Optimizing Immunosuppression, Precision Medicine, and Big Data:

The Required Path for Innovation in Transplantation

Supported by an educational grant from Novartis Pharmaceuticals Corporation

Provided by: CME Outfitters

#TransplantMed

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#TransplantMed

Learning Objectives

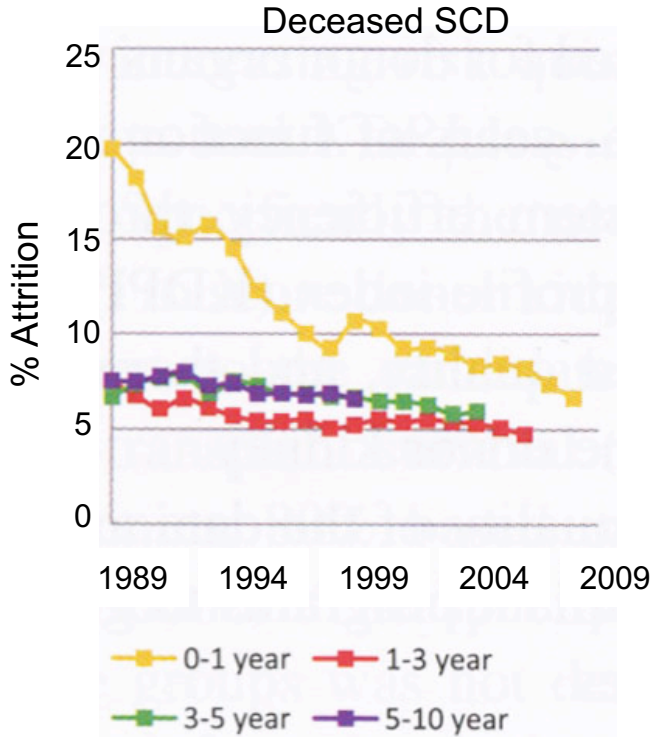
- Identify modifiable and non-modifiable risk factors for allograft loss in patients receiving a kidney transplant.
- Integrate strategies to optimize immunosuppression and minimize adverse events in transplant recipients.
- Explore the impact of big data on precision medicine and the future of transplant medicine.

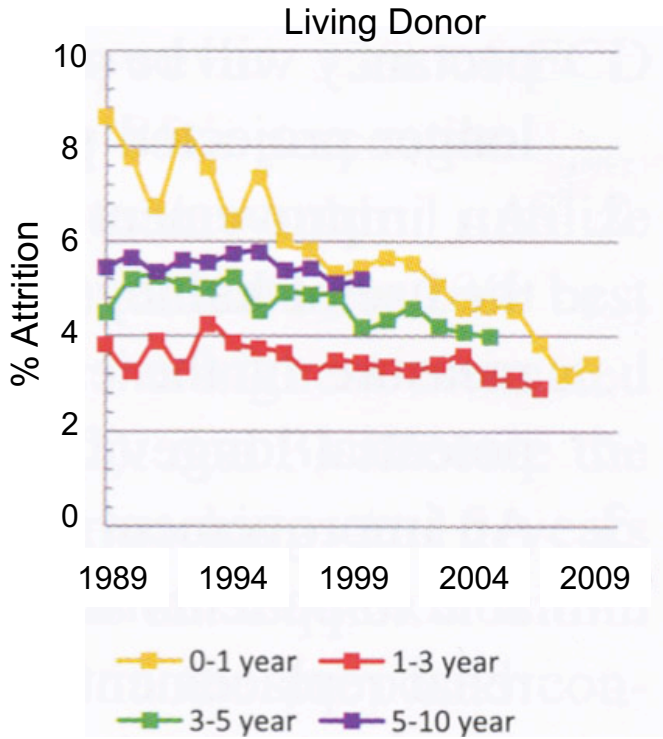
Learning Objective 1

Identify modifiable and non-modifiable risk factors for allograft loss in patients receiving a kidney transplant.

#TransplantMed FV

Cumulative Graft Failure Yearly Attrition Rates of First Kidney Transplants



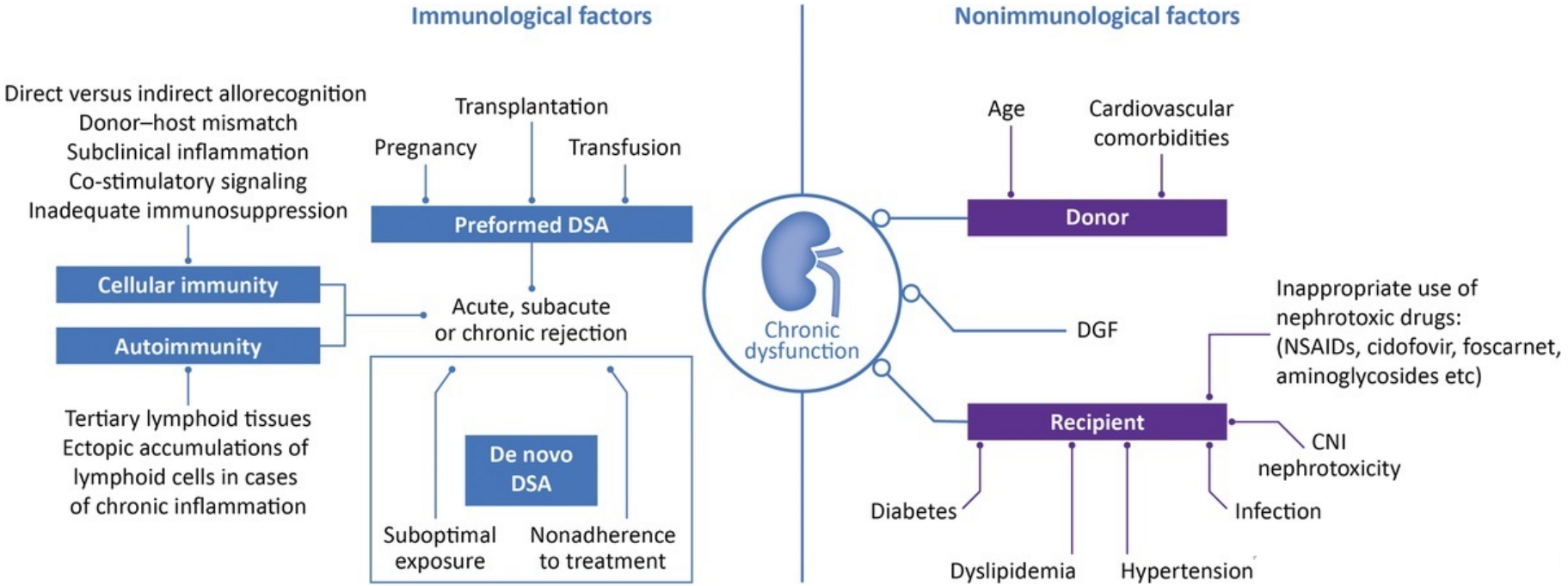


Lamb KE, et al. *Am J Transplant* 2011;11(3):450-462.

Risk Stratification

- The purpose of risk stratification is to individualize both immunosuppression and optimize the pre- and post-transplant management of transplant recipients
  - Donor risks
  - Recipient immunologic risks
  - Recipient non-immunologic risks

Causes of Late Stage Graft Loss in Kidney Recipients



Neuberger JM, et al. *Transplantation*. 2017;101(4S Suppl 2);S1:s56.

Modifiable Risk Factors That Impact Allograft Failure

- Laissez-Faire Immunosuppression (under/over) ➔ greater vigilance required
- DSA ➔ post-treatment monitoring and intervention
- Subclinical inflammation ➔ in protocol biopsies
- Immunosuppression related toxicities ➔ nephrotoxicity
- Cardiovascular/metabolic complications ➔ more aggressive diagnosis and treatment of NODAT and hypertension
- Nonadherence ➔ require predictive metrics and better patient education

Kidney Allocation System (KAS): Change in December 2014

- Give advantage to patients who are expected to have the longest survival
- Give the kidneys that have the longest time of expected function to those who are expected to survive the longest
- Increase priority for sensitized patients
- Replaces the binary system SCD and ECD with a more refined metric than KDPI

SCD = Standard criteria donor; ECD = Expanded criteria donor; KDPI = Kidney donor profile index

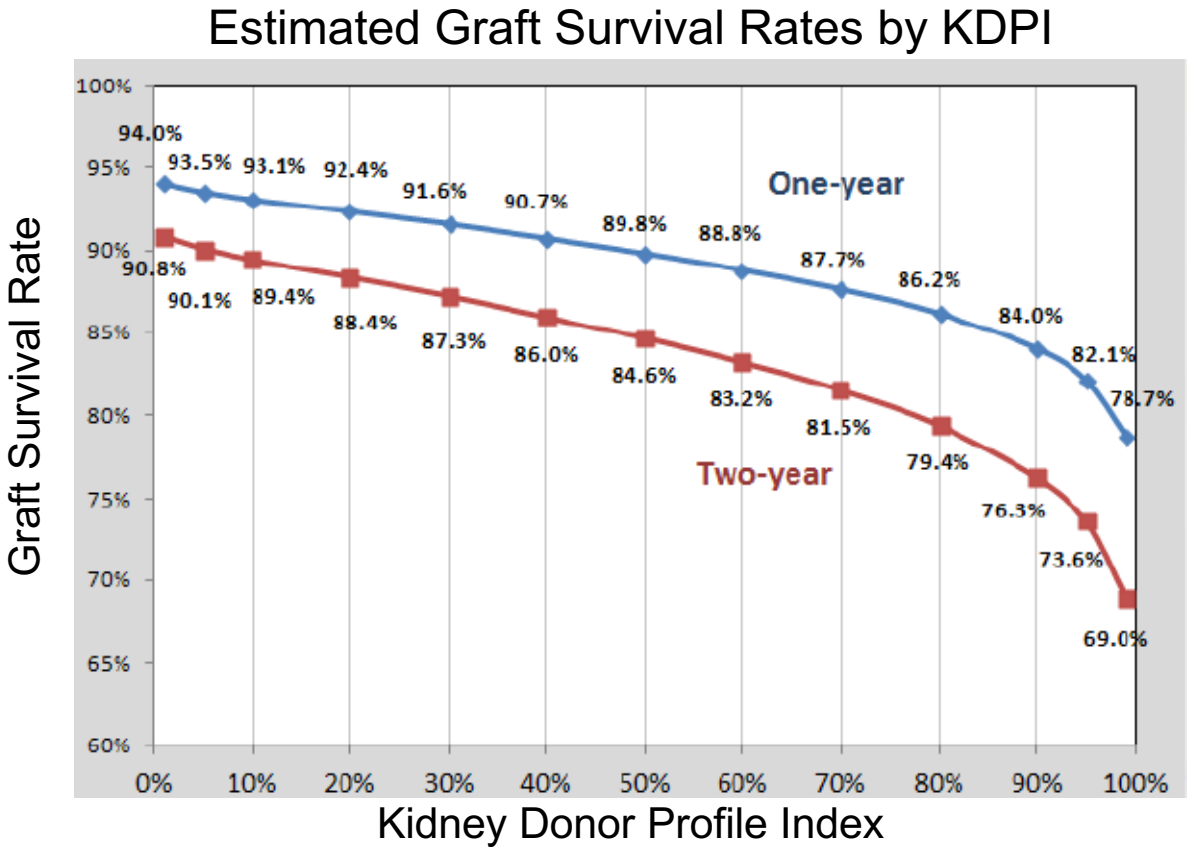
Organ Procurement and Transplantation Network, US Department of Health and Human Services. Available at https://optn.transplant.hrsa.gov/.

Kidney Donor Profile Index

Classified by KDPI based on:
Donor age
Height
Weight
Ethnicity
History of hypertension
History of diabetes
Cause of death
Serum creatinine
Hepatitis C virus status
Donation after circulatory death

Organ Procurement and Transplantation Network, US Department of Health and Human Services. Available at https://optn.transplant.hrsa.gov/.

KDPI: Correlated with Graft Survival



Organ Procurement and Transplantation Network, US Department of Health and Human Services. Available at https://optn.transplant.hrsa.gov/.

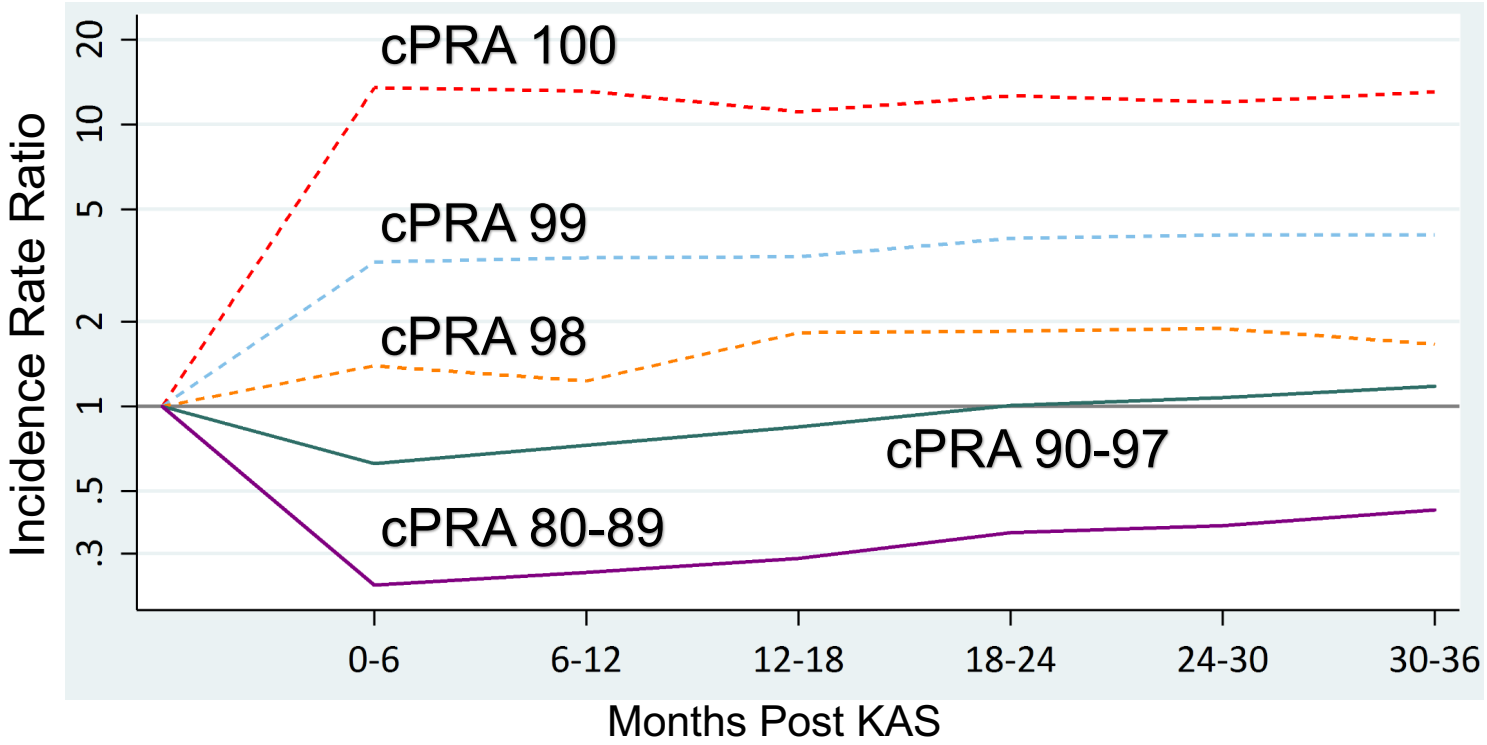
Winners and Losers with KAS: Changes in Transplant Rate

Subgroup	Transplant IRR	p
Non-AA, non-Hispanic	0.87 **0.92** 0.96	< .001
AA	1.13 **1.19** 1.25	< .001
Hispanic	1.05 **1.13** 1.20	< .001
ABO type O	0.99 1.04 1.09	.1
ABO type A	0.95 1.00 1.05	.9
ABO type B	0.98 1.06 1.14	.2
ABO type AB	1.13 **1.26** 1.41	< .001

Subgroup	Transplant IRR	p
Male	0.96 1.01 1.05	.8
Female	1.03 **1.09** 1.14	< .01
Age <18	0.90 1.03 1.17	.7
Age 18-40	1.38 **1.47** 1.57	< .001
Age 41-50	1.09 **1.17** 1.24	< .001
Age 51-60	0.87 **0.93** 0.98	.01
Age 61-70	0.85 **0.90** 0.96	< .001
Age >70	0.68 **0.76** 0.85	< .001

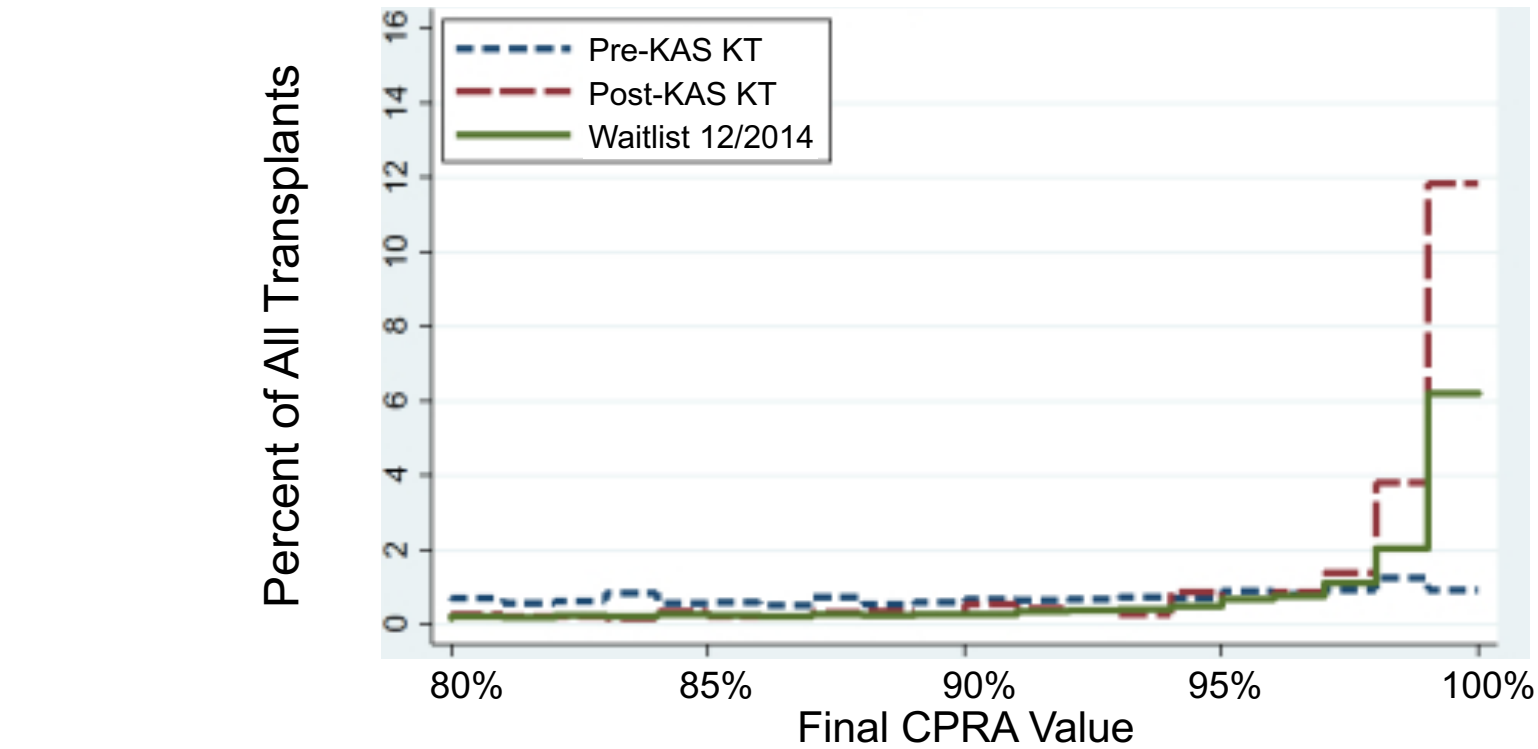
Massie AB, Muzaale AD, Luo X, Chow EKH, Locke JE, Nguyen AQ, Henderson ML, Snyder JJ, Segev DL. *J Am Soc Nephrol.* 2017;28(9):2749-2755.

The Winner Takes it All* (Abba 1980)



Massie AB, Muzaale AD, Luo X, Chow EKH, Locke JE, Nguyen AQ, Henderson ML, Snyder JJ, Segev DL. *J Am Soc Nephrol.* 2017;28(9):2749-2755.

The Winner Takes it All?* (Abba, 1980)



CPRA ≥ 99

14% post-KAS

1.6% pre-KAS

Massie AB, Muzaale AD, Luo X, Chow EKH, Locke JE, Nguyen AQ, Henderson ML, Snyder JJ, Segev DL. *J Am Soc Nephrol.* 2017;28(9):2749-2755.

Case Challenge: Mrs. Homa

- 60 year old African American woman who has been on hemodialysis for 4 years with PRA58% is offered a kidney with KDPI of 68%
- Receives thymoglobulin induction and immunosuppression of tacrolimus/mycophenolate mofetil (MMF) and prednisone
- Kidney has rapid improvement in function and by 3 weeks, her serum creatinine is stabilized between 1.2-1.4 mg/dl
- At 3 months follow-up visit, she is found to have BK viremia with 20,000 copies

Audience Response

What would you do next?

A. Do nothing and wait for the next month BK
B. Start cidofovir .25 mg/kg IV x 5 infusions
C. Discontinue MMF and convert tacrolimus to mTori
D. Decrease MMF to 500 mg BID from 1,000 mg BID and repeat in one month
E. I'm not sure

Case Challenge: Mrs. Homa

- At 6 months, BK viremia is cleared by she complains of insomnia, tremors and memory loss
- She complains about “taking all those pills” and wonders if staying on hemodialysis would have been better
- Tacrolimus level is 5.3 ng/ml

Audience Response

What would be your next step?

A. Stay the course, reassure her
B. Discontinue tacrolimus and convert to mTori
C. Convert to belatacept
D. Try once a day long acting tacrolimus
E. I’m not sure

Case Challenge: Mrs. Homa at 2 Years

- She has a creatinine of 2.1
- A urine protein creatinine ration of 1.2
- DQ DSA with 1900 MFI
- She admits that she has occasionally been missing doses of her medication

Where did we go wrong in the management of this patient?

Could a Big Data algorithm have predicted her course?

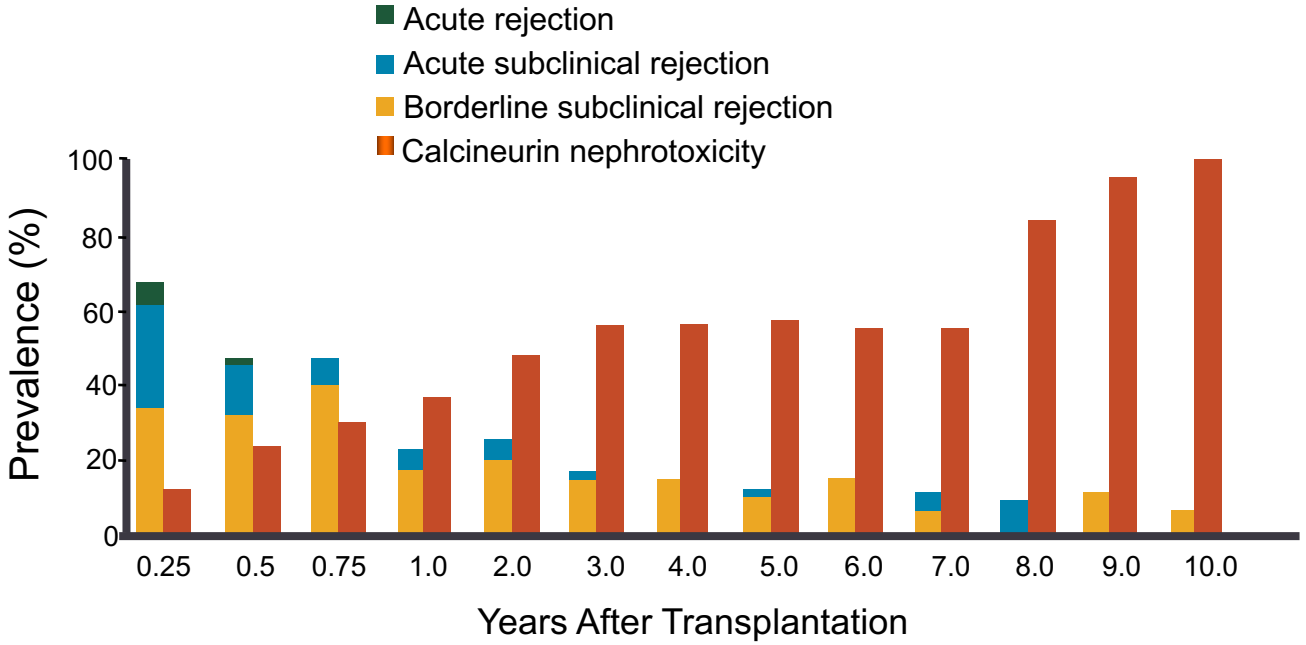
What Should Be Driving Risk Stratification?

- Should risk stratification be based on the risk of developing CNI nephrotoxicity?

OR

- Should risk stratification be based on immunologic-mediated graft loss?

The Incidence of Calcineurin Inhibitor (CNI) Nephrotoxicity Increases with Time after Transplant

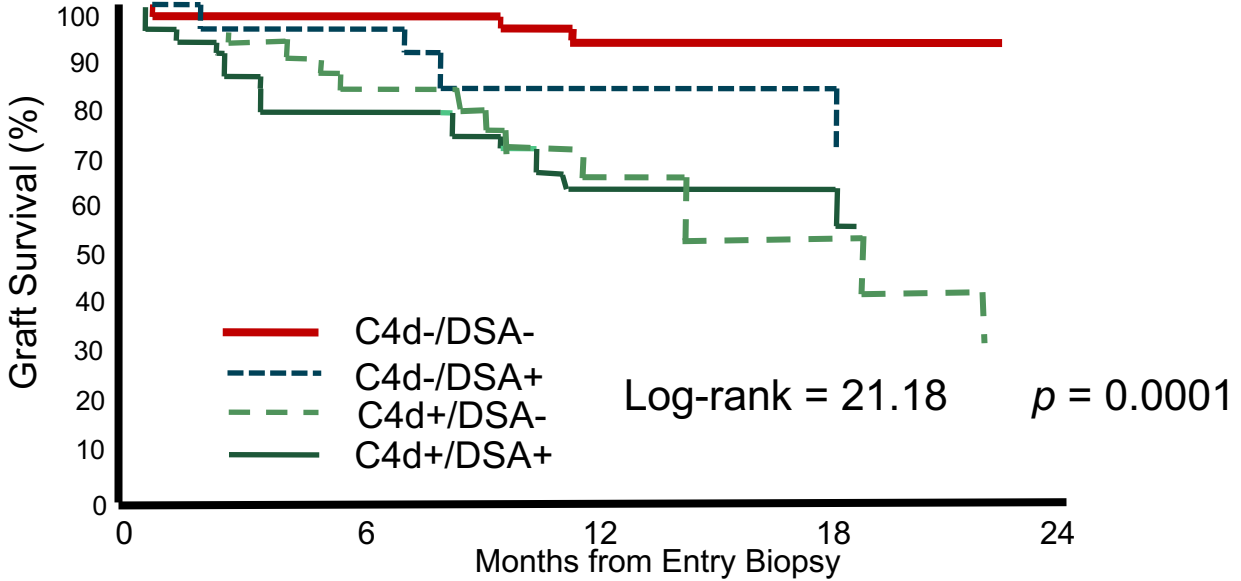


Study Limitations

- Conducted in the cyclosporine era
- All but one of the renal transplant recipients were kidney-pancreas transplants
- No DSA C4D analyses were performed

Nankivell BJ, et al. *N Engl J Med.* 2003;349:2326–2333.

DeKAF Study Graft Survival by C4d/DSA Group Long-Term Cohort Entry Biopsies (n = 173)

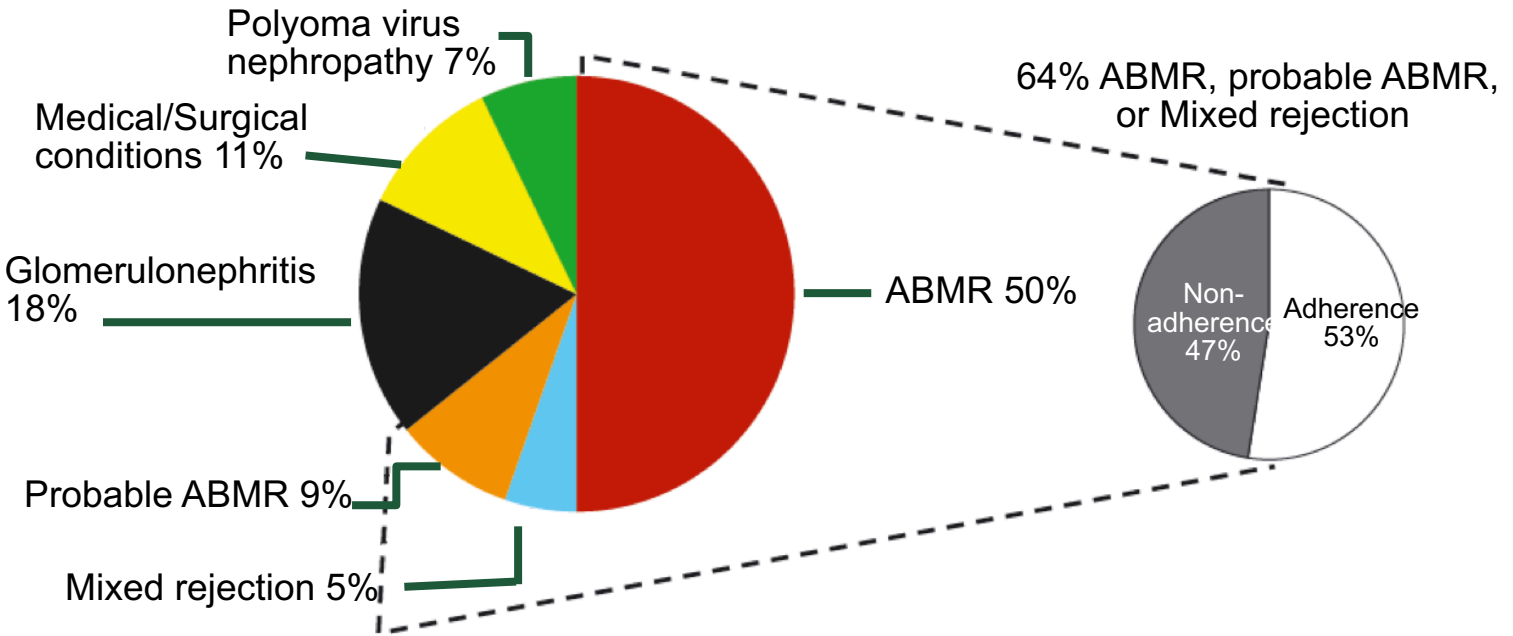


	6	12	18	24
C4d-/DSA- :56	48	33	12	7
C4d-/DSA+ :25	19	13	8	5
C4d+/DSA- :29	21	16	9	6
C4d+/DSA+ :34	22	13	6	3

Gaston R, et al. *Transplantation*. 2010;90:68-74.

The Role of AMR and Nonadherence in Kidney Transplant

Distribution of Attributed Causes of Failure Almost Half of Antibody-Mediated Rejection (AMR) is Due to Nonadherence



N = 315

Sellarés J, et al. *Am J Transplant*. 2012;12(2):388-399.

Mayo Clinic Study of Renal Allograft Histology at 10 Years After Transplantation in the Tac Era: Evidence of Pervasive Chronic Injury

- Major lesions at 10 years (n = 575) included the following:
  - Arteriolar hyalinosis (66%)
  - Mesangial sclerosis (67%)
  - Global glomerulosclerosis > 20% (43%)
  - 48% of grafts having more than one major lesion
  - Transplant glomerulopathy and moderate-to-severe interstitial fibrosis were uncommon (12% each)

Stegall MD, et al. *Am J Transplant*. 2018;18(1):180-188.

Is Graft Failure a Function of Zip Code?

- Causes of late graft failure is dependent of the population that is analyzed
- All kidneys don’t die because of AMR, it’s the patients you study
- If patients are adherent and well cared for, they have better outcomes
- The role of big data
  - Takes into consideration all these factors to offer a better understanding of outcomes

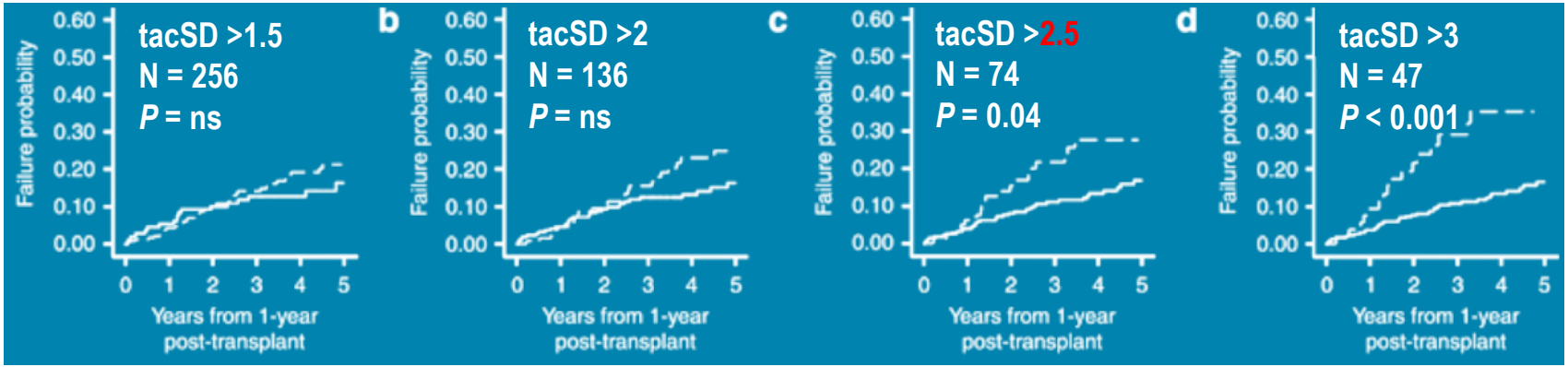
Learning Objective 2

Integrate strategies to optimize immunosuppression and minimize adverse events in transplant recipients.

#TransplantMed DS

Use of Drug Level Monitoring (Intra-Patient Variability) to Assess Under-Immunosuppression and Adherence

- 356 patients, measured tacrolimus variability while on stable dose ("tacSD"= tacrolimus standard deviation), median follow-up 3.72 years
- Composite end point: late allograft rejection, transplant glomerulopathy, or graft loss (including death)



- For every 1-unit increase in TacSD, a 27% increase in composite end point [HR 1.27 (95% CI 1.03-1.56)]

Sapir-Pichhadze R, et al. *Kidney Int.* 2014;85:1404-1411.

Learning Objective 3

Explore the impact of precision medicine and big data on the future of transplant medicine.

#TransplantMed

What Does Success in Transplant Look Like in 2018?

What will define success in 2025?

Defining What is NOT Success in Transplantation

- Desensitization and AMR therapies
- Managing subclinical inflammation/fibrosis
- Continued dependence on CNI regimens
- Tolerance trials in kidney transplantation

Beyond Clinical Stratification

- Can we apply genomic and biomarker information in selecting therapy that improves clinical care and outcomes in transplantation?
- The need: biomarkers that are accurate, reliable and are associated with events and endpoints that may lead to better patient outcome

Personalized/Individualized Medicine vs. Precision Medicine

- Personalized medicine has been practiced in transplantation (i.e. low risk vs. high risk)
- Precision medicine requires new diagnostics or biomarkers to select or modify immunosuppression regimens preferable with novel therapies

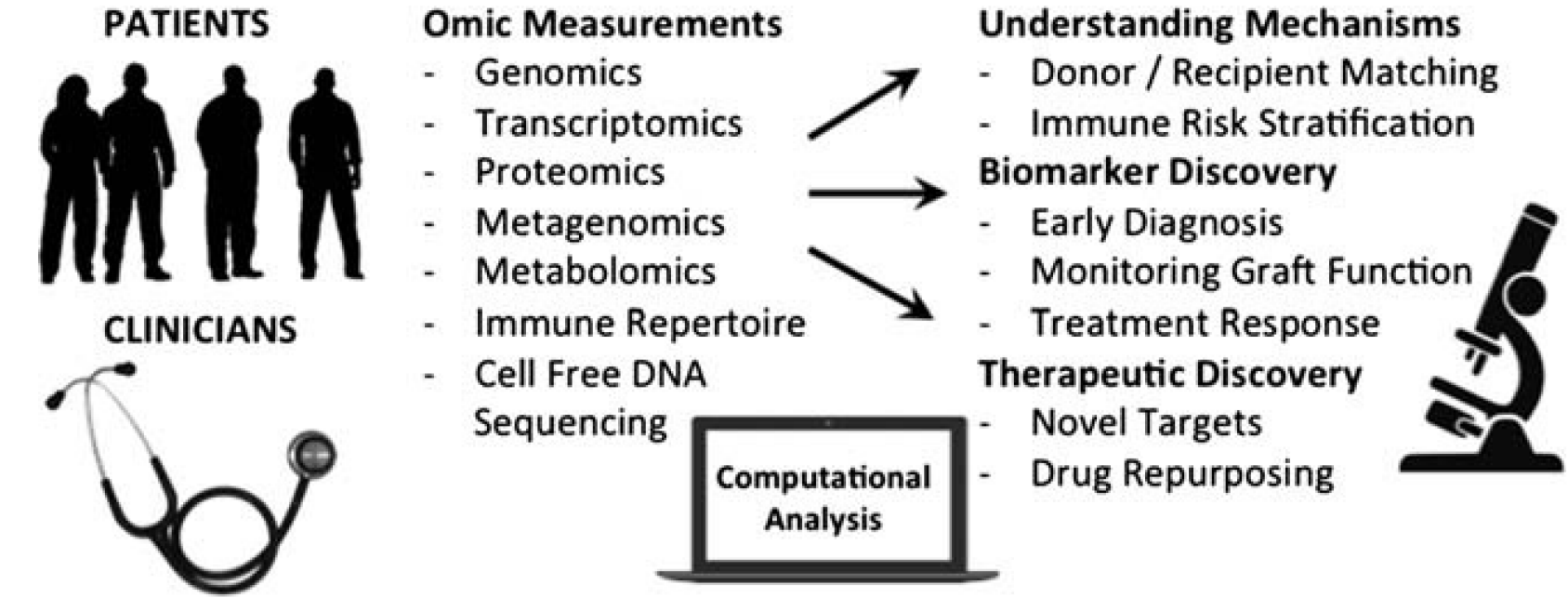
Personalized Medicine in Transplantation

- Choice of induction agent (PRA, DSA, DGF)
- Choice of CNI
- Maintaining or discontinuing steroids
- Choice of anti-proliferatives

Precision Medicine

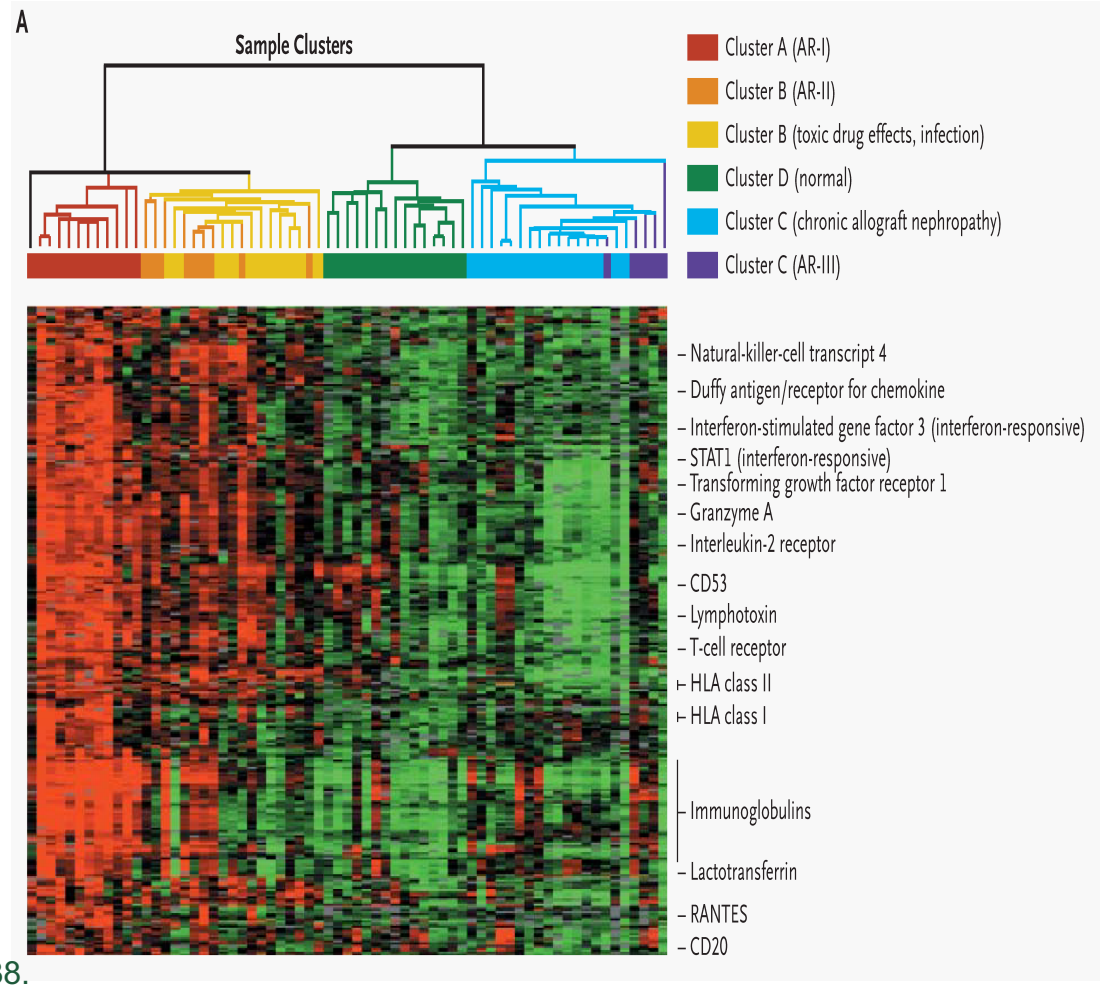
- Precision medicine is defined as treatments targeted to the particular patient on the basis of genetics, biomarkers or phenotypic characteristics that maximize efficacy and minimizes toxicities

Tranplantomics: Toward Precision Medicine in Transplantation Research



Sirota M, Sarwal MM. *Transplantation*. 2017;101(8):1777-1782.

Molecular Heterogeneity in Acute Renal Allograft Rejection Identified by DNA Microarray Profiling



Sarwal M, et al. *N Engl J Med*. 2003;349(2):125-138.

Real Time Central Assessment of Kidney Transplant Indication Biopsies by Microarrays: The INTERCOMEX Study

ATAGC

Alberta Transplant Applied Genomics Centre
250 Heritage Medical Research Centre, University of Alberta
Edmonton, AB T6G 2S2, ph. 780-407-8880, fax 780-407-3417

INTERCOM Study: Molecular Diagnostic Report

General		
Patient ID	-	Name: -
Biopsy Site ID	-	
INTERCOM Study ID	-	DOB (Y-M-D): -
Attending Physician	-	
Date Reported (Y-M-D)	-	Age at Bx: -
Date Received (Y-M-D)	-	
Date of Transplant (Y-M-D)	-	
Date of Biopsy (Y-M-D)	-	

Clinical Information			
Time of Biopsy Post-Tx	1.9 years	Biopsy Indication	-
Primary Disease	-	Transplant Type	-
GFR (CG) at Biopsy	-	Tx before Biopsy	-
Proteinuria	-	DSA Status at Biopsy	-
Haematuria		PRA Status at Biopsy	-

Local Histopathology Phenotype: the Banff System							
Inflammatory/TCMR Lesions		ABMR Lesions		Atrophy/Scarring		Other	
i	-	ptc	-	ci	-	BK	-
t	-	g	-	ct	-		
v	-	cg	-	cv	-		
total i	-	C4d	-	ah	-		
		mm	-				
Banff Diagnosis 1	-			Banff Diagnosis 2	-		

Molecular Phenotype: the Edmonton Molecular Microscope System				
Classifier/PBT	Biopsy Score	Range in Reference Set	Percentile compared to Reference Set	Interpretation
Global Disturbance Score	2.16	-5.6 -> 9.33	All:81.3 Late:85.1	High
Acute kidney injury (AKI) Score	0.46	-0.92 -> 1.98	All:53 Late:57.9	Moderate
Atrophy-Fibrosis Score	0.35	0.0 -> 1.0	All:59.2 Late:43	Moderate
Rejection Score	0.77	0.0 -> 1.0	All:89.8 Late:88.7	High
TCMR Score	0.00	0.0 -> 1.0	All:42.8 Late:48.7	Low
ABMR Score	0.98	0.0 -> 1.0	All:99.6 Late:99.3	Very High

Pure molecular interpretation

Severe ABMR with g, ptc and cg molecular features. No TCMR. Extensive inflammation with associated AKI and moderate atrophy-fibrosis.

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INTERCOM Study: Molecular Diagnostic Report

Signed out by Dr. P.F. Halloran

Classifier/PBT	Biopsy Score	Range in Reference Set	Percentile Compared to Reference Set	Interpretation
TCMR				
TCMRt	0.00	0.0 -> 1.0	All:42.8 Late:48.7	Low
TCMRt[bkx]	0.00	0.0 -> 1.0	All:48.7 Late:56	Low
Mean of 2 TCMR classifiers	0.00	0.0 -> 1.0	All:44.5 Late:50.3	Low
IFNG related				
Rejection	0.77	0.0 -> 1.0	All:89.8 Late:88.7	High
Rejection[bk]	0.84	0.0 -> 1.0	All:87.7 Late:89.1	High
Mean of 2 Rejection classifiers	0.81	0.0 -> 1.0	All:89.2 Late:89.4	Moderate
Injury-scarring related				
AKI score	0.46	-0.92 -> 1.98	All:53 Late:57.9	Moderate
KT2	-0.93	-2.84 -> 0.24	All:12.6 Late:11.6	Moderate
cigt1	0.35	0.0 -> 1.0	All:59.2 Late:43	Moderate
ABMR related				
DSASTs (late only)	1.21	-0.36 -> 1.32	All:99.6 Late:99.3	High
ABMRpm	0.98	0.0 -> 1.0	All:99.6 Late:99.3	Very High
ABMRpm[x]	0.97	0.0 -> 1.0	All:98.1 Late:96.7	Very High
ABMRpmx	0.95	0.0 -> 1.0	All:97.2 Late:95	Very High
Mean of 3 ABMR classifiers	0.97	0.0 -> 1.0	All:99.1 Late:98.3	Very High
ABMRp	0.11	0.0 -> 1.0	All:91.9 Late:86.8	Low
ABMRp[mx]	0.11	0.0 -> 1.0	All:91.9 Late:86.8	Low

g > 0 prob	0.93	ci > 1 prob	0.35
cg > 0 prob	0.97	ct > 1 prob	0.53
ptc > 1 prob	0.80	mm > 1 prob	0.69
DSA+ prob	0.96	ah > 0 prob	0.76
i > 1 prob	0.28	cv > 0 prob	0.87
t > 1 prob	0.06	Prot+ prob	0.65
		GFR < 30 prob	0.15

For classifiers:
t = TCMR, b= Borderline, k=BK virus, x=Mixed, p=C4d+, m=C4d-, [] = contents of square brackets left-out.
E.g. TCMRt(bkx) is a classifier comparing TCMR with everything else, with borderline, BK virus, and Mixed left out.

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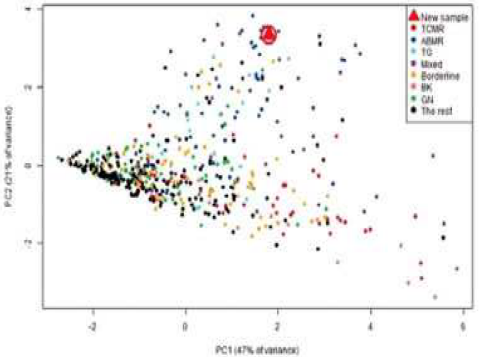
INTERCOM Study: Molecular Diagnostic Report

Histology Diagnosis of the 50 Nearest Neighbors	Molecular Diagnosis of the 50 Nearest Neighbors	Proportion of the 50 Nearest Neighbors surviving
C4d-ABMR: 0.33 C4d+ABMR: 0.16 Mixed: 0.13 TG: 0.12 Borderline: 0.09 GN: 0.06 TCMR: 0.03 Other: 0.03 IFTA: 0.02 NOMOA: 0.01 AKI: 0.01	Rejection: 0.68 IRRATs: 0.57 ABMR: 0.56 cigt1: 0.46 TCMR: 0.04	1-year: 0.70 3-years: 0.49



LOCATION OF SAMPLE RELATIVE TO THOSE IN THE REFERENCE SET

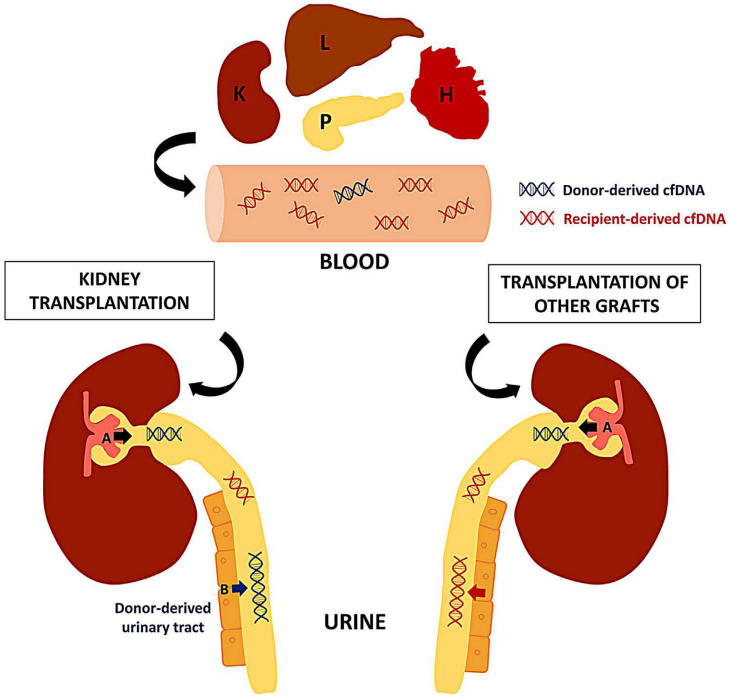
Halloran PF, et al. *Am J Transplant*. 2017;17(11):2851-2862.

Minireview

Cell-Free DNA: An Upcoming Biomarker in Transplantation

E. M. Gielis[1,2], K. J. Ledeganck[1], B. Y. De Winter[1], J. Del Favero[3], J.-L. Bosmans[1,4], F. H. J. Claas[2], D. Abramowicz[1,4] and M. Eikmans[2,*]

[1]Laboratory of Experimental Medicine and Pediatrics, University of Antwerp, Antwerp, Belgium
[2]Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, the Netherlands
[3]Multiplicom N. V., Niel, Belgium
[4]Department of Nephrology and Hypertension, Antwerp University Hospital, Antwerp, Belgium
[*]Corresponding author: Michael Eikmans, M.Eikmans@lumc.nl



Gielis EM, et al. *Am J Transplant*. 2015;15:2541-2551.

KIDNEY DISEASE

A circulating antibody panel for pretransplant prediction of FSGS recurrence after kidney transplantation

Marianne Delville,[1]* Tara K. Sigdel,[2]* Changli Wei,[3]* Jing Li,[3] Szu-Chuan Hsieh,[2] Alessia Fornoni,[4] George W. Burke,[5] Patrick Bruneval,[6] Maarten Naesens,[7] Annette Jackson,[8] Nada Alachkar,[8] Guillaume Canaud,[1] Christophe Legendre,[1] Dany Anglicheau,[1†] Jochen Reiser,[3†‡] Minnie M. Sarwal[2†‡]

Recurrence of focal segmental glomerulosclerosis (rFSGS) after kidney transplantation is a cause of accelerated graft loss. To evaluate pathogenic antibodies (Abs) in rFSGS, we processed 141 serum samples from 64 patients with and without primary rFSGS and 34 non-FSGS control patients transplanted at four hospitals. We screened about 9000 antigens in pretransplant sera and selected 10 Abs targeting glomerular antigens for enzyme-linked immunosorbent assay (ELISA) validation. A panel of seven Abs (CD40, PTPRO, CGB5, FAS, P2RY11, SNRPB2, and APOL2) could predict posttransplant FSGS recurrence with 92% accuracy. Pretransplant elevation of anti-CD40 Ab alone had the best correlation (78% accuracy) with rFSGS risk after transplantation. Epitope mapping of CD40 with customized peptide arrays and rFSGS sera demonstrated altered immunogenicity of the extracellular CD40 domain in rFSGS. Immunohistochemistry of CD40 demonstrated a differential expression in FSGS compared to non-FSGS controls. Anti-CD40 Abs purified from rFSGS patients were particularly pathogenic in human podocyte cultures. Injection of anti-CD40/rFSGS Ab enhanced suPAR (soluble urokinase receptor)–mediated proteinuria in wild-type mice, yet no sensitizing effect was noted in mice deficient in CD40 or in wild-type mice that received blocking Ab to CD40. In conclusion, a panel of seven Abs can help identify primary FSGS patients at high risk of recurrence before transplantation. Intrarenal CD40 (and possibly other specific glomerular antigens) is an important contributor to FSGS disease pathogenesis. Human trials of anti-CD40 therapies are warranted to evaluate their efficacy for preventing rFSGS and improving graft survival.

Delville M, et al. *Sci Transl Med*. 2014;6(256):256ra136.

JAMA | Original Investigation

Diagnostic Assessment of Deep Learning Algorithms for Detection of Lymph Node Metastases in Women With Breast Cancer

Babak Ehteshami Bejnordi, MS; Mitko Veta, PhD; Paul Johannes van Diest, MD, PhD; Bram van Ginneken, PhD; Nico Karssemeijer, PhD; Geert Litjens, PhD; Jeroen A. W. M. van der Laak, PhD; and the CAMELYON16 Consortium

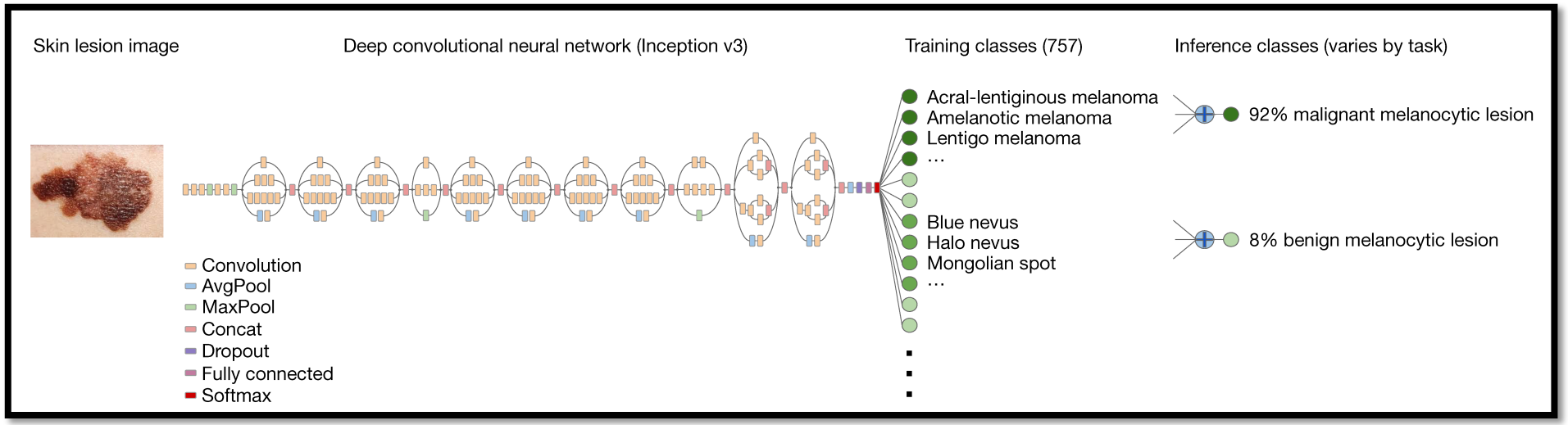
Ehteshami Bejnordi E, et al. *JAMA.* 2017;318(22):2199-2210.

LETTER

doi:10.1038/nature21056

Dermatologist-level classification of skin cancer with deep neural networks

Andre Esteva[1]*, Brett Kuprel[1]*, Roberto A. Novoa[2,3], Justin Ko[2], Susan M. Swetter[2,4], Helen M. Blau[5] & Sebastian Thrun[6]



Esteva A, et al. *Nature.* 2017;542(7639):115-118.

Ibox: Advancing Beyond the Current State-of-the-Art in Prognostication

- Systematic review (April 12th 2018)
- «Kidney transplantation», «graft survival», «prognostic score»

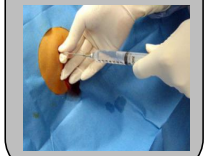
- Long-term allograft survival

- Externally validated + Structural / functional parameters combined

- ✓ Multidimension assessment based
- ✓ Mechanistically informed
- ✓ Large unselected populations
- ✓ Addressing individual risk prediction
- ✓ Generalizable / exportable
- ✓ Transposable / updatable at different times post-transplant

Courtesy of A Loupy.

Allograft Phenotyping



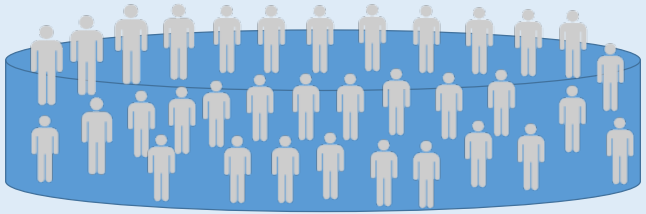
Data homing, Computational

Clinical parameters, Biological parameters Outcome parameters Treatments

EMR

DSA data Standard Histopahtology

Application Program Interface



Cloud-Based Unified Database Infrastructure & Computations Server

Non invasive biomarkers

Molecular platforms

MACHINE KNOWLEDGE

220,0000 patient years ; 18,900 Allograft biopsies; >1200 graft failures ; >20,000,000 of data

Exportability & Validation cycle

Precision Medicine Cycle

Risk Stratification

Machine learning

Identifying Appropriate Recipients for CDC Infectious Risk Donor Kidneys

E. K. H. Chow[1,†], A. B. Massie[1,2,†], A. D. Muzaale[1,2], A. L. Singer[1], L. M. Kucirka[1], R. A. Montgomery[1], H. P. Lehmann[3] and D. L. Segev[1,2,*]

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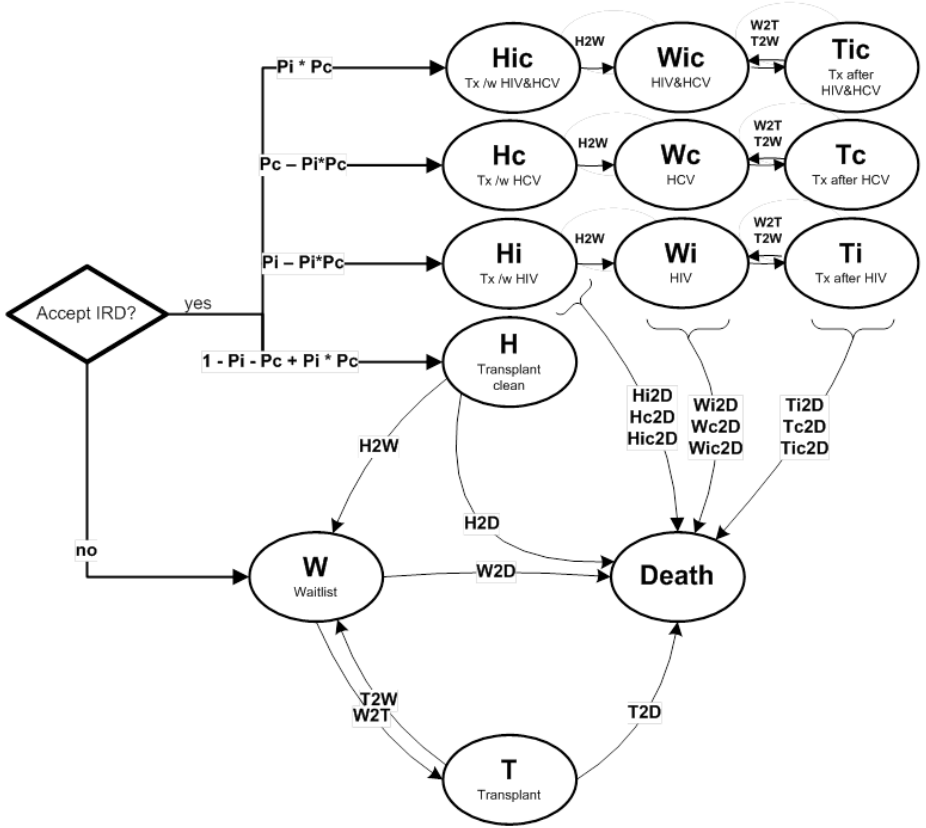
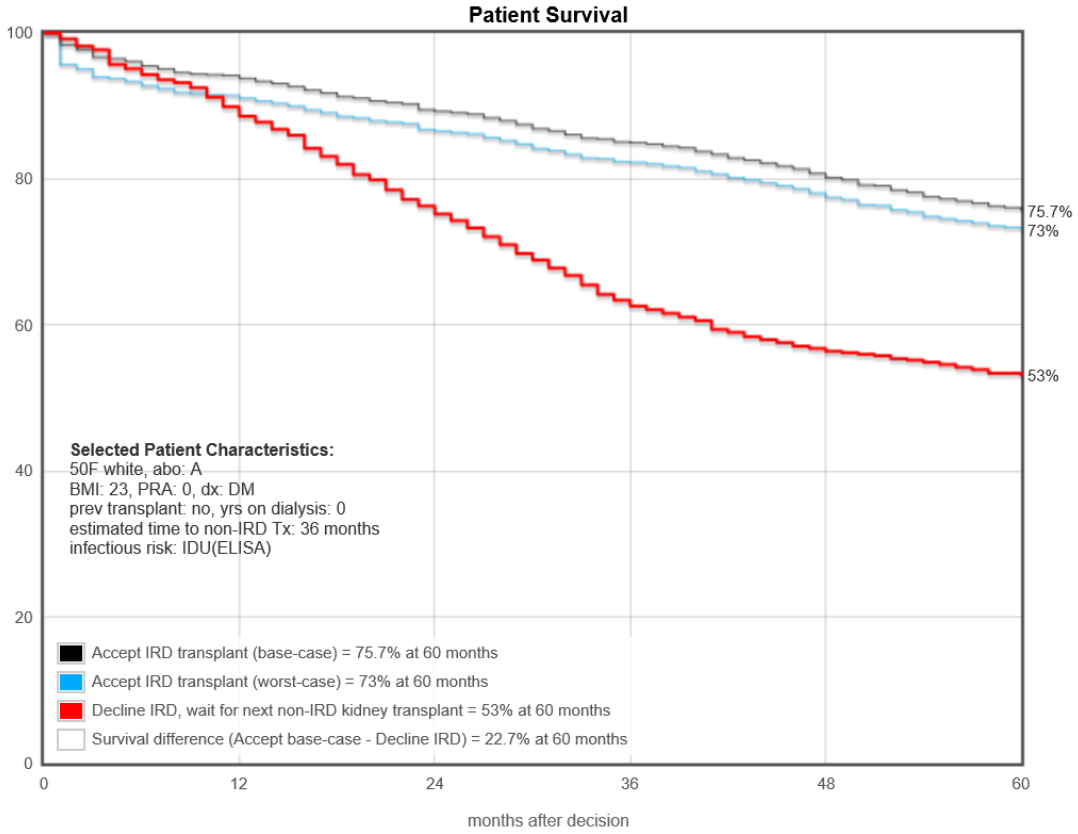
[3]Division of Health Sciences Informatics, Johns Hopkins University School of Medicine, Baltimore, MD
**Corresponding author: Dorry Segev, dorry@jhmi.edu*
[†]Both authors contributed equally.



Chow EKH, et al. *Am J Transplant*. 2013;13:1227-1234.

Johns Hopkins IRD Kidney Transplant Calculator www.TransplantModels.com/IRD



base-case estimate: mortality risk (if seroconverted) increased by 4.12% HIV, 3.42% HCV per year
worst-case estimate: mortality risk (if seroconverted) equivalent to immediate (100% chance) death

Recipient Characteristics:

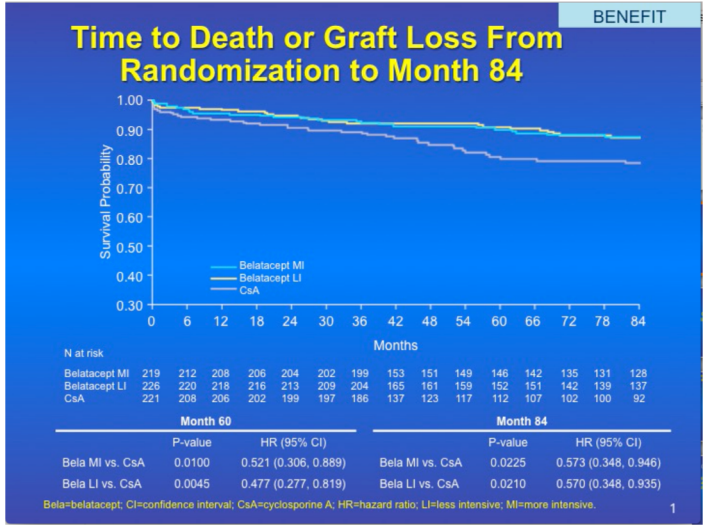
Age: (20-75)	50
Gender:	female
ABO:	Type A
Ethnicity:	White
BMI: (19-39)	23
PRA: (0-100)	0
Renal failure diagnosis:	diabetes mellitus
Previous transplant:	no
Years on waitlist:	0
Estimated time remaining until non-IRD transplant *:	36 months

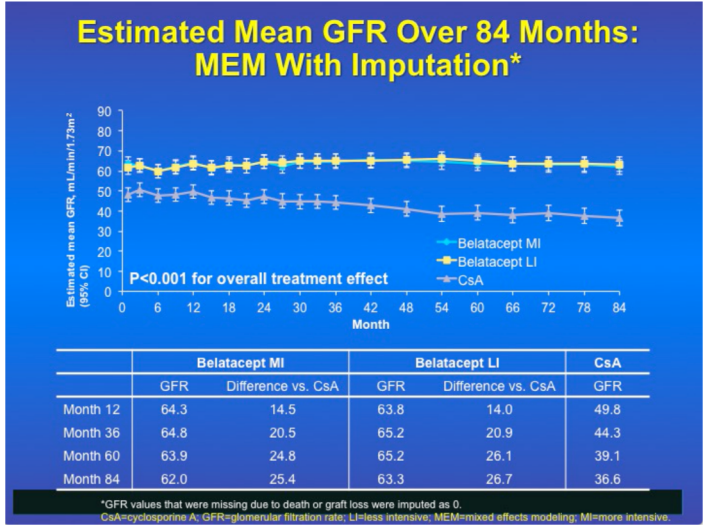
* This is time in addition to the time the patient may have already waited. eg: if a patient has spent 1 year on the waitlist, and the estimated time remaining until a non-IRD transplant is 18 months, the patient is expected to have waited 30 months since listing, before a non-IRD transplant.

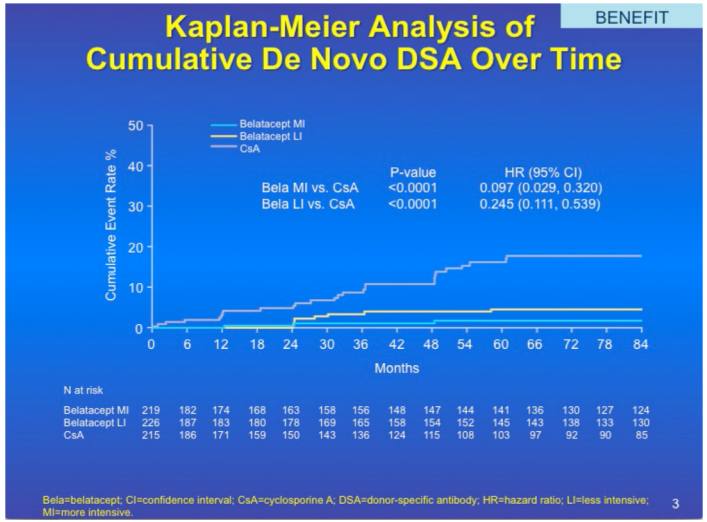
Donor Characteristics:

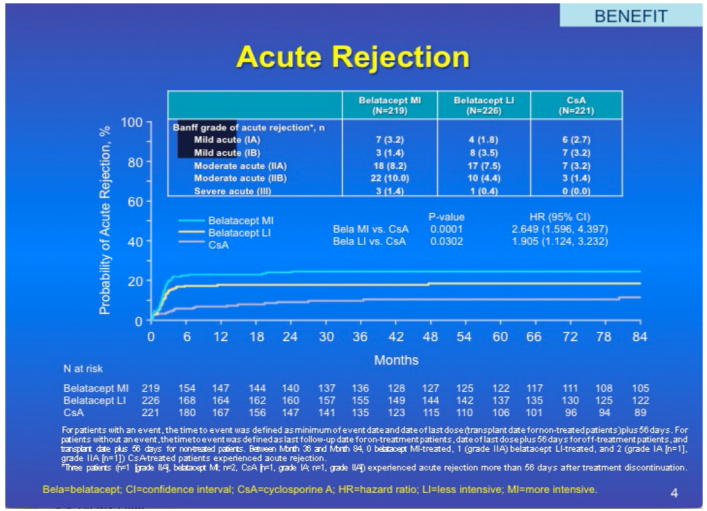
Infectious Risk Behavior:	Intravenous drug users
Serology Testing Used:	ELISA

Belatacept Long-Term Outcomes









Vincenti F, et al. *N Engl J Med* 2016;374(4):333-343.

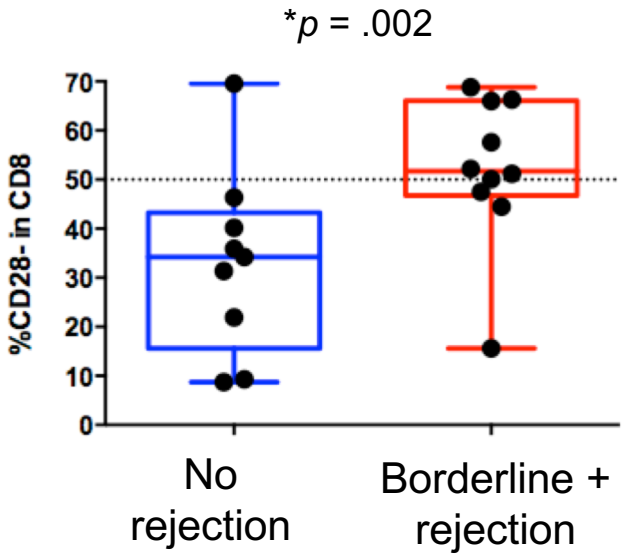
Precision Medicine For Optimizing the Belatacept Regimen

- 20 kidney transplant recipients (8 DDRT; 12 living) to receive denovo belatacept
- Results: On cause biopsies
  - 2 patients were noted to have ACR 1a (at 4 wks; at 6 wks)
  - 1 with ACR 2b (at 2 mons)
  - 1 with AMR (at 4 mons)
- 6 patients were found to have borderline rejection on protocol biopsies, 9 patients had no inflammation on biopsies
- 18 patients remained on belatacept
  - 2 patients were converted to tacrolimus
  - 3 of 4 rejections in those who remained on MMF and not on mTORi

Shoji J, Leung J, Tavares E, Tang Q, Vincenti F. Abstract 123. Presented at 2018 American Transplant Congress. http://atcmeetingabstracts.com/abstract/precision-medicine-for-determining-the-efficacy-of-a-novel-belatacept-regimen/. Accessed May 21, 2018.

Pretransplant Immunologic Predictors of Rejection in Patients Treated with Belatacept

- Patients who had biopsy-proven rejection or borderline changes had significantly higher % of CD8+CD28- T cells in pre-transplant PBMC vs. those who had normal biopsy.
- Patients with > 50% of CD8+CD28- T cells pre-transplant were more likely to experience rejection (odds ratio was 18.7, sensitivity 87.5% with false positive of 12.5%, p = 0.02)



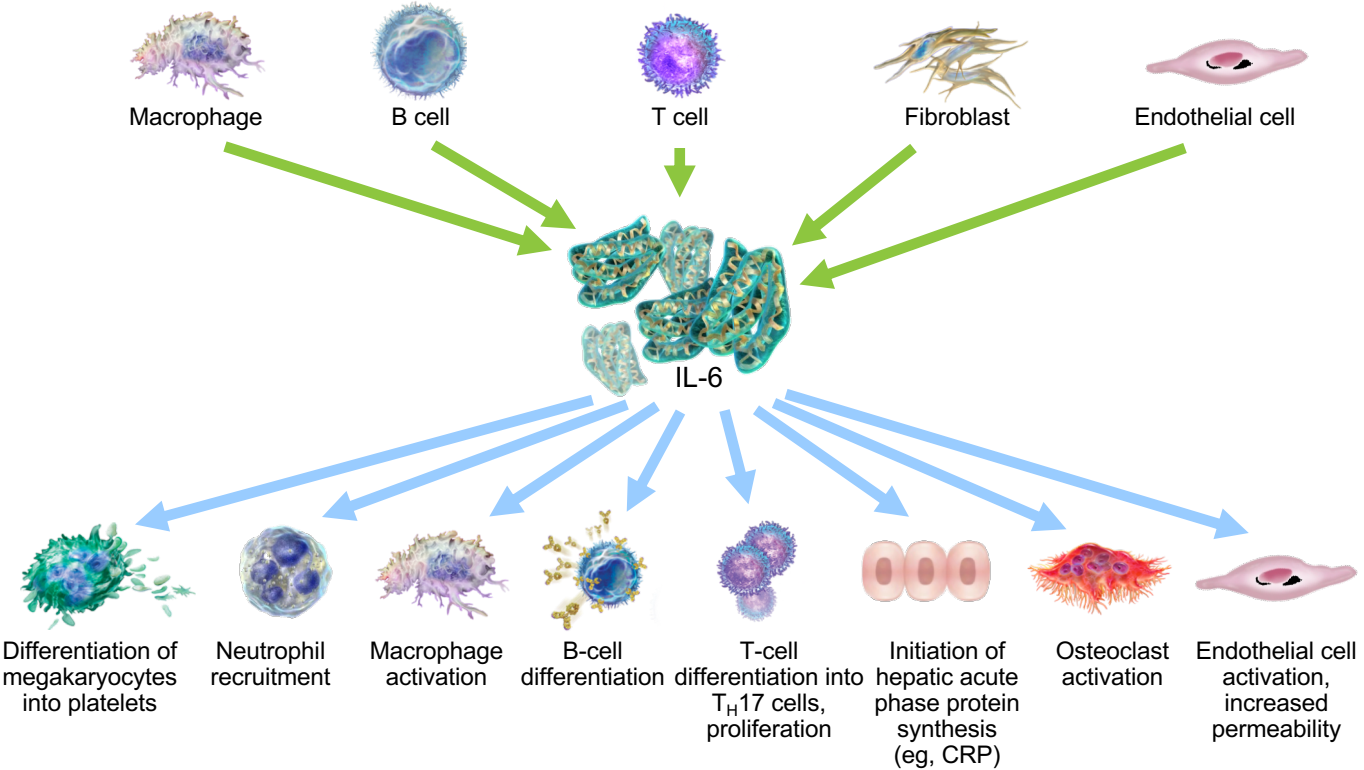
N = 20 kidney transplant recipients

Shoji J, Leung J, Tavares E, Tang Q, Vincenti F. Abstract 123. Presented at 2018 American Transplant Congress. http://atcmeetingabstracts.com/abstract/precision-medicine-for-determining-the-efficacy-of-a-novel-belatacept-regimen/. Accessed May 21, 2018.

The Pipeline

- Reappraisal IL6 blockade
- A better belatacept ➔ antibodies to CD28
- Anti-CD40s
- A novel approach to desensitization/AMR therapy

IL-6 is a Pleiotropic Cytokine With Multiple Sources and Targets



[1]Cronstein BN. *Bull NUY Hosp Jt Dis.* 2007;65(suppl 1):S11-S15. [2]Naka T, et al. *Arthritis Res.* 2002;4(suppl 1):S233-S242. [3]Jones SA, et al. *J Interferon Cytokine Res.* 2005;25:241-253. [4]Maruo N, et al. *Endocrinology*. 1992;131:710-714. [5]Nishihara et al. *Int Immunol.* 2007;19:695-702.

Is There a More Effective Costimulation Blockade than Belatacept?

- Selective anti-CD28s antibodies will enhance inhibitory pathways and spare T-regs
  - Lulizumab (anti-CD28 dAb)
  - FR104 (a human pegylated Fab antagonist)

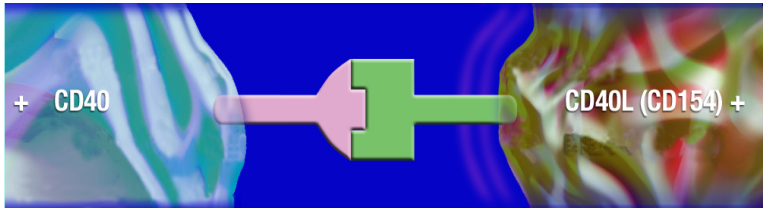
CD40:CD40L Signalling Regulates Immune Responses

CD40

- Constitutively expressed on APCs
- Directly affects APC maturation and cytokine release
- Up-regulates CD80/CD86 expression
- Indirectly increases T-cell proliferation
- Essential for B-cell activation and antibody production

CD40L (CD154)

- Induced on T cells
- Up-regulated by signals from CD28
- Enhances T-cell activation
- May control thrombotic and inflammatory processes



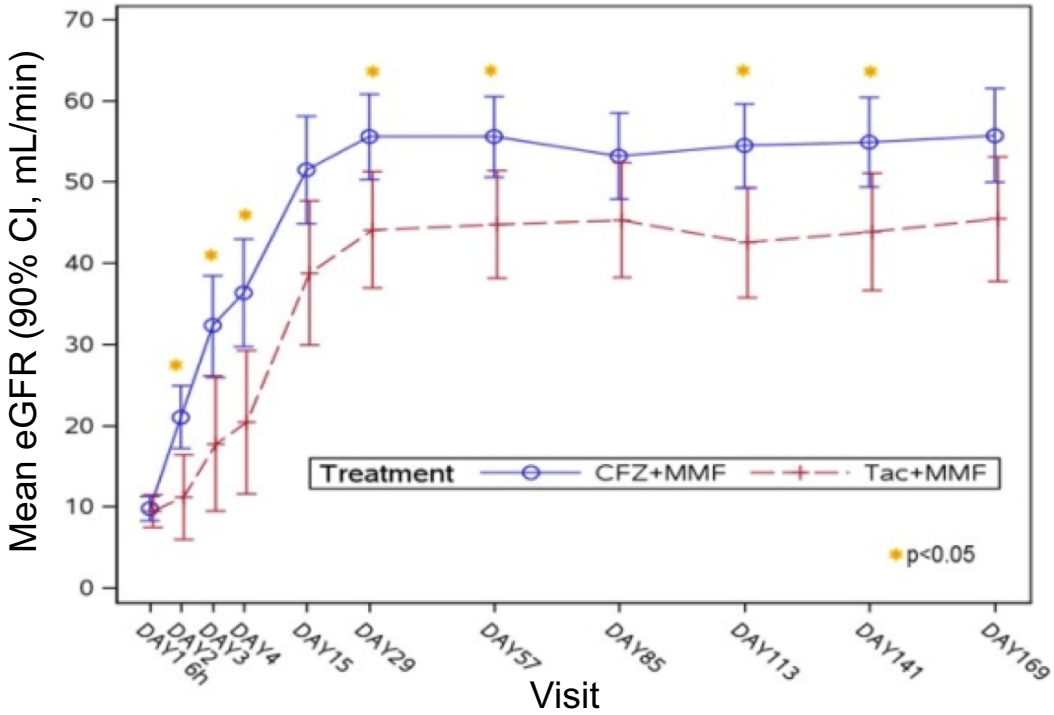
Larsen C, Pearson T. *Curr Opin Immunol* 1997;9 641-647.; Larsen CP, et al. *Am J Transplant* 2006;6:876-883.

400-CFZ533, a New Anti-CD40 mAB Demonstrates Comparable Efficacy and Better Renal Function vs. Tacrolimus in De-Novo CNI-Free Kidney Transplantation

Nashan B, et al. Abstract 400.
2018 American Transplant Congress.
http://atcmeetingabstracts.com/abstract/cfz533-a-new-anti-cd40-mab-demonstrates-comparable-efficacy-and-better-renal-function-versus-tacrolimus-in-de-novo-cni-free-kidney-transplantation/.
Accessed May 21, 2018.

Evolution of Renal Function as Measured as eGFR (mL/min)

- 51 patients were transplanted and randomized (2:1) to either CFZ (N = 33) or TAC (N = 18).
- 25/51 patients (49%) received a living donor allograft
- After CD40 target saturation, CFZ dosed IV every 4 wks
- CFZ was well tolerated with no infusion related nor thromboembolic events
- No difference in composite endpoints



Nashan B, et al. Abstract 400. 2018 American Transplant Congress. http://atcmeetingabstracts.com/abstract/cfz533-a-new-anti-cd40-mab-demonstrates-comparable-efficacy-and-better-renal-function-versus-tacrolimus-in-de-novo-cni-free-kidney-transplantation/. Accessed May 21, 2018.

SMART Goals

Specific, **M**easurable, **A**ttainable, **R**elevant, **T**imely

- Prevent and treat DSA and antibody-mediated rejection AMR
- Understand the pathogenesis of inflammation and fibrosis and treat it
- Optimize immunosuppression
- Apply big data and precision medicine to optimize clinical trials of novel drugs in transplantation

Questions & Answers

Obtaining CME/CE Credit

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Don’t forget: If claiming ABIM MOC credit, please write ABIM # on your form.

Thank you!

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1. Actively participate in the meeting by **responding to ARS** and/or **asking the faculty questions**
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   (For live stream participants, follow the credit claim link)
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How to Claim this Activity as a QPP Improvement Activity

- **Actively participate** by responding to ARS and/or asking the faculty questions
- **Complete the 2 forms** found on your table:
  - Evaluation form found on your table
  - The Quality Payment Program Improvement Activity form
- Over the next 90 days, **actively work to incorporate improvements** in your clinical practice from this presentation
- **Complete the follow-up survey** from CME Outfitters in approximately 3 months

CME Outfitters will send you confirmation of your participation to submit to CMS attesting to your completion of a QPP Improvement Activity.

Downloadable Resources

Presentation slides, the course guide booklet, and the credit request/evaluation form will be available for download at:

www.CMEOutfitters.com/transplant2018resources

Thank You

Don’t forget to turn in your forms so you can collect your credit.

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