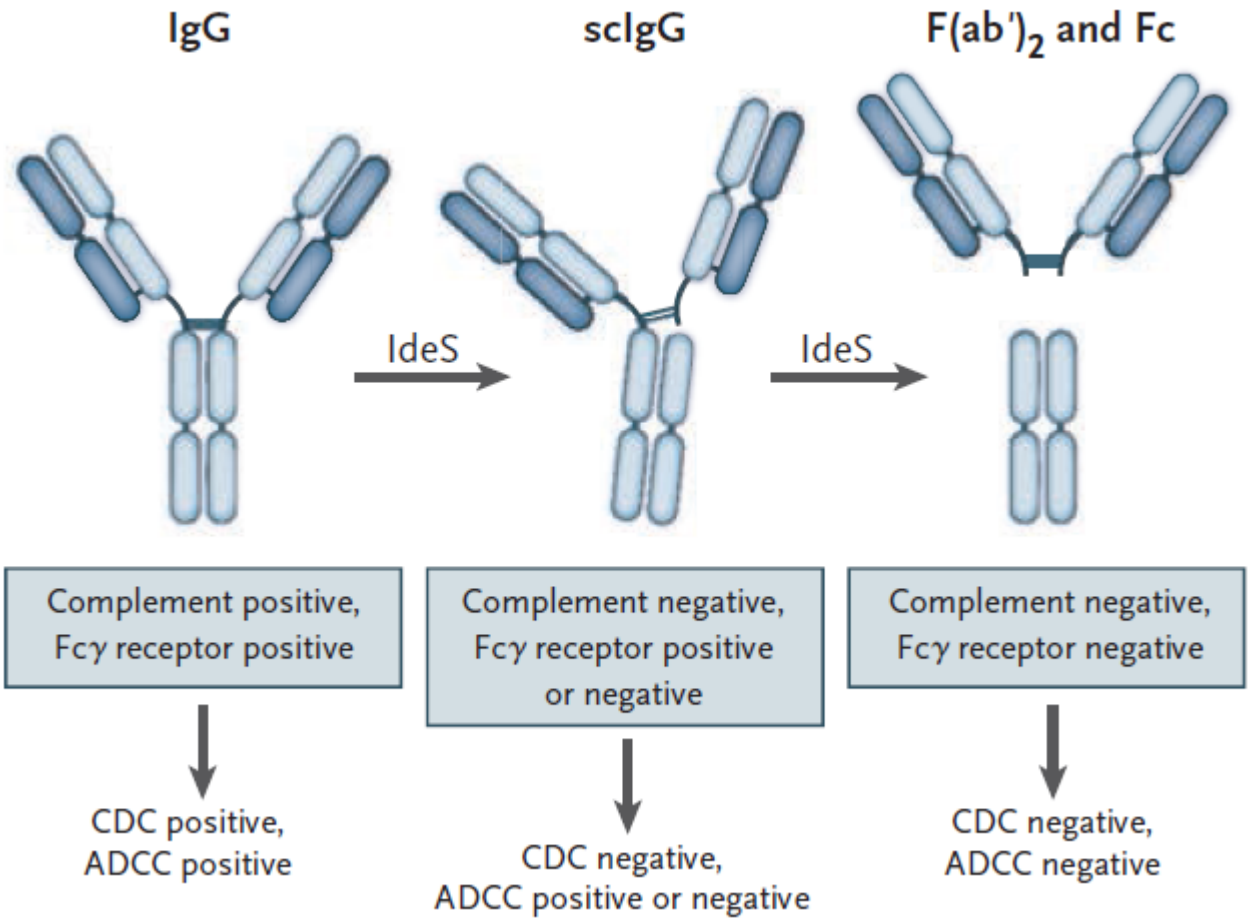
State of the Art – incompatible transplant is cost effective



Axelrod DA et al. Am J Transplant. 2018 May;18(5):1168-1176.

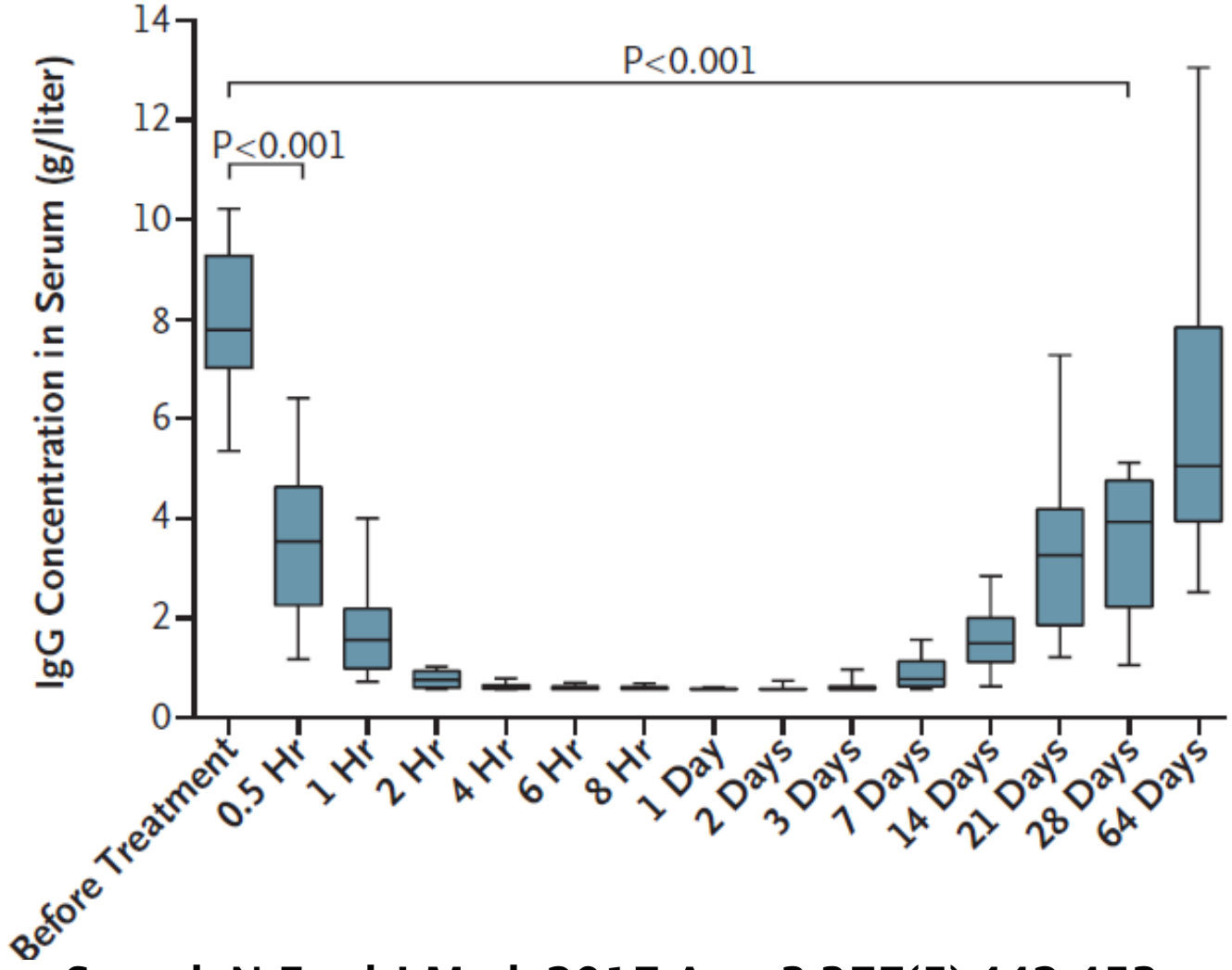
Clearing of intact IgG by IdeS

(Immunoglobulin G-degrading enzyme of Streptococcus pyogenes)



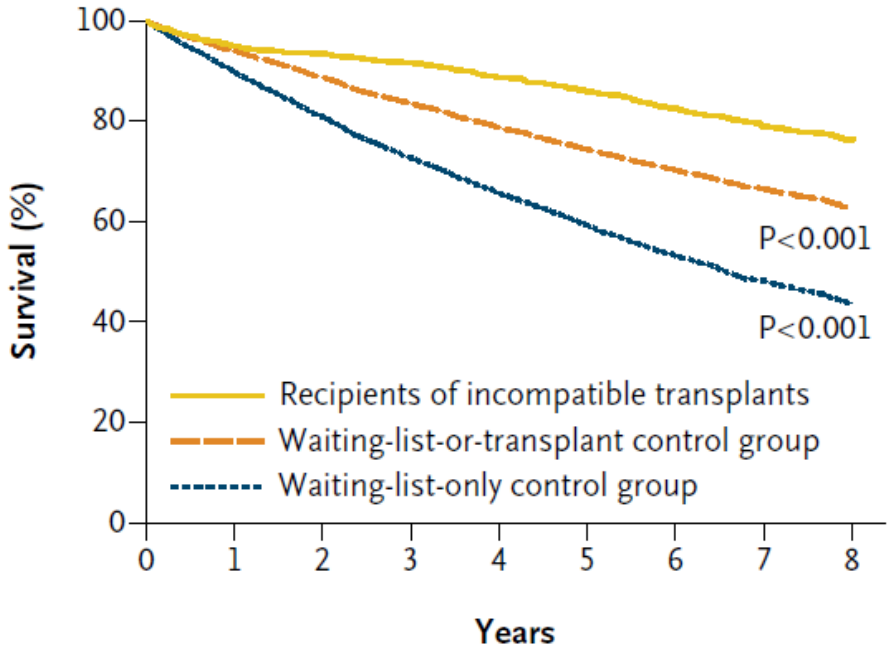
Jordan S et al. N Engl J Med. 2017 Aug 3;377(5):442-453

Effect of IdeS on IgG



Jordan S et al. N Engl J Med. 2017 Aug 3;377(5):442-453

Survival Benefit of HLAi-TX



No. at Risk					
Recipients of incompatible transplants	1025	958	832	584	327
Waiting-list-or-transplant control group	5125	4546	3673	2493	1414
Waiting-list-only control group	5125	4141	3024	1810	916

Orandi BJ, et al. NEJM. 2016; 374(10): 940-50.

Take-Home Message

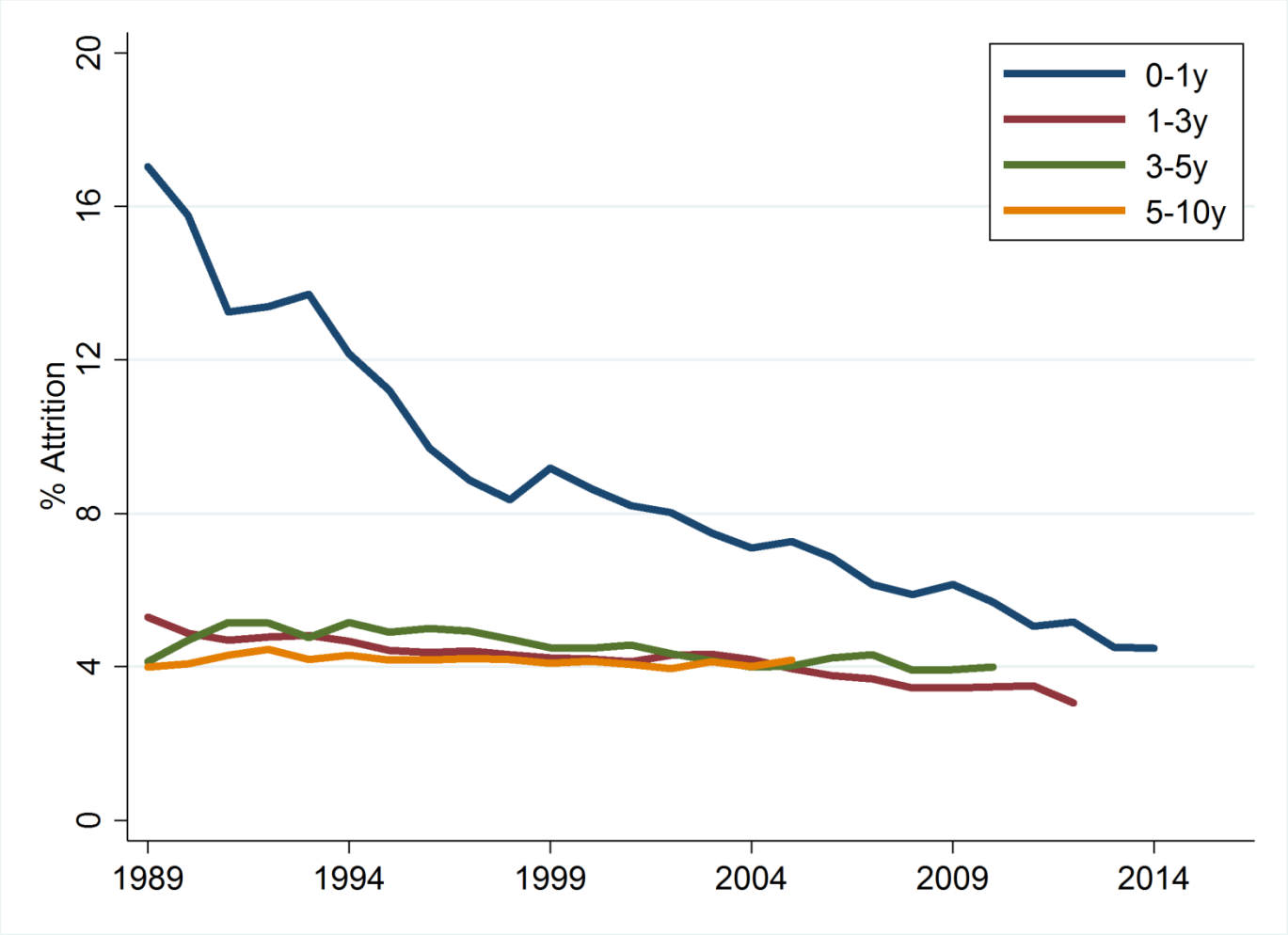
- Incompatible transplant is cost effective
- Desensitization protocols available (AB0i & HLAi)
- HLA and non-HLA alloimmunity contribute to graft loss
- Better ‚Kidney Swap‘ (KPD)

List of References

1. De Weerd AE, Betjes MGH. ABO-Incompatible Kidney Transplant Outcomes: A Meta-Analysis.Clin J Am Soc Nephrol. 2018 Jul 16. pii: CJN.00540118.
2. Axelrod DA et al. An economic assessment of contemporary kidney transplant practice. Am J Transplant. 2018 May;18(5):1168-1176..
3. Reindl-Schweighofer R, et al. Genome-wide non-HLA incompatibility between donor and recipient contributes to kidney allograft attrition. The Lancet 2018 (pending)
4. Wekerle T, Segev D, Lechler R, et al. Strategies for long-term preservation of kidney graft function. Lancet 2017; 389: 2152-2162.
5. Jordan S et al. IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation. N Engl J Med. 2017 Aug 3;377(5):442-453
6. Orandi BJ, Luo X, Massie AB, et al. Survival Benefit with Kidney Transplants from HLA-Incompatible Live Donors. N Engl J Med 2016; 374: 940-950.

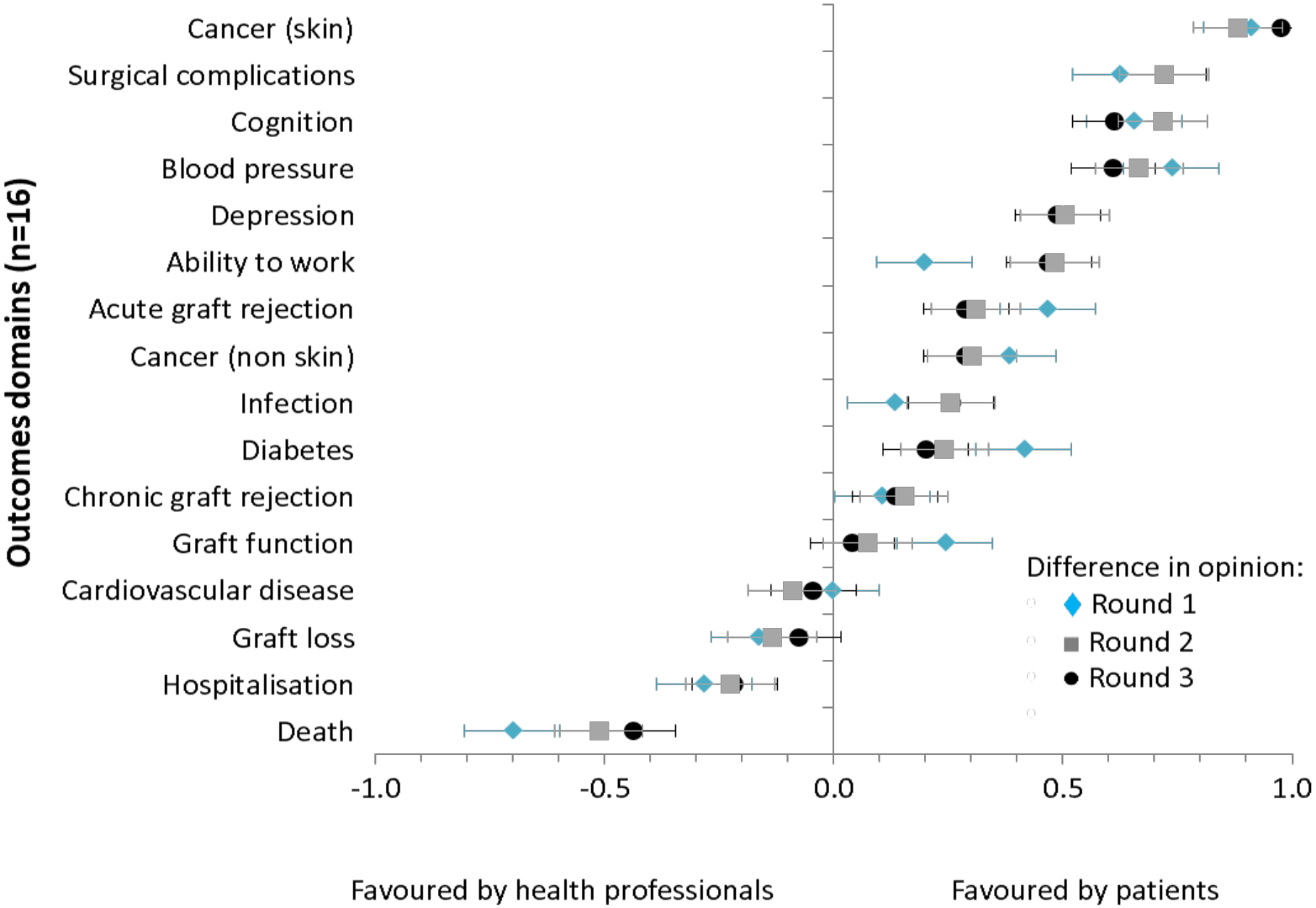
How to improve (which) outcomes

State of the Art – Graft survival



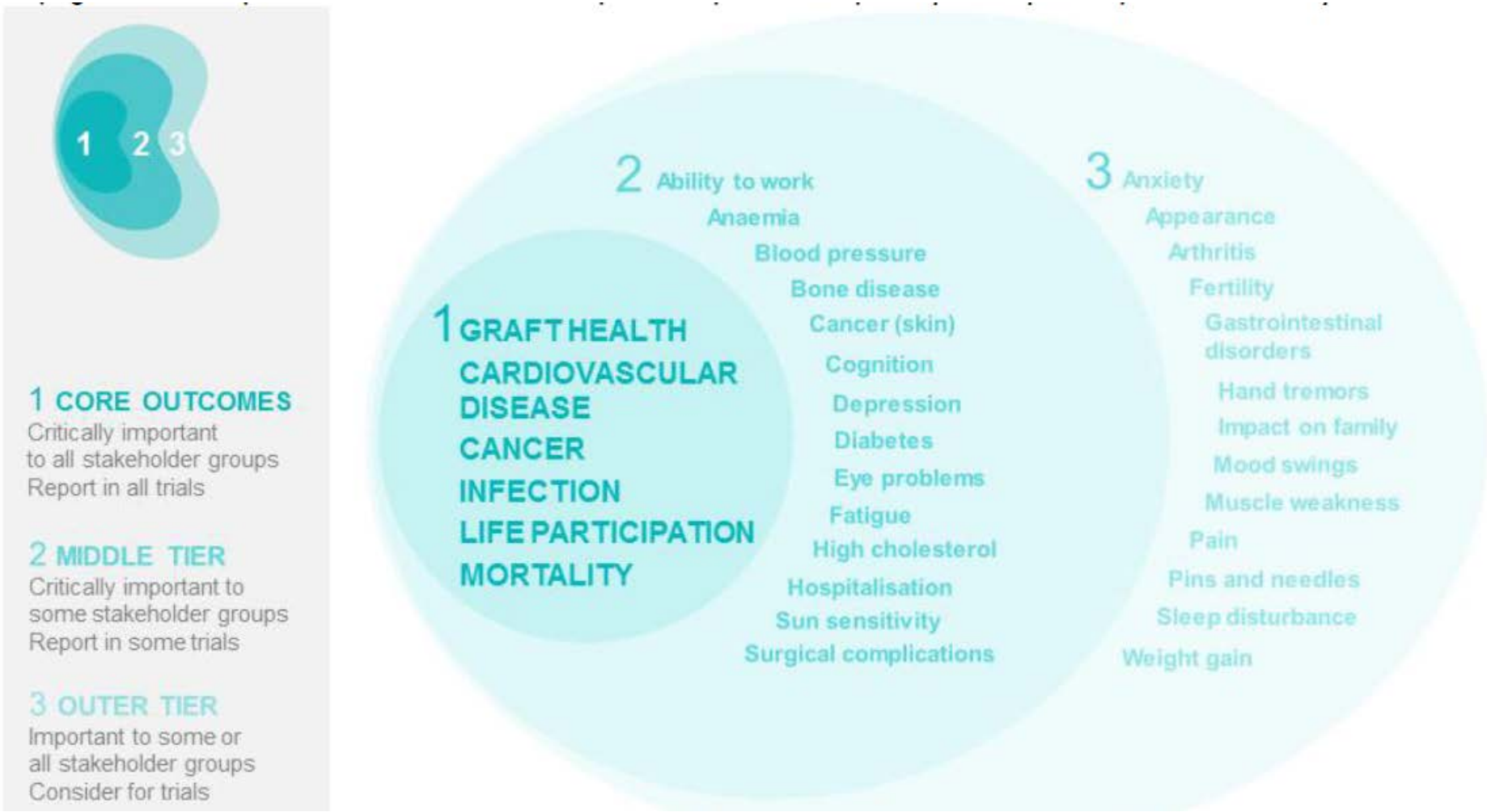
Wekerle T et al. The Lancet 2017 May 27;389(10084):2152-2162

Which outcomes matter?



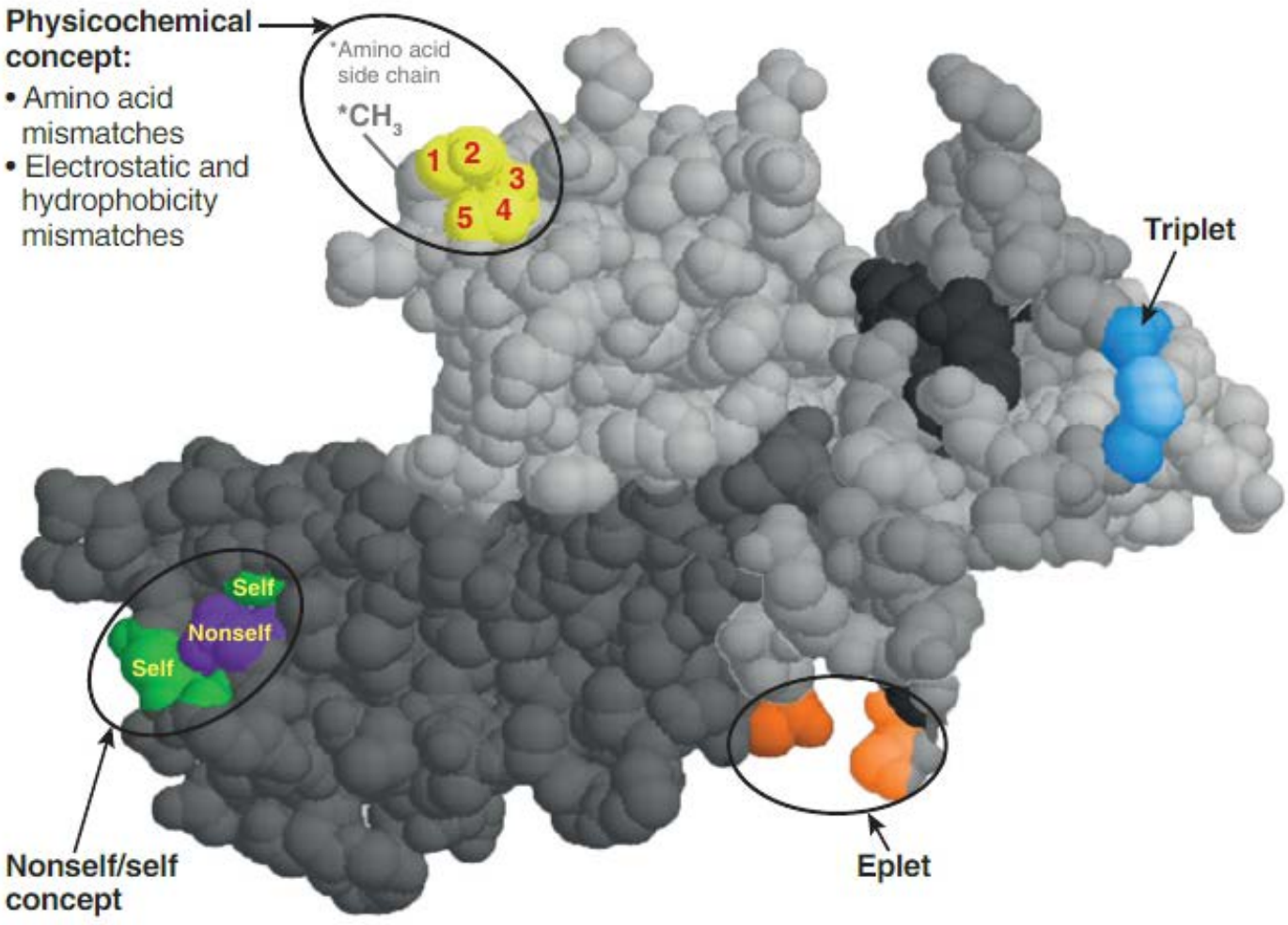
Sautenet B et al. Transplantation. 2017;101(8):1875-1886

SONG: Core outcomes for kidney transplantation



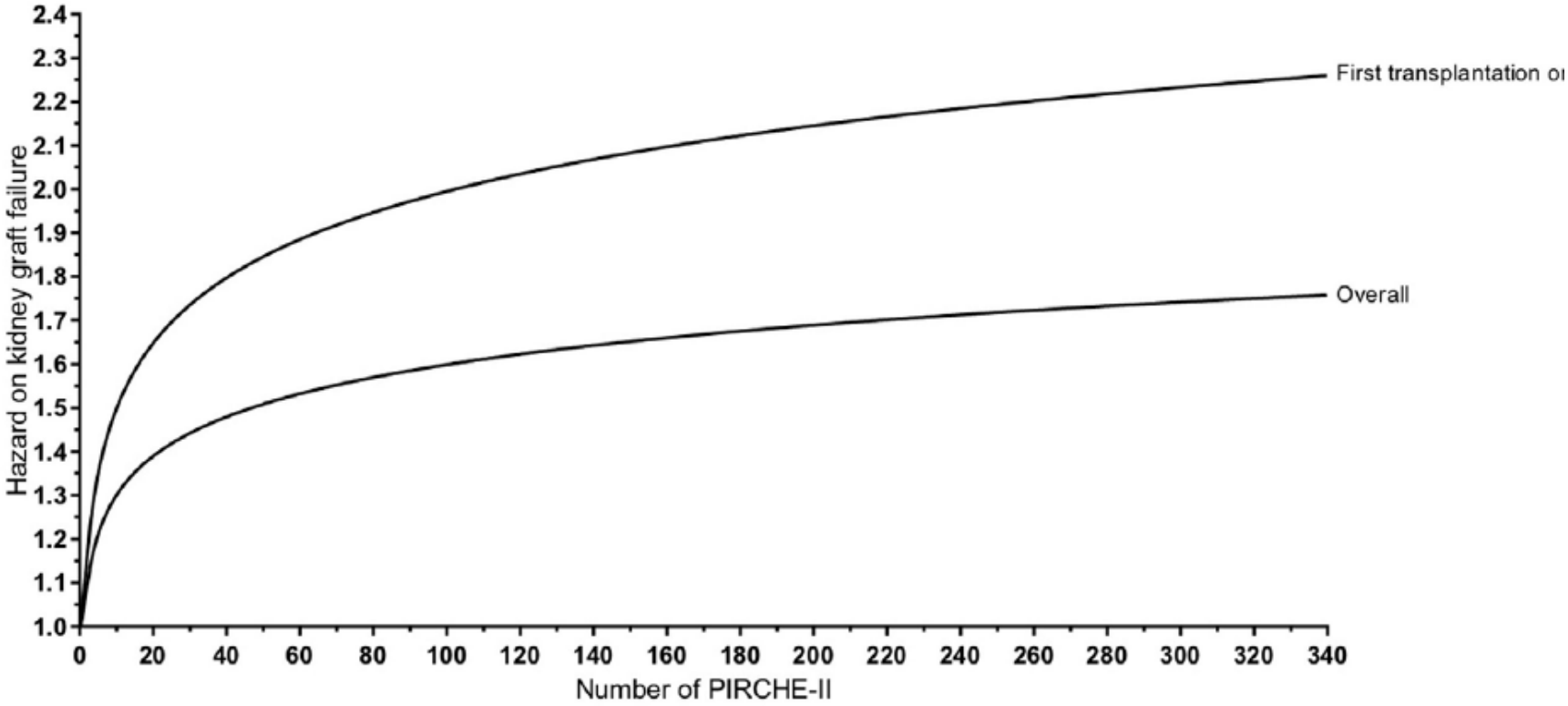
http://songinitiative.org

Concept of HLA-Epitopes



Lim W et al. Kidney Int. 2018 Feb;93(2):314-324.

HLA-Epitope matching and graft loss



Geneugelink K et al. Front Immunol. 2018 Mar 5;9:321

Take-Home Message

- The Transplant field has fast advanced and results are excellent
- Better Histocompatibility matching (Epitopes)
- Improving adherence
- Future outlook: Tolerance via mixed chimerism of non-toxic regimens

List of References

1. Tong A et al. Establishing a Core Outcome Measure for Graft Health: a Standardized Outcomes in Nephrology - Kidney Transplantation (SONG-Tx) Consensus Workshop Report. Transplantation. 2018 Feb 22. doi: 10.1097/TP.0000000000002125.
2. Lim W et al. Novel aspects of epitope matching and practical application in kidney transplantation. Kidney Int. 2018 Feb;93(2):314-324.
3. Geneugelink K et al. PIRCHE-II Is Related to Graft Failure after Kidney Transplantation. Front Immunol. 2018 Mar 5;9:321.

Complete List of References

1. Haller MC, Kammer M, Oberbauer R. Nephrol Dial Transplant. 2018 Apr 20. doi: 10.1093/ndt/gfy099
2. Kramer A et al. Clin Kidney J. 2018 Feb;11(1):108-122.
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5. European Directorate for the Quality of Medicines & HealthCare (EDQM) Volume 21: 2016
6. KDIGO Guidelines on waitlisting – 2018 (pending)
7. Haller MC, Wallisch C, Mjøen G, Holdaas H, Dunkler D, Heinze G, Oberbauer R. AJT 2018 (pending)
8. Calisa V et al.Transplantation 2018, Feb 26. doi: 10.1097/TP.0000000000002144.
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15. Jordan S et al. N Engl J Med. 2017 Aug 3;377(5):442-453
16. Orandi BJ, Luo X, Massie AB, et al. N Engl J Med 2016; 374: 940-950.
17. Tong A et al. Kidney Transplantation (SONG-Tx) Consensus Workshop Report. Transplantation. 2018 Feb 22. doi: 10.1097/TP.0000000000002125.
18. Lim W et al. Kidney Int. 2018 Feb;93(2):314-324.
19. Geneugelink K et al.Front Immunol. 2018 Mar 5;9:321.