Are Long-Term Outcomes after Kidney Transplantation Improving?

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Glickman Urological and Kidney Institute

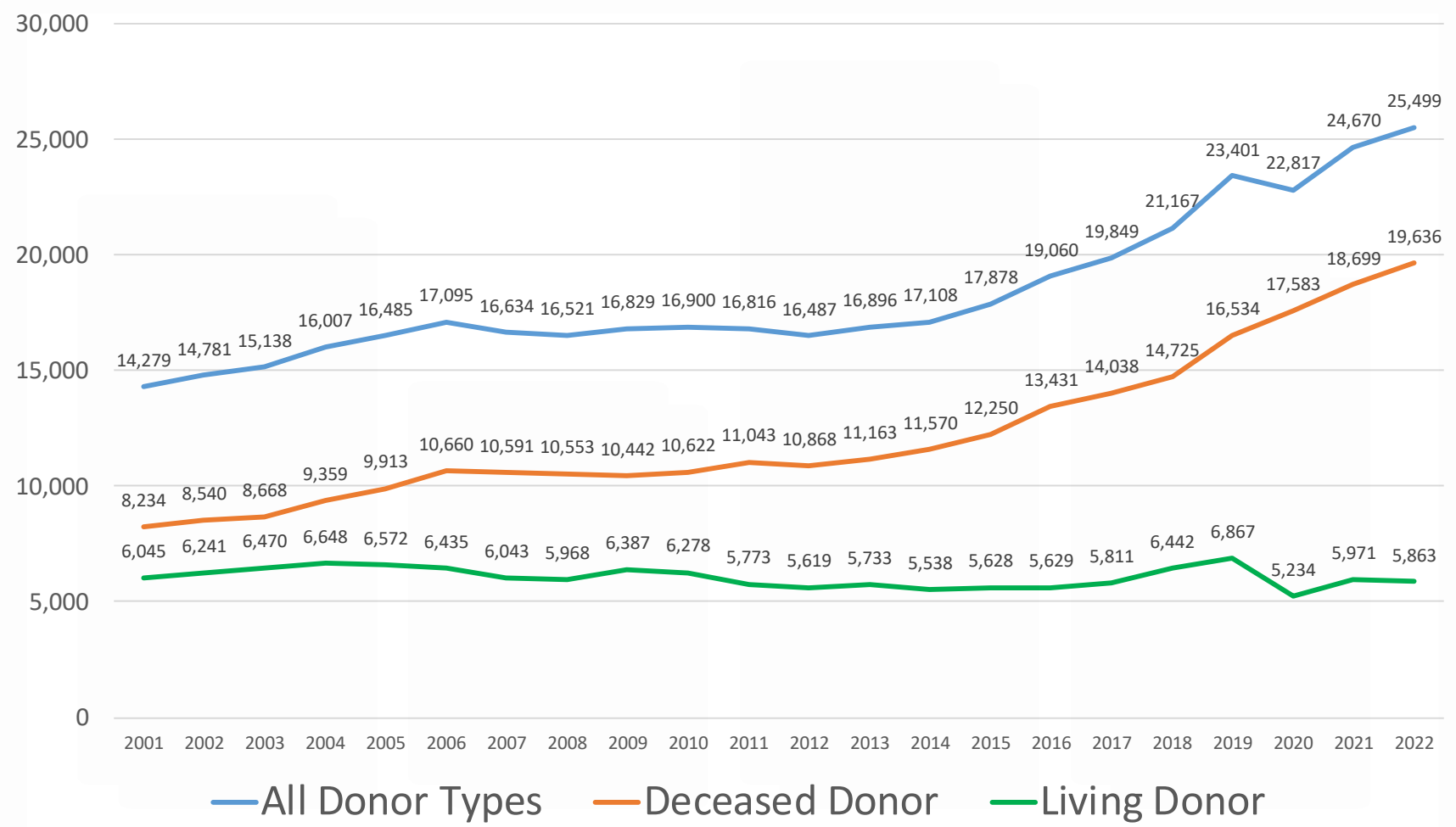
Are long-term outcomes after kidney transplantation improving?

Are long-term outcomes after kidney transplantation improving?

YES!

Growing number of kidney transplants in the US

UNOS source



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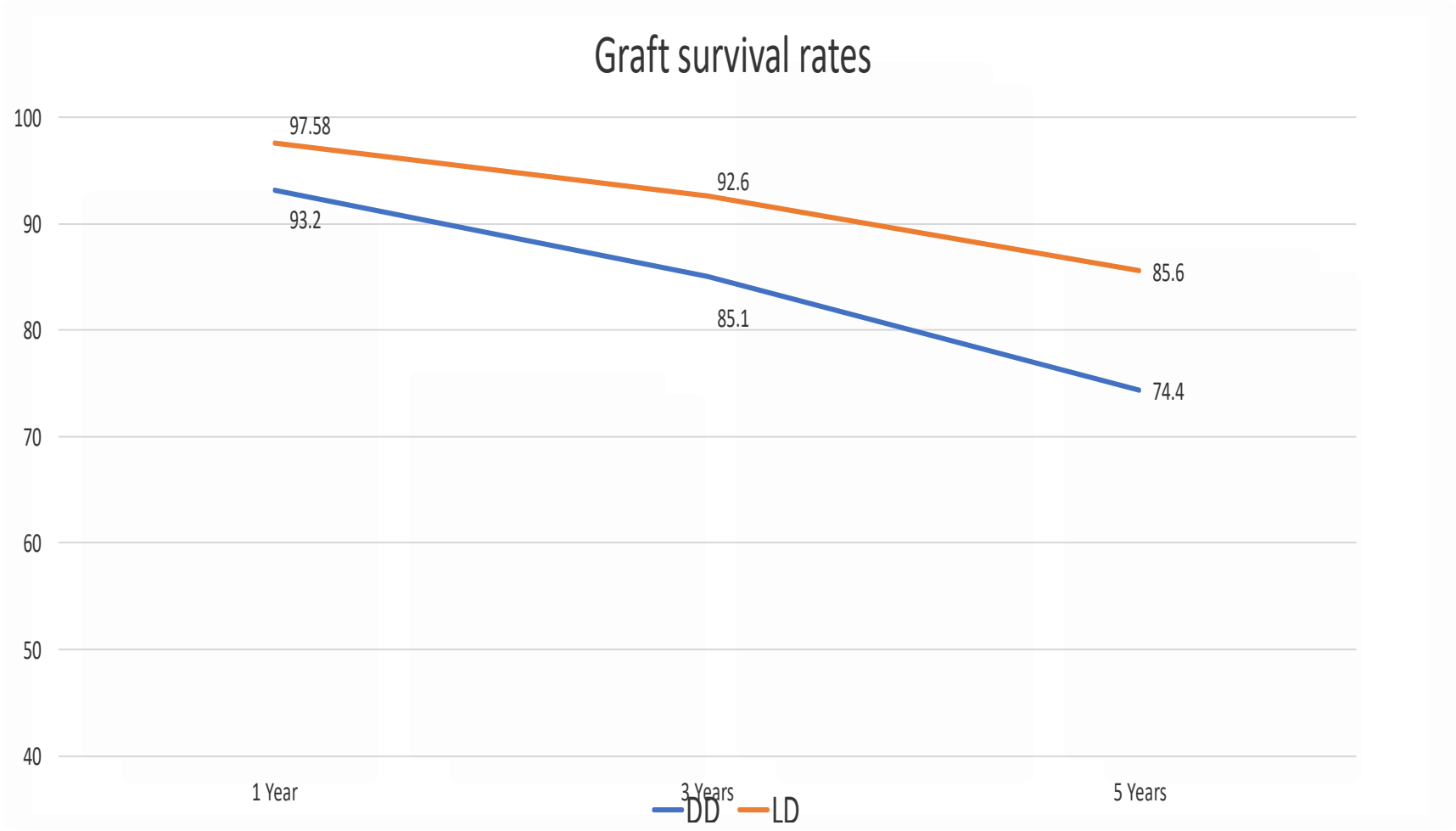
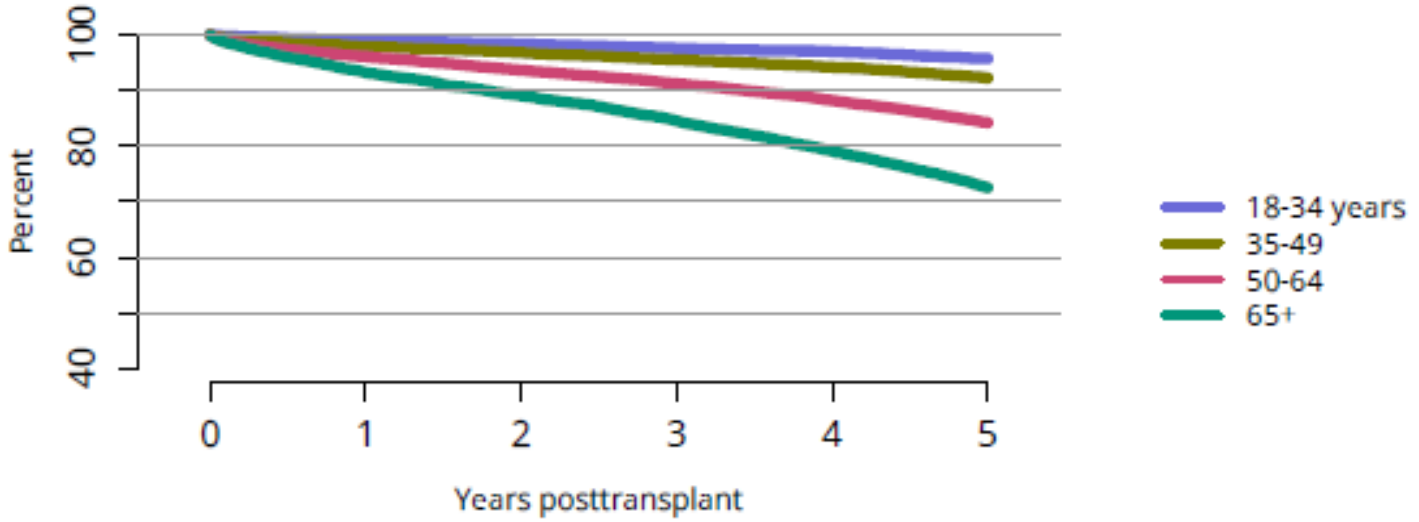
Unadjusted graft survival – UNOS data 2008-2015



Unadjusted patient survival

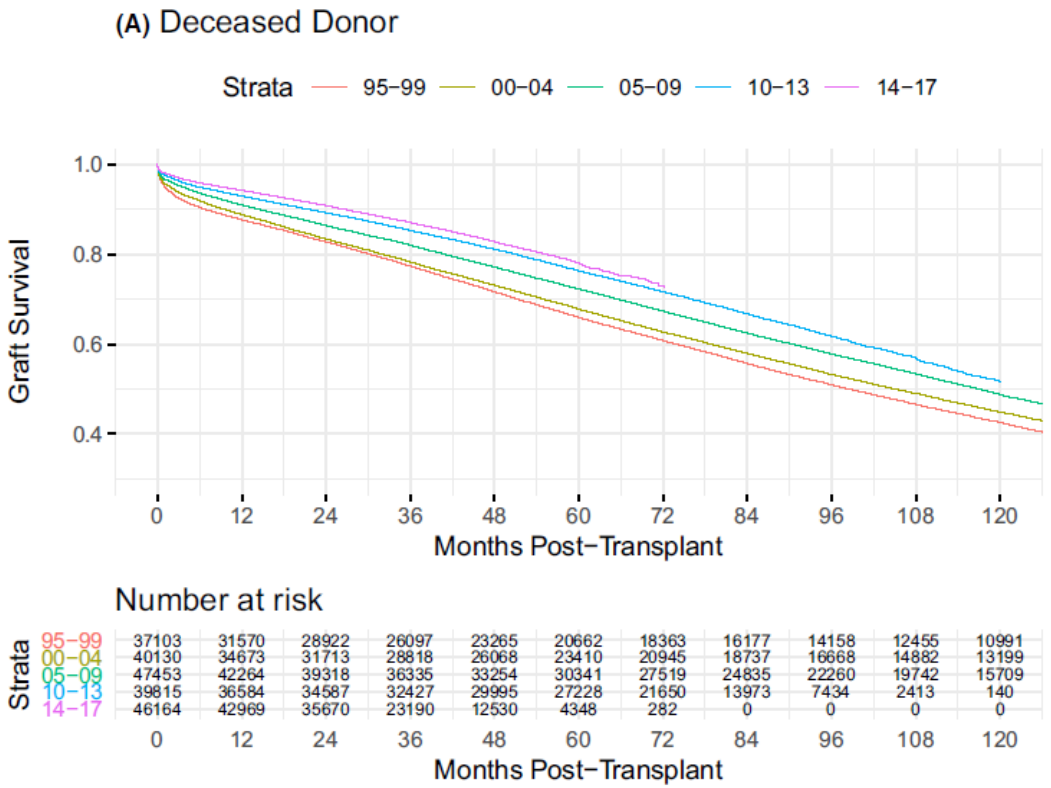


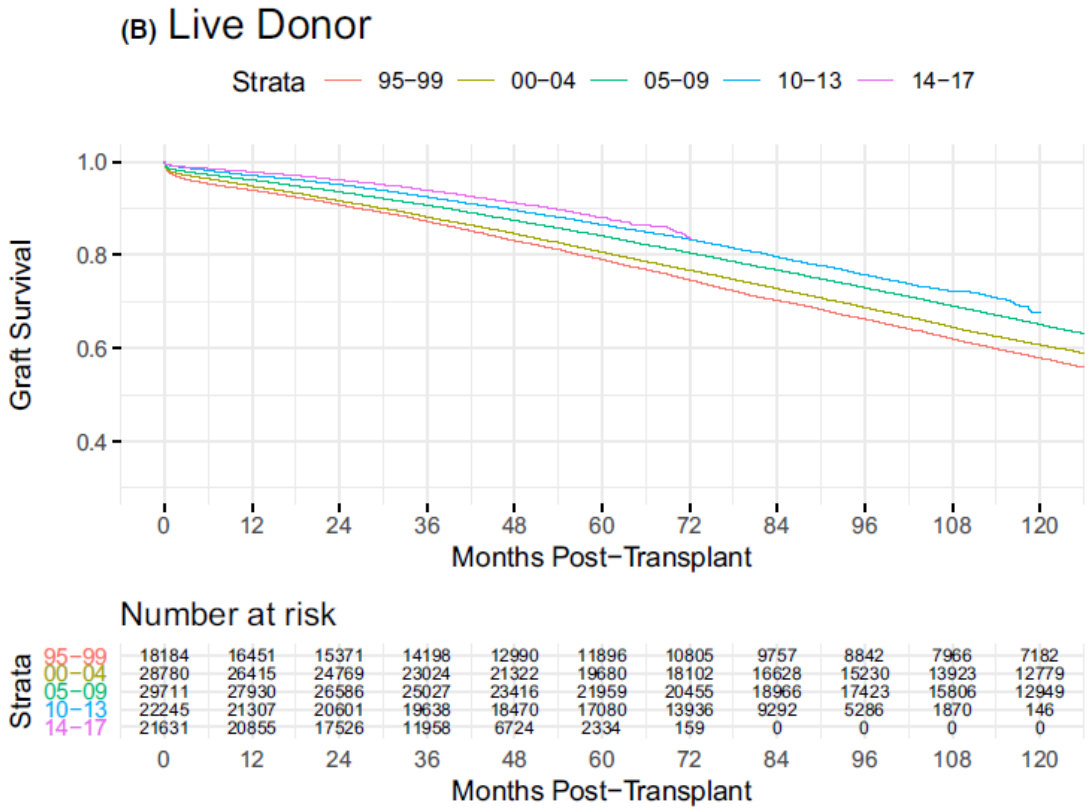
OPTN/SRTR 2021 Annual Data Report

Figure KI 93: Patient survival among adult deceased donor kidney transplant recipients, 2014-2016, by age. Patient survival estimated using unadjusted Kaplan-Meier methods.

Long-term kidney transplant graft survival—Making progress when most needed

Emilio D. Poggio[1,2] | Joshua J. Augustine[1,2] | Susana Arrigain[3,4] | Daniel C. Brennan[5] | Jesse D. Schold[2,3,4]





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Poggio et al, AJT 2021

Improving half-life of kidney allografts over time

TABLE 2 Kaplan-Meier graft survival by era of transplantation and half-lives

Donor type	N	1 year	3 years	5 years	10 years	Median survival in years
Deceased						
1995–1999	37103	87.7 (87.4, 88.1)	77.4 (76.9, 77.8)	65.9 (65.4, 66.4)	42.6 (42.0, 43.1)	8.2 (8.1, 8.3)
2000–2004	40130	88.9 (88.6, 89.2)	78.3 (77.9, 78.7)	67.8 (67.3, 68.3)	44.9 (44.4, 45.4)	8.8 (8.6, 8.9)
2005–2009	47453	91.0 (90.7, 91.2)	82.0 (81.7, 82.4)	72.3 (71.8, 72.7)	48.8 (48.3, 49.3)	9.7 (9.6, 9.8)
2010–2013	39815	93.0 (92.8, 93.3)	85.3 (85.0, 85.7)	76.3 (75.9, 76.7)	51.6 (50.0, 53.3)	10.5 (10.4, 10.7)[a]
2014–2017	46164	94.3 (94.1, 94.5)	87.1 (86.8, 87.4)	78.1 (77.5, 78.6)		11.7 (11.4, 12.1)[a]
Live						
1995–1999	18184	93.9 (93.6, 94.3)	87.2 (86.7, 87.7)	79.0 (78.4, 79.6)	57.9 (57.1, 58.7)	12.1 (11.9, 12.3)
2000–2004	28780	94.8 (94.5, 95.1)	88.1 (87.8, 88.5)	80.6 (80.1, 81.1)	60.7 (60.1, 61.3)	12.9 (12.7, 13.1)
2005–2009	29711	96.1 (95.9, 96.3)	90.7 (90.3, 91.0)	84.1 (83.7, 84.5)	65.0 (64.5, 65.6)	13.9 (13.7, 14.2)
2010–2013	22245	97.1 (96.9, 97.3)	92.5 (92.1, 92.8)	86.5 (86.1, 87.0)	67.6 (65.6, 69.6)	15.7 (15.2, 16.1)[a]
2014–2017	21631	97.8 (97.6, 98.0)	93.9 (93.5, 94.2)	88.0 (87.3, 88.7)		19.2 (18.1, 20.7)[a]

[a]Predicted median survival derived from linear regression analysis for transplant recipients where median survival has not been observed at latest follow-up (March 2020), and predicted 95% confidence intervals obtained from 1,000 bootstrap sample analysis.

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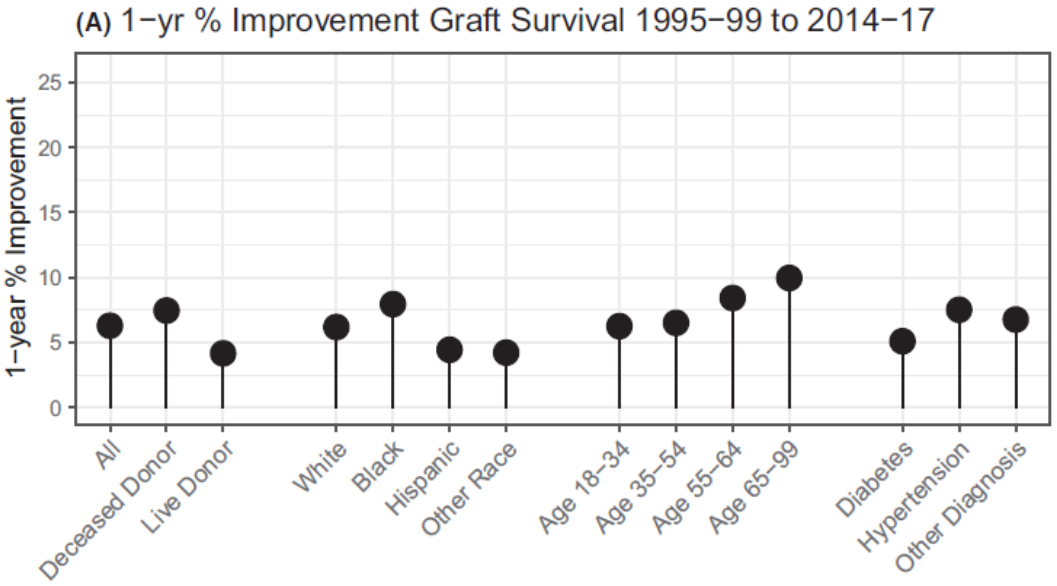
Poggio et al, AJT 2021

Increased relative improvement of long-term survival



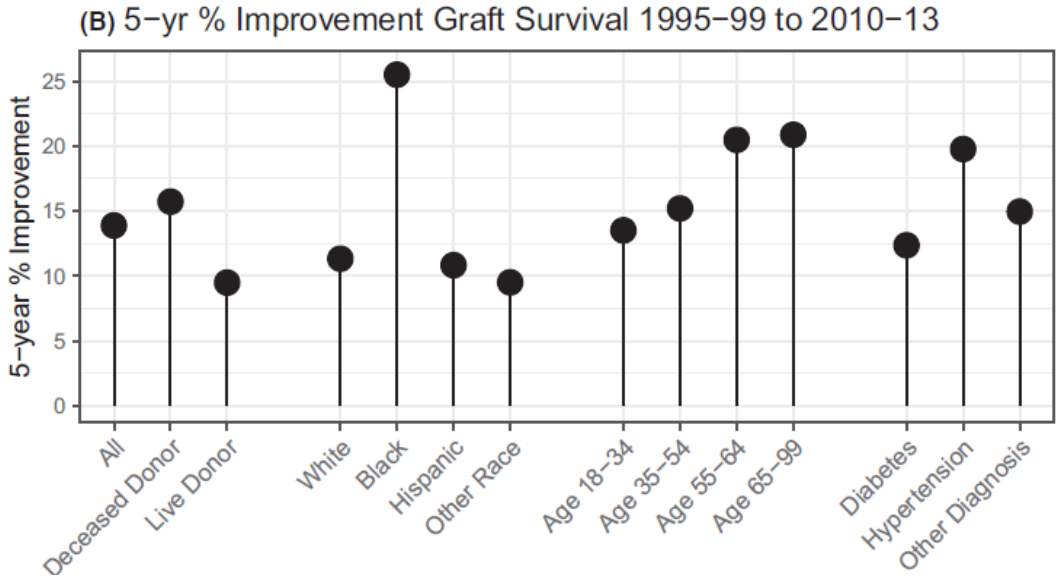


TABLE 3 Adjusted Cox proportional hazards model of time to graft failure censored at death, competing risks analysis of graft failure with death as a competing risk, Cox proportional hazards model of time to death censored at graft failure, and competing risks analysis of death with graft failure as a competing risk

	Graft failure censored at death HR (95% CI)	Graft failure with death as a competing risk SHR (95% CI)	Mortality censored at graft failure HR (95% CI)	Mortality with graft failure as a competing risk SHR (95% CI)
Era (year)				
1995–1999	Ref	Ref	Ref	Ref
2000–2004	0.86 (0.84, 0.88)	0.85 (0.83, 0.86)	0.92 (0.90, 0.94)	0.91 (0.89, 0.93)
2005–2009	0.69 (0.67, 0.71)	0.67 (0.66, 0.69)	0.72 (0.71, 0.74)	0.71 (0.70, 0.73)
2010–2013	0.54 (0.53, 0.56)	0.52 (0.51, 0.54)	0.59 (0.58, 0.61)	0.56 (0.54, 0.57)
2014–2017	0.43 (0.41, 0.44)	0.40 (0.39, 0.41)	0.51 (0.49, 0.53)	0.46 (0.44, 0.48)

Poggio et al, AJT 2021

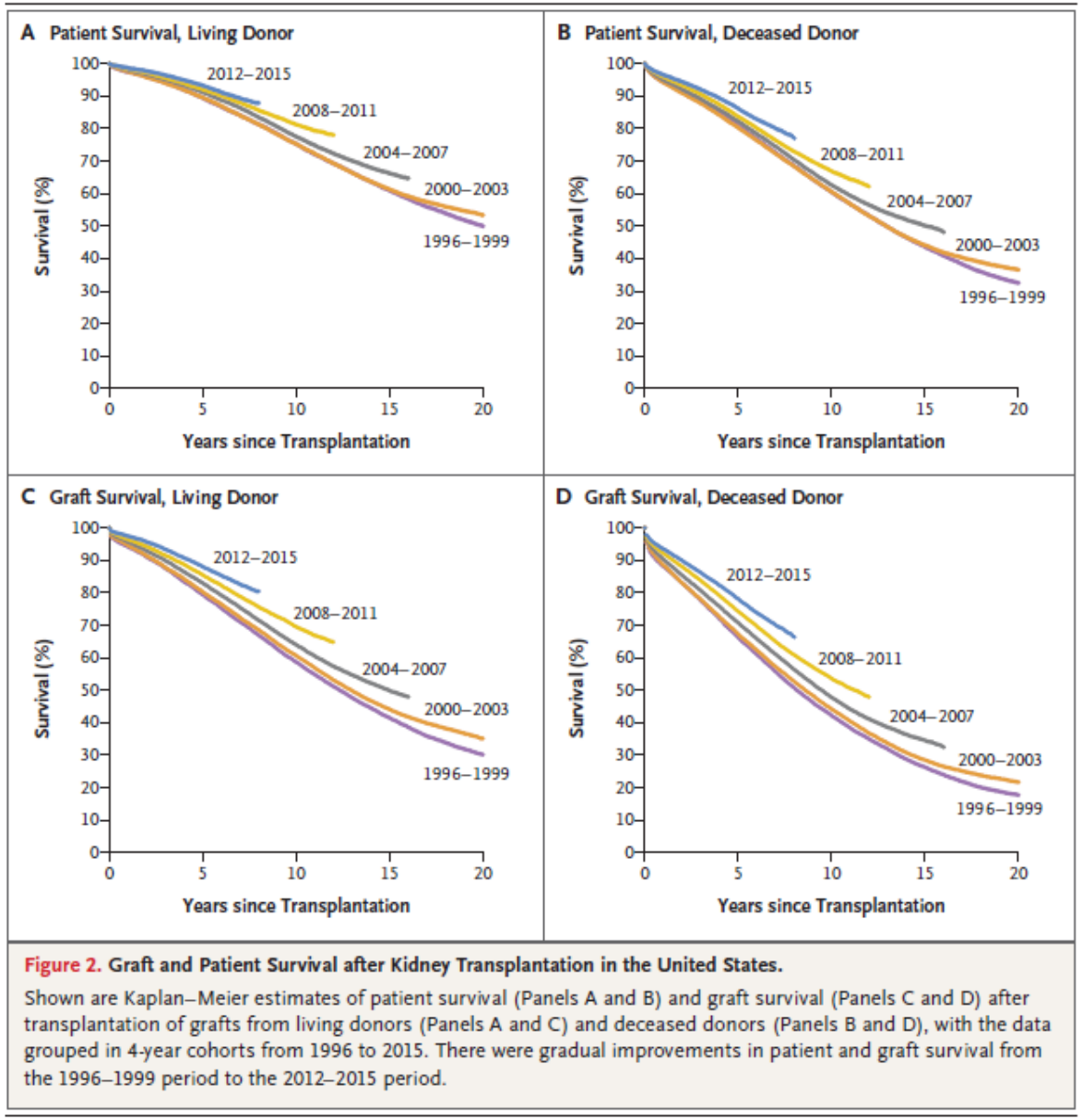


Figure 2. Graft and Patient Survival after Kidney Transplantation in the United States.

Shown are Kaplan–Meier estimates of patient survival (Panels A and B) and graft survival (Panels C and D) after transplantation of grafts from living donors (Panels A and C) and deceased donors (Panels B and D), with the data grouped in 4-year cohorts from 1996 to 2015. There were gradual improvements in patient and graft survival from the 1996–1999 period to the 2012–2015 period.

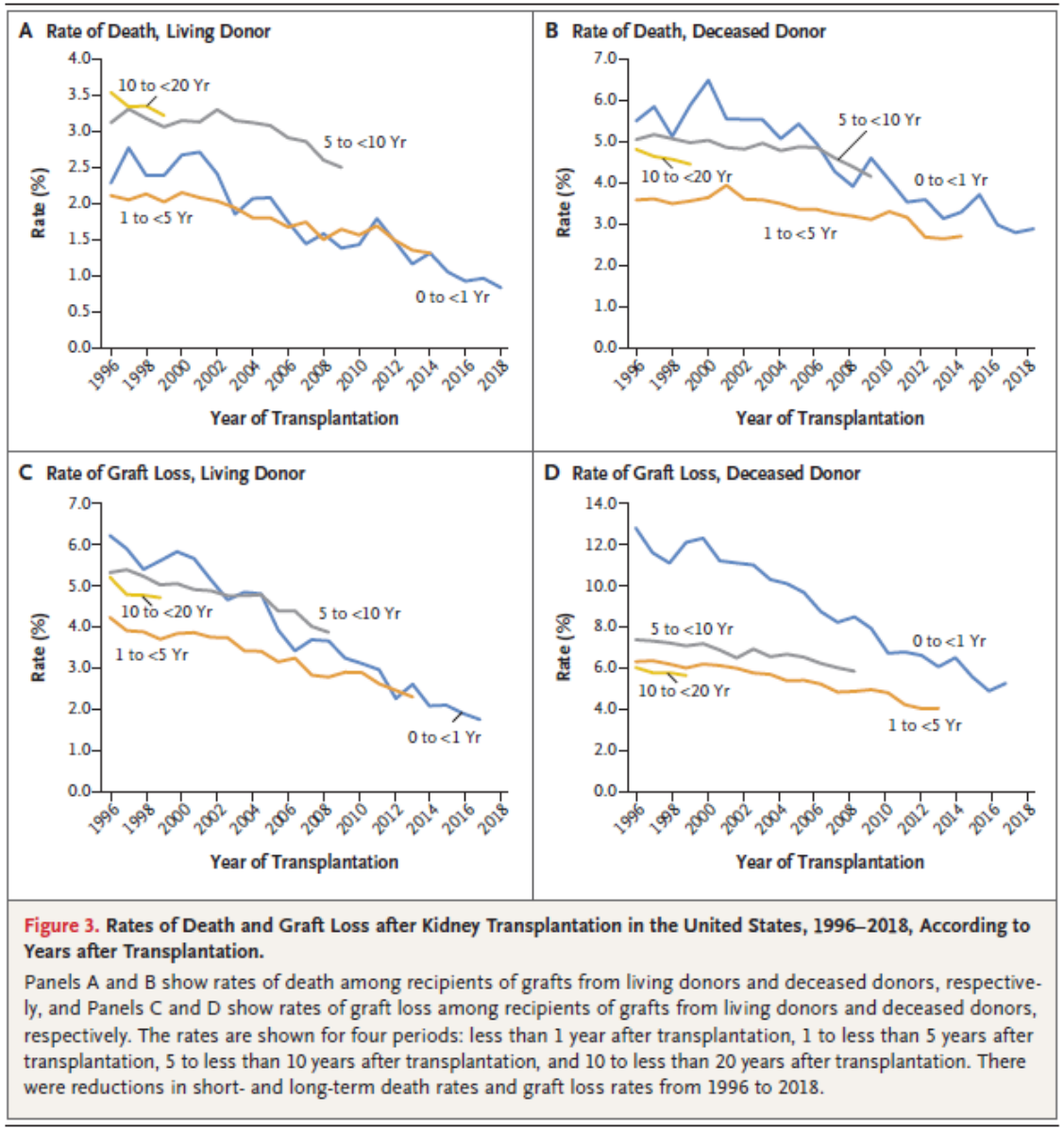


Figure 3. Rates of Death and Graft Loss after Kidney Transplantation in the United States, 1996–2018, According to Years after Transplantation.

Panels A and B show rates of death among recipients of grafts from living donors and deceased donors, respectively, and Panels C and D show rates of graft loss among recipients of grafts from living donors and deceased donors, respectively. The rates are shown for four periods: less than 1 year after transplantation, 1 to less than 5 years after transplantation, 5 to less than 10 years after transplantation, and 10 to less than 20 years after transplantation. There were reductions in short- and long-term death rates and graft loss rates from 1996 to 2018.

Are long-term outcomes after kidney transplantation improving?

YES!

Are we there yet?

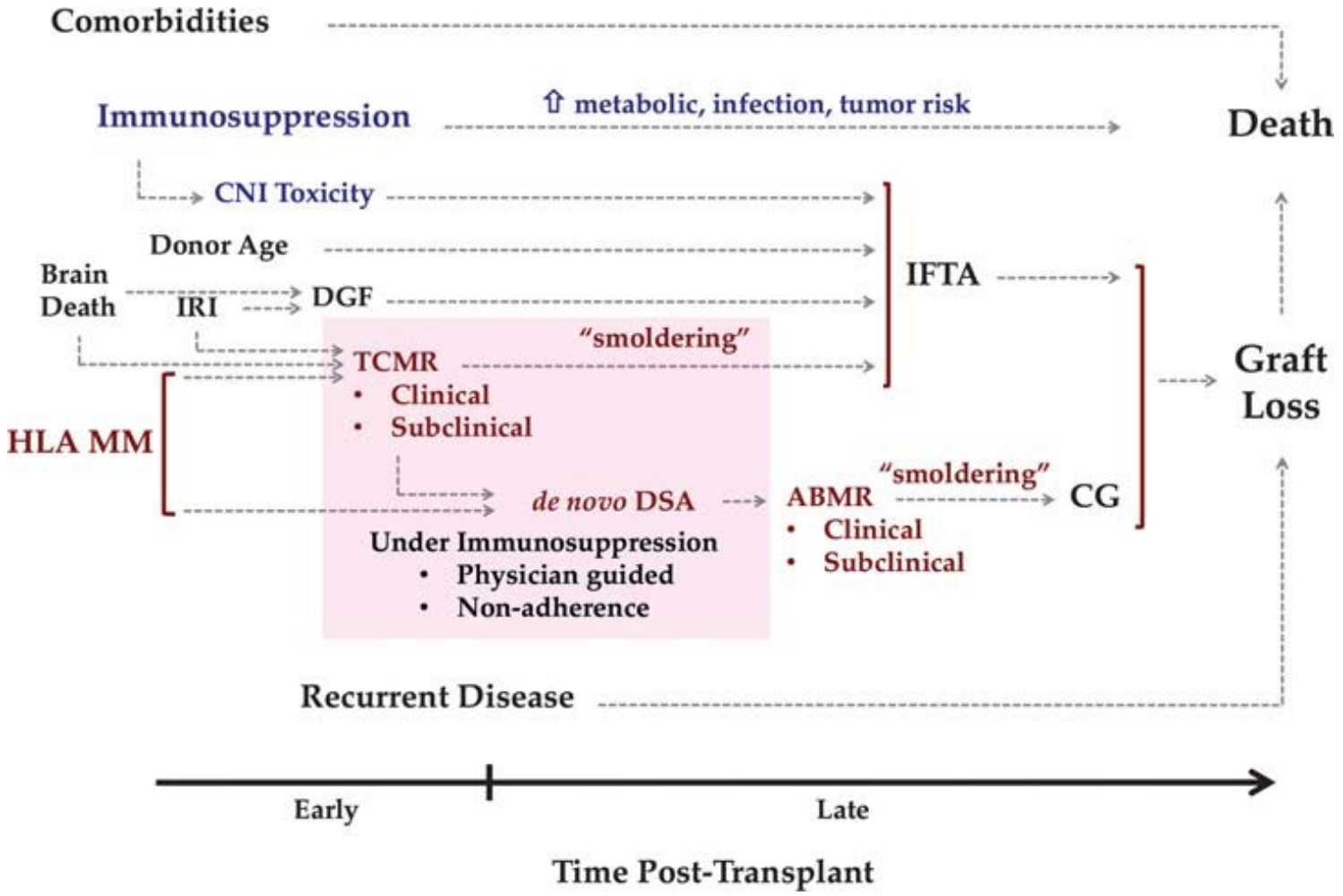
Are long-term outcomes after kidney transplantation improving?

YES!

Are we there yet?

Absolutely NOT!

Complex and multifactorial causes of graft loss



Wiebe and Nickerson, Transplantation 2016

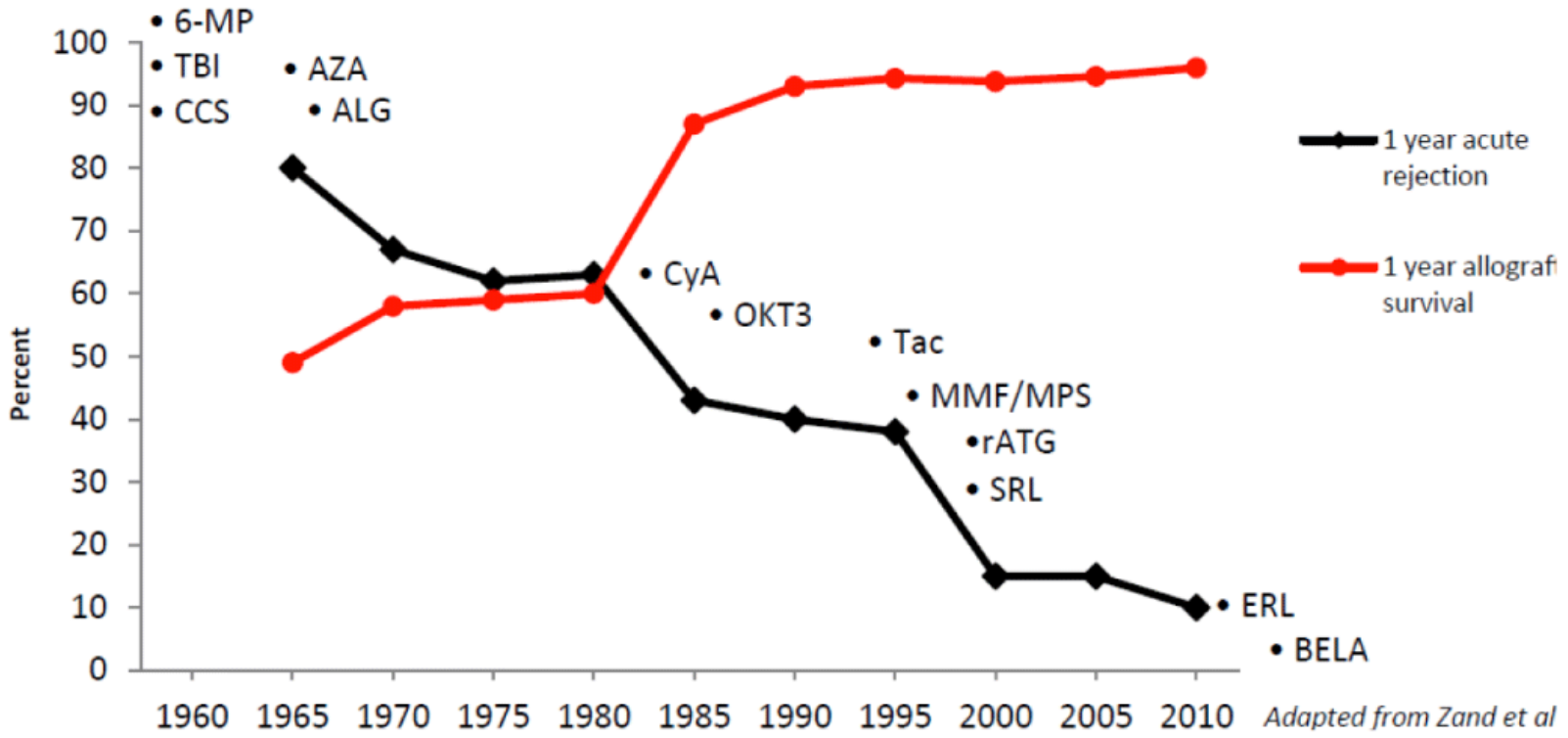
A significant number of kidney transplant recipients still lose their graft and need a re-transplant!!!

TABLE 1 Recipient and donor characteristics by era of transplantation

Factor	Overall (*N* = 331,216)	1995–1999 (*N* = 55,287)	2000–2004 (*N* = 68,910)	2005–2009 (*N* = 77,164)	2010–2013 (*N* = 62,060)	2014–2017 (*N* = 67,795)
Donor type						
Deceased	210,665 (63.6)	37,103 (67.1)	40,130 (58.2)	47,453 (61.5)	39,815 (64.2)	46,164 (68.1)
Living	120,551 (36.4)	18,184 (32.9)	28,780 (41.8)	29,711 (38.5)	22,245 (35.8)	21,631 (31.9)
Previous kidney transplant	40,832 (12.3)	6,555 (11.9)	8,574 (12.4)	9,250 (12.0)	7,629 (12.3)	8,824 (13.0)

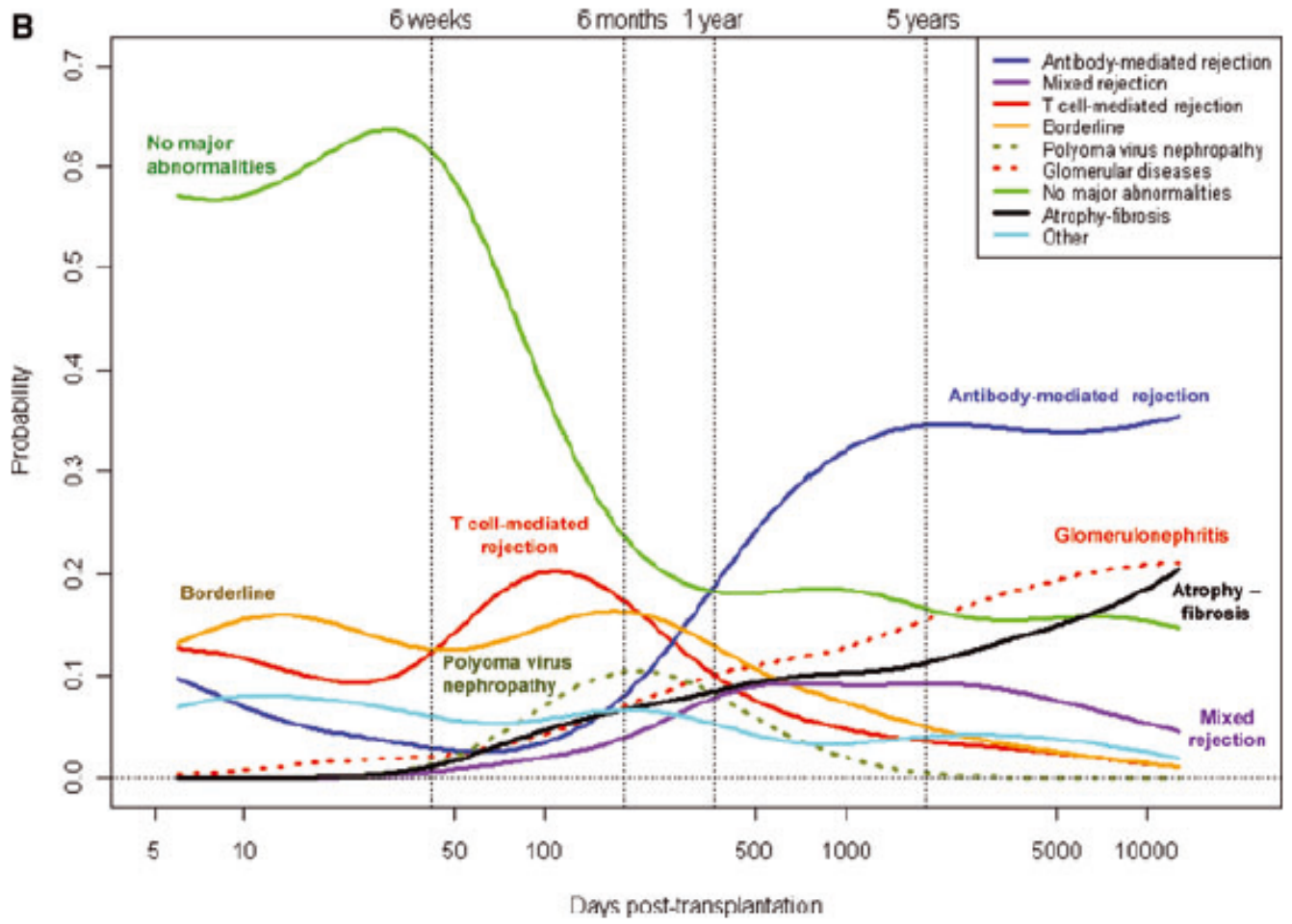
Poggio et al, AJT 2021

Impact of immunosuppressive drugs on graft rejection and outcomes



CCS – corticosteroids; ATG – anti thymocyte globulin; TBI – total body irradiation SRL - sirolimus; 6-MP – 6 mercaptopurine; ERL - everolimus; Aza – azathioprine BELA - belatacept; ALG – anti lymphocyte globulin; CyA – cyclosporine; Tac - tacrolimus; MMF – mycophenolate

Causes of graft injury according to time after transplantation



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Sellares et al, AJT 2012

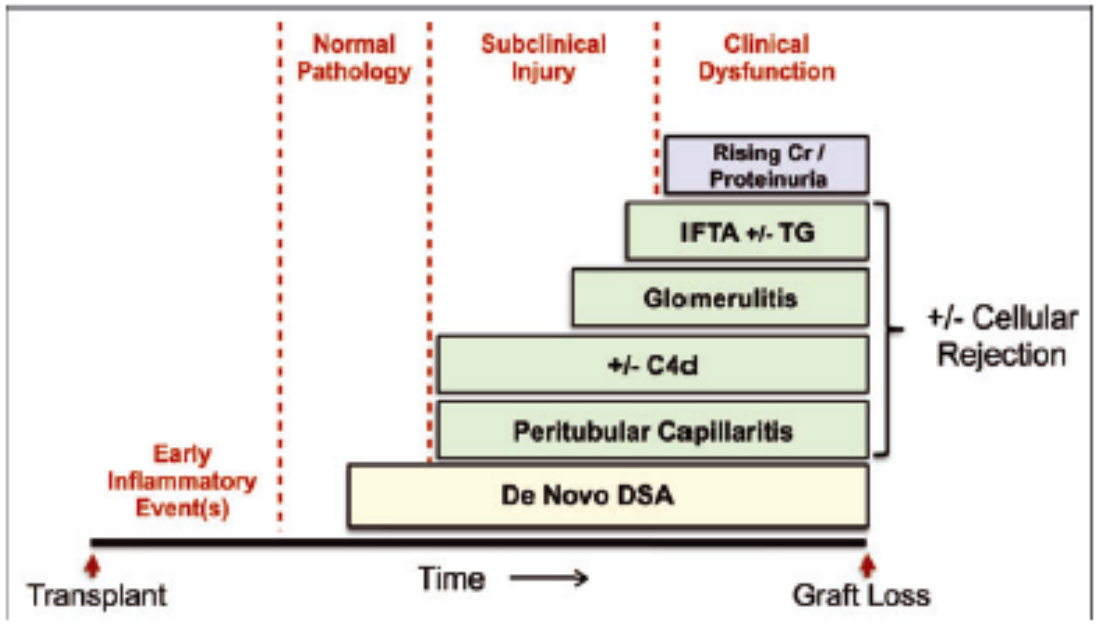
American Journal of Transplantation 2012; 12: 1157–1167
Wiley Periodicals Inc.

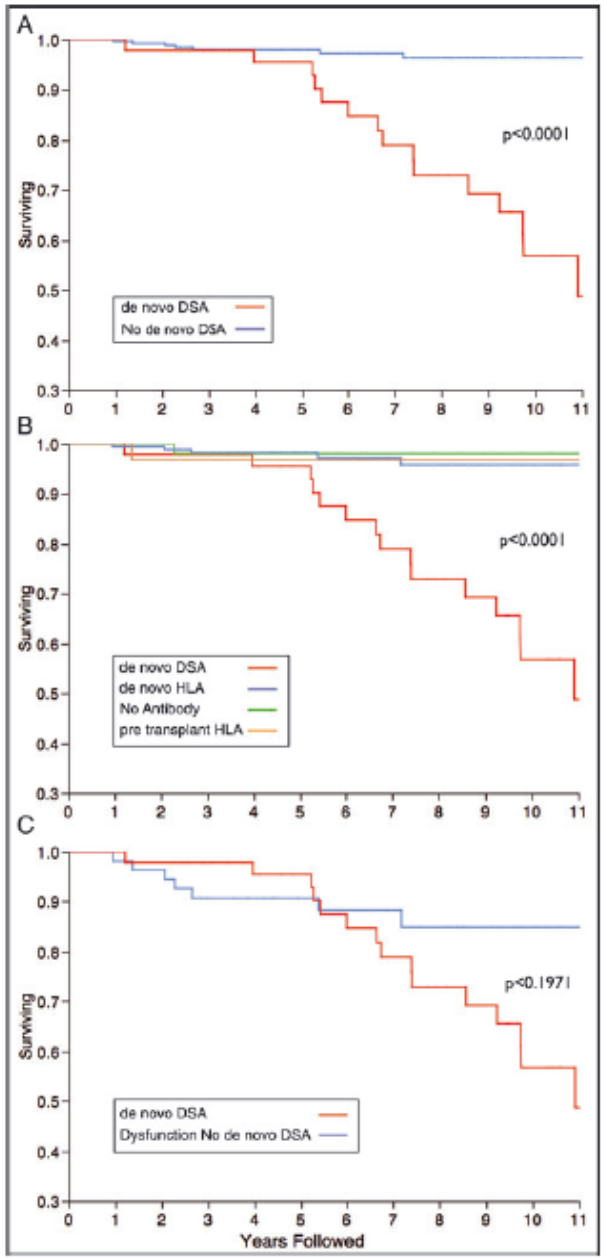
doi: 10.1111/j.1600-6143.2012.04013.x

Evolution and Clinical Pathologic Correlations of *De Novo* Donor-Specific HLA Antibody Post Kidney Transplant

C. Wiebe[a,†], I. W. Gibson[b,c,†], T. D. Blydt-Hansen[d], M. Karpinski[e], J. Ho[e], L. J. Storsley[e], A. Goldberg[d], P. E. Birk[d], D. N. Rush[e] and P. W. Nickerson[a,c,*]

Received 12 October 2011, revised 29 November 2011 and accepted for publication 22 December 2011





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Model of CAN - Multifactorial

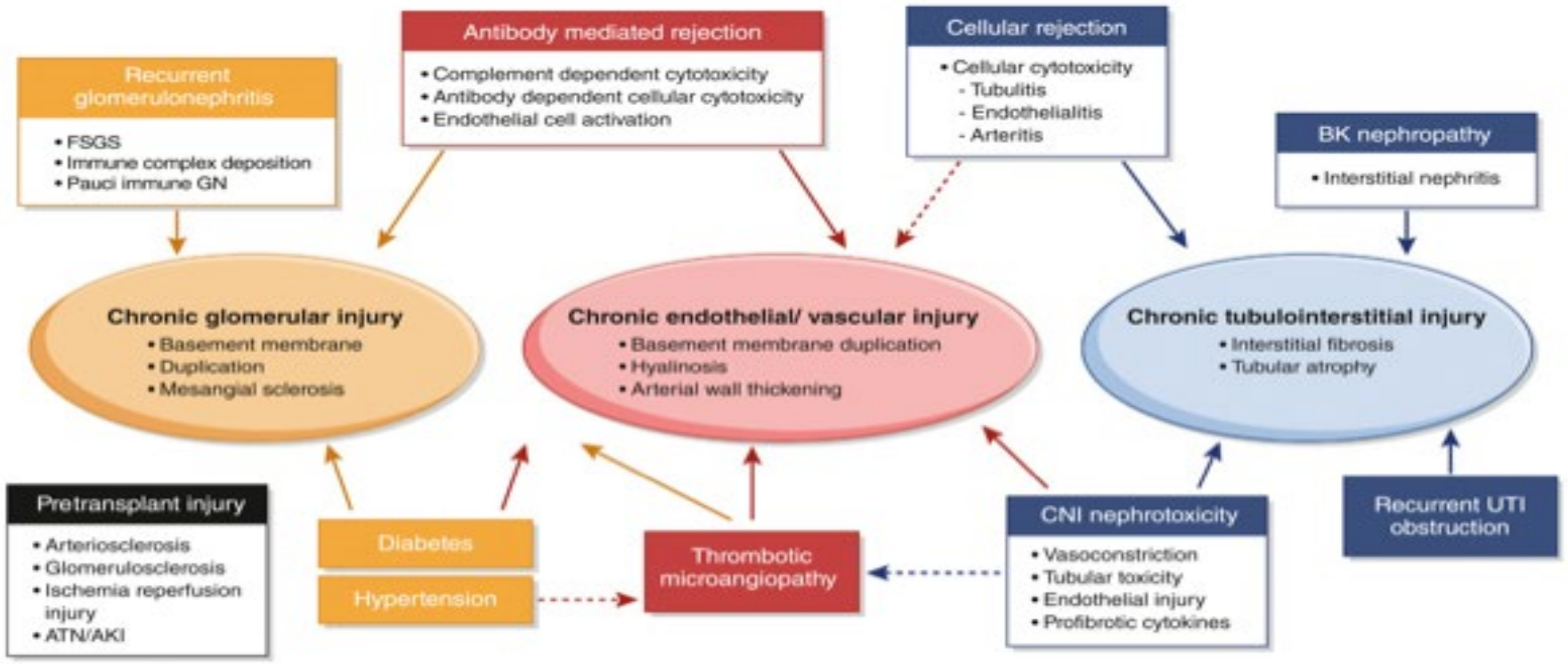

Figure 1. | Schema of the potential sites of injury associated with late allograft failure. There may be "fixed" injury as a consequence of the donation and transplant process ("pretransplant injury"). Three target sites of injury within the kidney are shown, with defined histologic characteristics. The entities that contribute to these sites directly (solid arrows) are shown aligned to their injury at that site. There may also be "crosstalk" of disease processes between compartments (hashed arrows) as well as cumulative injury from multiple entities directly (solid arrows) or indirectly (hashed arrows). ATN, acute tubular necrosis; CNI, calcineurin inhibitor; UTI, urinary tract infection.

Langewisch and Mannon, CJASN 2021

Traditional endpoints are now not sufficient!!!

Success in the prevention of graft rejection within a year of kidney transplantation makes it a challenging endpoint

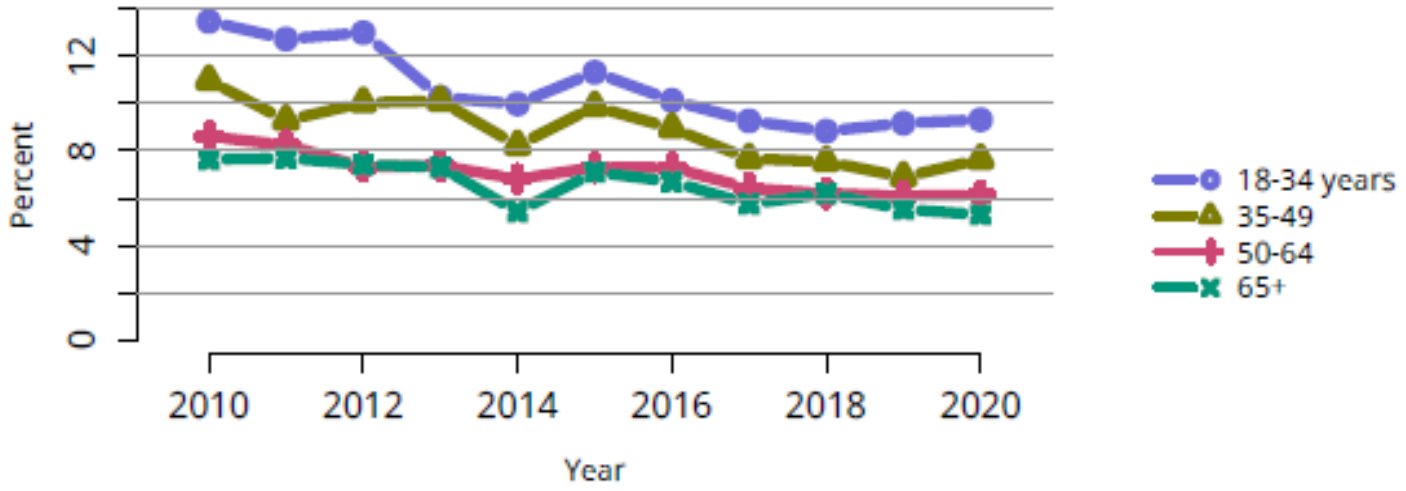

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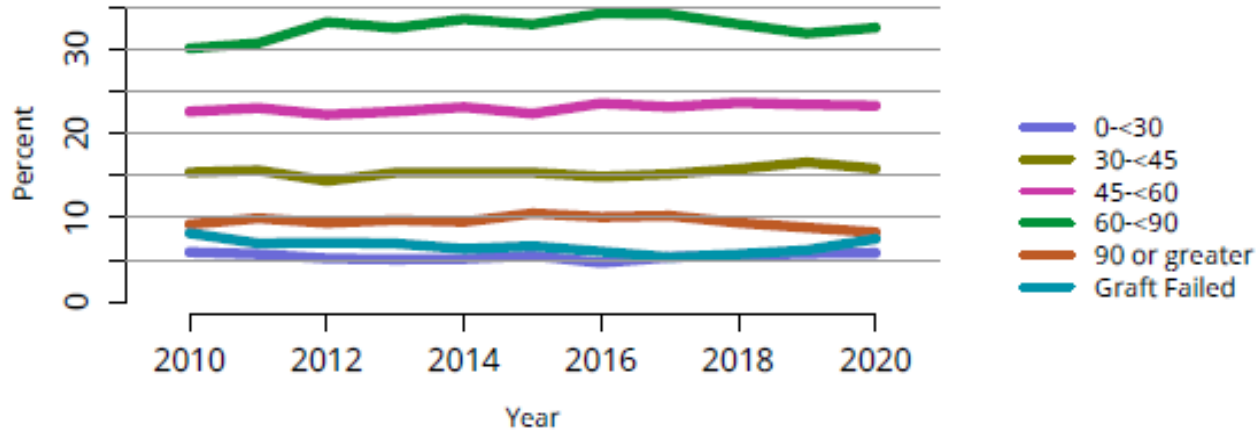
Figure KI 90: Incidence of acute rejection by 1 year posttransplant among adult kidney transplant recipients by age. Only the first reported rejection event is counted. Cumulative incidence is estimated using the Kaplan-Meier method.

OPTN/SRTR 2021 Annual Data Report, Lentine et al, AJT 2023

GFR as a surrogate endpoint – not good enough alone



OPTN/SRTR 2021 Annual Data Report

Figure KI 88: Distribution of eGFR at 12 months posttransplant among adult deceased donor kidney transplant recipients. GFR (mL/min/1.73 m^2) estimated using the Chronic Kidney Disease Epidemiology Collaboration equation, and computed by SRTR for patients alive with graft function at 12 months post-transplant.

OPTN/SRTR 2021 Annual Data Report, Lentine et al, AJT 2023

What may account for the improvement of graft and patient survival?

- No new immunosuppressive drugs since more than a decade ago
- None of the drugs in the market address antibody mediated rejection
- However…
  - Many new drugs to prevent CV disease
  - Many new drugs to control/cure cancer
  - Many new antibiotics/anti-viral drugs
  - And even now, many novel drugs to treat GN!!!

What do we need?

- New immunosuppressive drugs directed at conditions that manifest late in the transplant process but take years to evolve
- Rethink our endpoints and find new surrogates/tools that project the expected outcomes rather than wait for the outcome to occur
- These new tools will likely incorporate several surrogates as not a single one will be enough

Conclusions

- Short-term outcomes such as rejection within a year of transplant are excellent and basically “maximized” as an endpoint for clinical trials
- Current short-term outcomes do not address late graft loss
- Long-term outcomes are improving, but likely due to advance in the overall care of patients in general
- There is a need for surrogate outcomes to facilitate novel drug development directed at late immune mediated graft loss and related conditions

Patients, Policy Leaders & Science:
The Forces Driving America's Demand for Change in Transplant Drugs

Paul T. Conway

Chair, Policy & Global Affairs

3 Myths of Transplant Drugs

1.) There are no unmet patient needs.

2.) The status quo is good enough.

3.) Scientific & regulatory decisions are too complicated for patients to grasp; and they occur separately from patients and policies set by the President and Congress.

FDA: Patient Voice/Unmet Needs

"I'm pleased to be with you today to help kick of this meeting addressing the most important areas of focus at the FDA – how we incorporate the patient voice in support of the development of new products to treat disease."

"….the FDA as a whole is committed to better understand and advance diverse patient perspectives, preferences and unmet needs to inform our work."

"One of the most important aspects of our mission to protect and promote public health involves the responsibility to consider, to the extent we can, the needs and characteristics of all people and populations in the policies we advance, the science we support, and the workplace in which we operate."

FDA Commissioner Dr. Robert M. Califf
Remarks to the Patient Engagement Advisory Committee (PEAC)
September, 2023

FDA: Listening to Patient Needs

2023: “Endpoints and Trial Designs to Advance Drug Development in Kidney Transplantation”

2018: “Evidence Based Treatment Decisions: The Right Dose and Regimen - the Right Patient/Individualized Treatment.”

2017: “Antibody Mediated Rejection in Kidney Transplantation”

2016: “Patient Focused Drug Development in Patients Who Have Received an Organ Transplant”

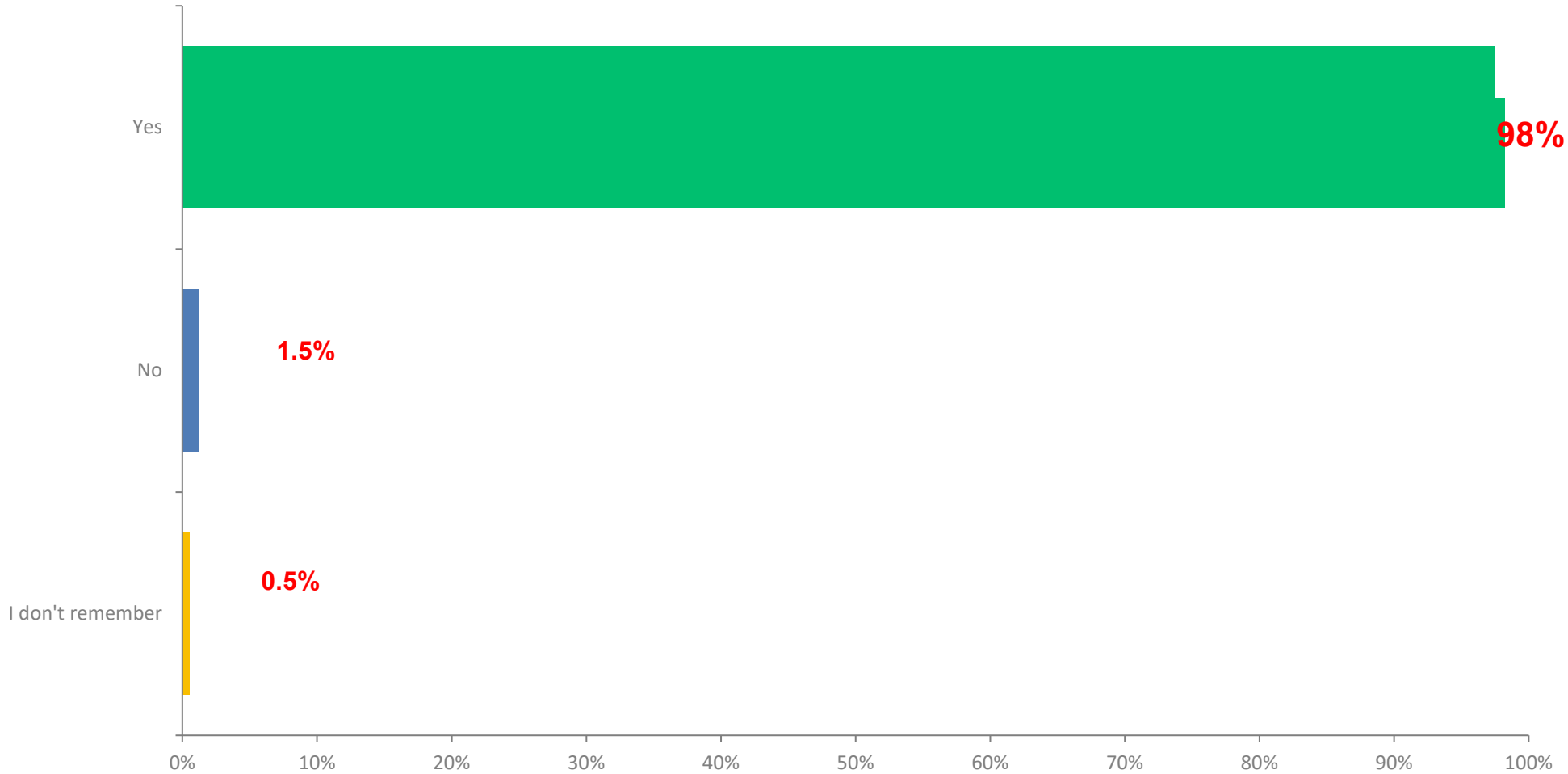
2015: “Surrogate Endpoints for Clinical Trials in Kidney Transplantation”

Survey Results:
Future of Transplant Drug Innovation

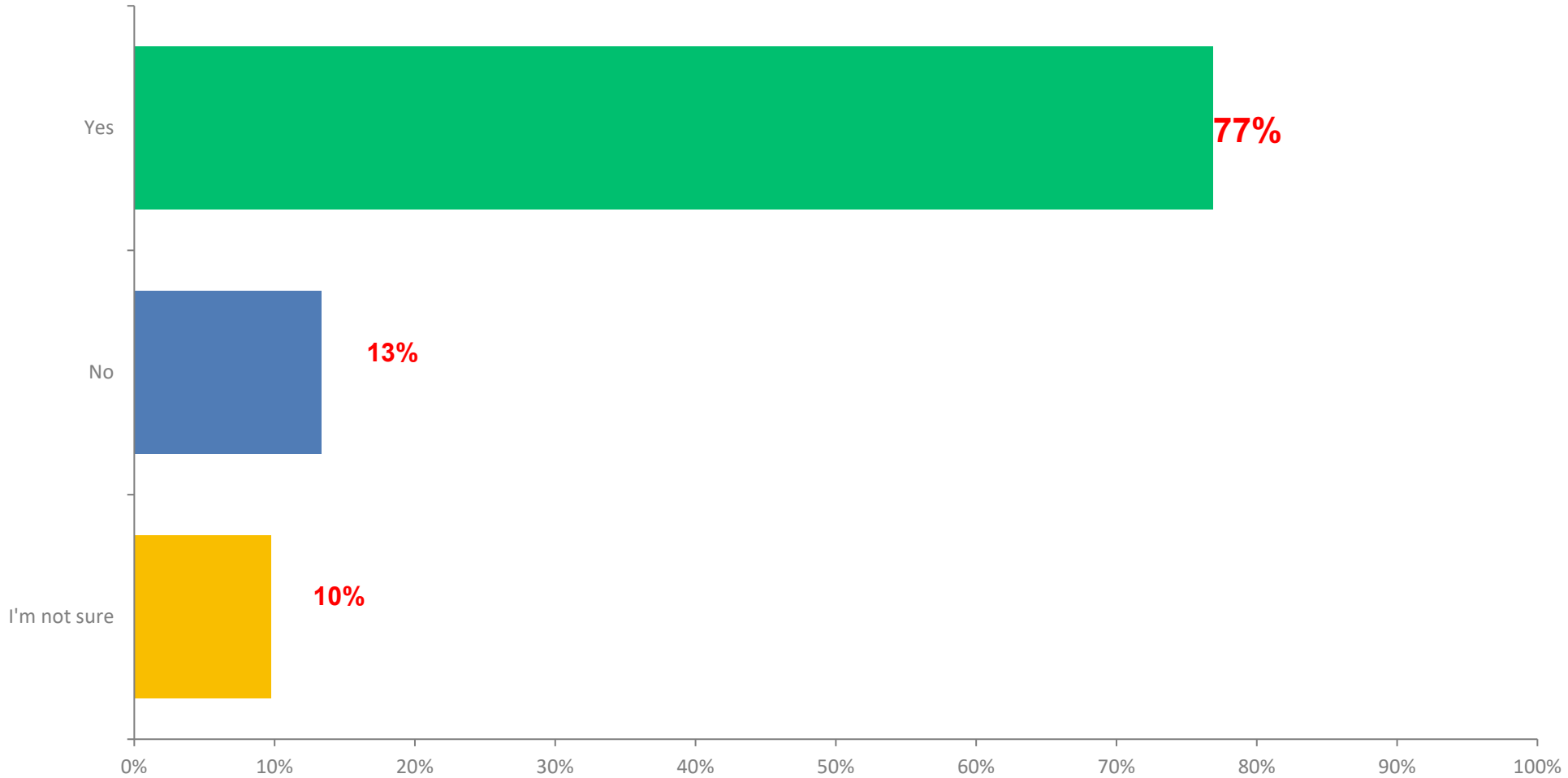
October, 2023 - 1,215 Participants

Center for Patient Research and Education

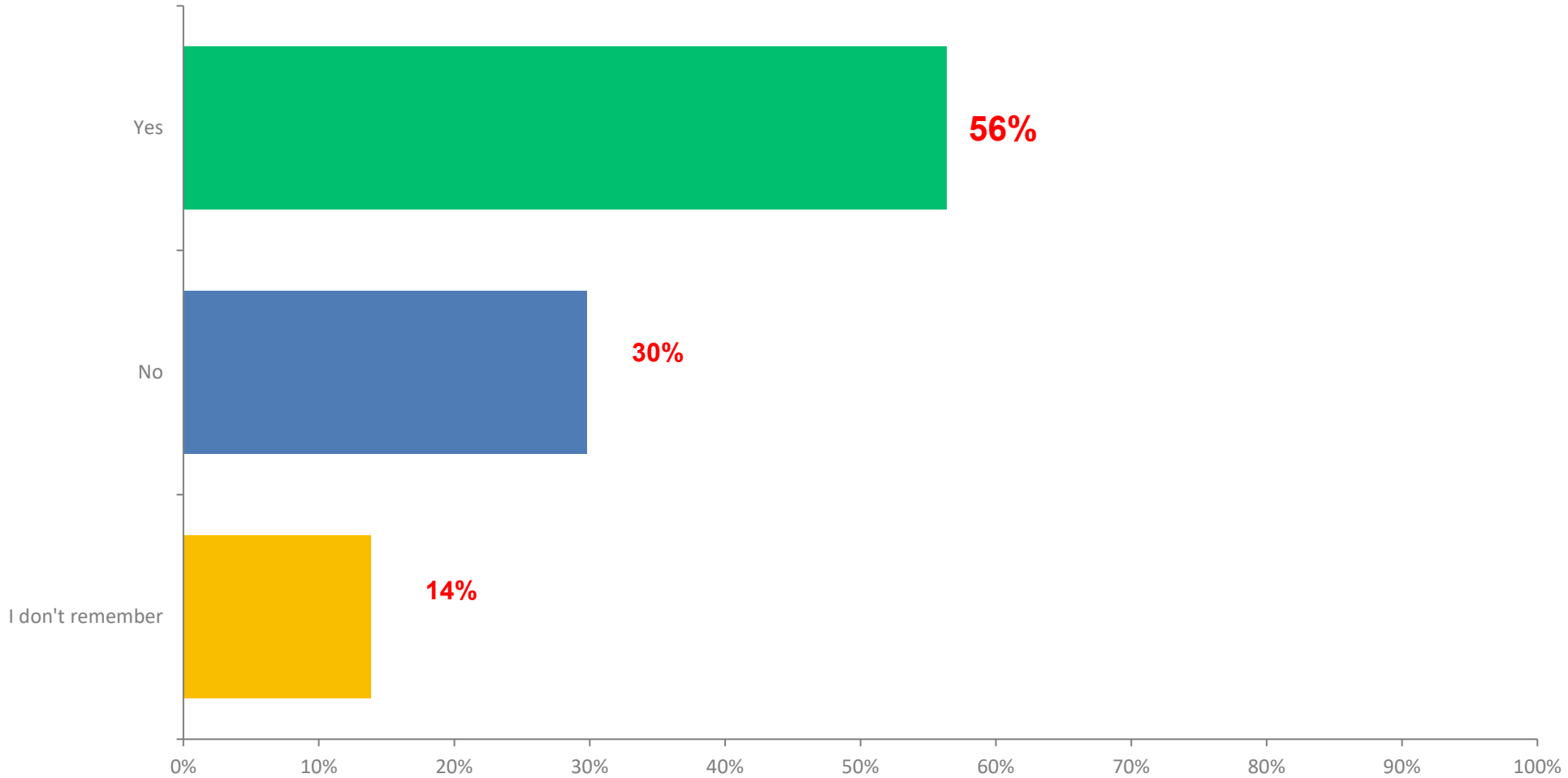
Q: When you first thought about getting a kidney transplant, did you think of it as a treatment that was better, in terms of your health and renewed capacity to do what you wanted to do in life, than dialysis?



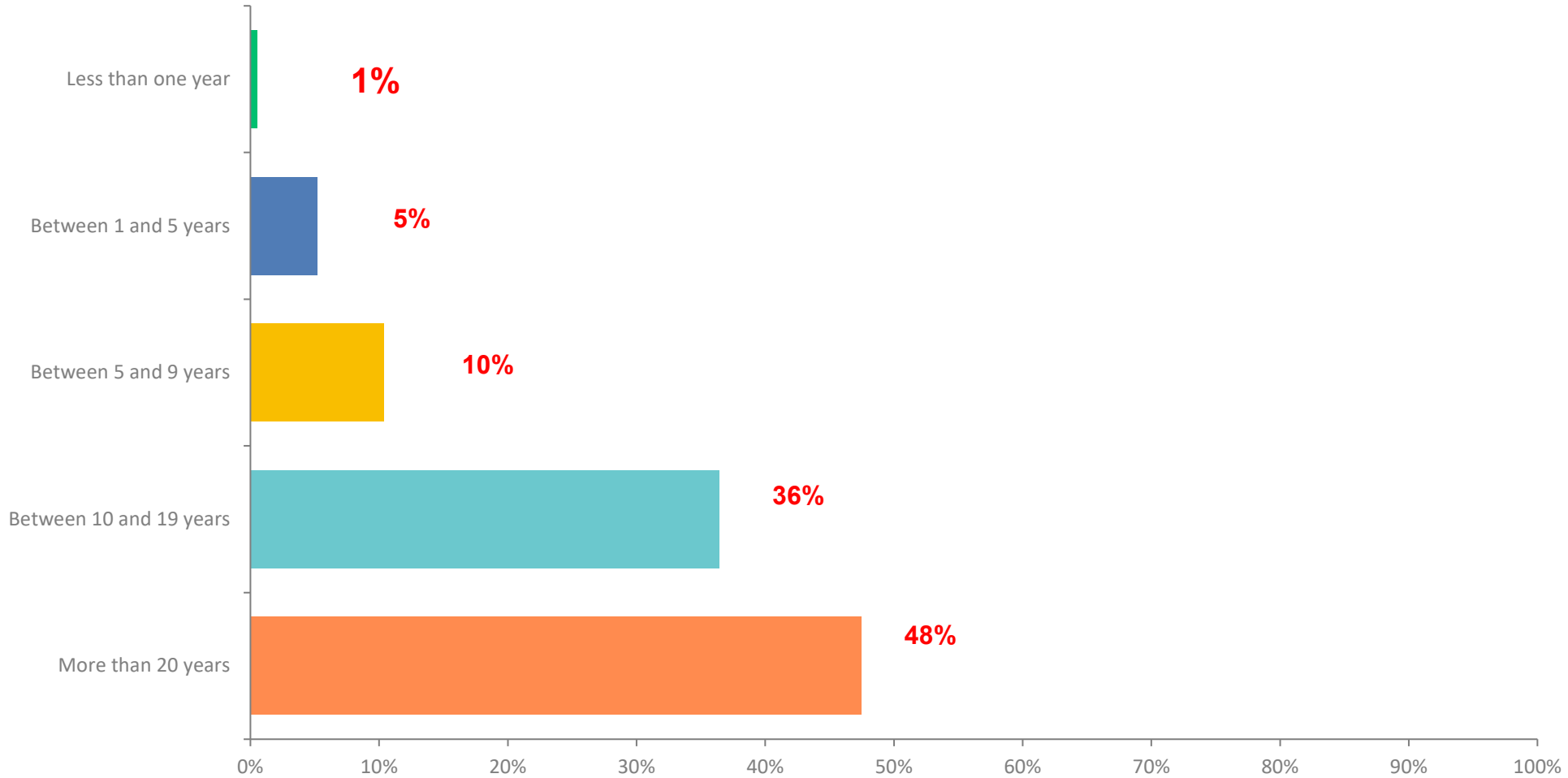
Q: As a transplant recipient, would you want to know how long a kidney transplant might last before going ahead with a decision to get a transplant?



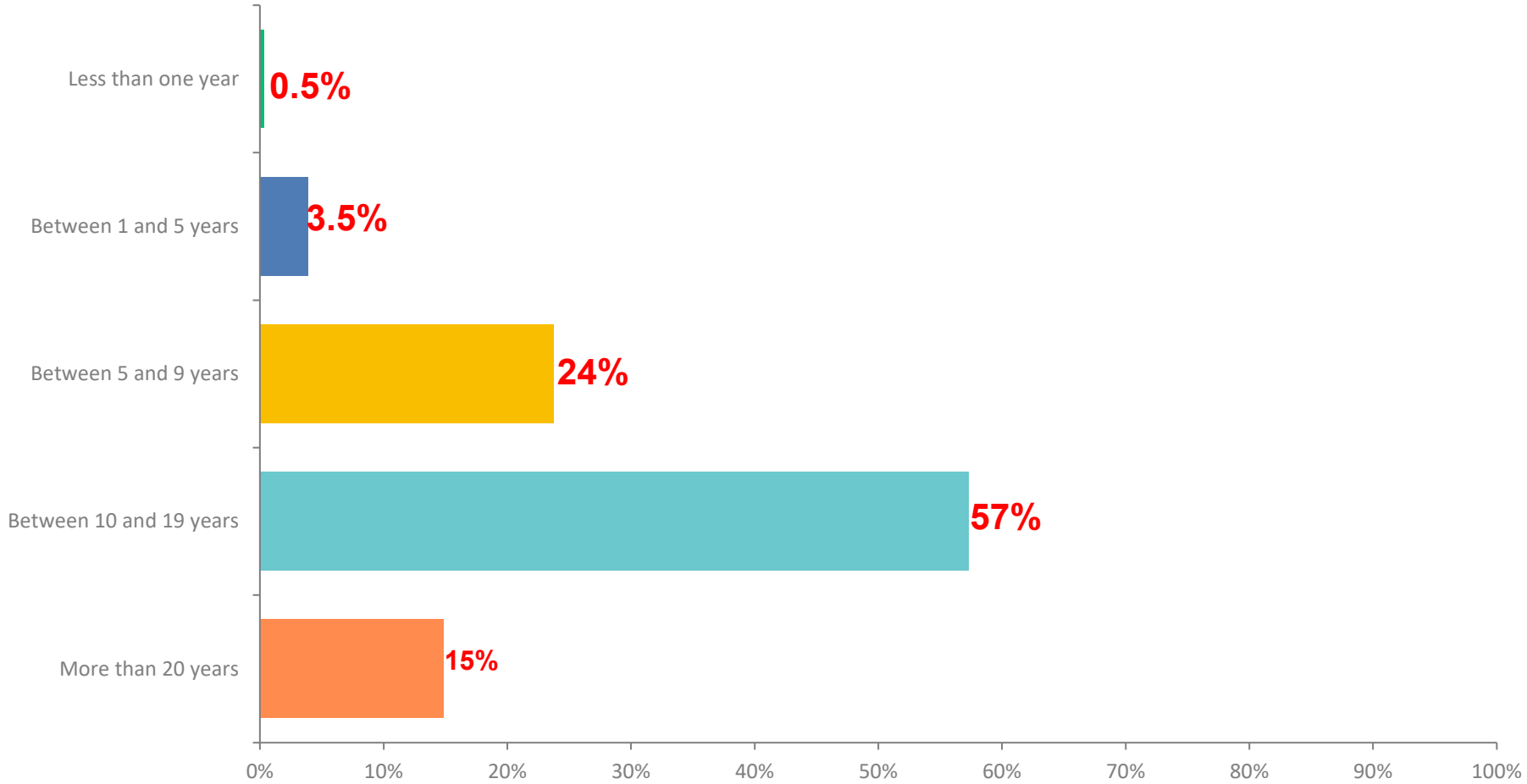
Q: When you first discussed getting a kidney transplant with a family member, friend or loved one, did you discuss how long a kidney transplant might last?



Q: As a transplant recipient, how long do you think a kidney transplant should last to make the surgery worth it for yourself and for the living donor who provides the gift of life?



Q: How long did your medical team say your transplanted kidney might last if you took your transplant medications exactly as prescribed, without missing any doses?



Patients are Top Influencers

40% of the Top 10 All Time pieces published by *Clinical Journal of the American Society of Nephrology* (CJASN) were written by kidney patients *in the past 5 years*.

CJASN pieces typically receive a mean Altmetric Attention Score of 30.8. The current #1 All Time CJASN piece scored higher than 99% of its peers.

It is #1 of 3,953 tracked CJASN pieces of similar age and #22,713 of the 24,631,014 tracked articles of a similar age across *all peer-reviewed medical journals.*

"12 Tips to Nephrology Teams Supporting Patients with Advanced Kidney Disease: An Advocate's Dozen," 2018, Edward V. Hickey, III (Current AAKP President):

> "Leave nobody behind. Never underestimate the innate human desire to live and prevail, and remember your responsibility to make certain your patients are not set adrift in the care system or left to fully coordinate the burden of their own care."

3 Realities of Transplant Survival

1.) Longer transplant survival is the priority of the U.S. Government & American people.

2.) Longer transplant survival matters to patients and donors, families, taxpayers and industry.

3.) Kidney disease is both a U.S. workforce *and* healthcare issue.

U.S. Transplant Policy Evolved

Presidents & Congress responded to patients, donors & allies:

2023: President Joe Biden signs bipartisan U.S. Congressional bill "The Securing the U.S. Organ Procurement and Transplantation Network Act" - greater transparency, accountability & innovation to increase transplantation and reducing waiting list.

2020: President Donald Trump signs bipartisan U.S. Congressional budget act - lifetime immunosuppressive drugs coverage for transplants secured after 20+ year fight.

2019: President Donald Trump signs bipartisan *Executive Order on Advancing American Kidney Health*, prioritizes transplant over dialysis, increases focus on home dialysis & artificial organs

2018-2019: U.S. Secretary of HHS Alex Azar engages kidney patients, transplant recipients and donors to learn widespread unmet patient needs and demand innovation – including new transplant drugs.

U.S. Transplant Policy Evolved

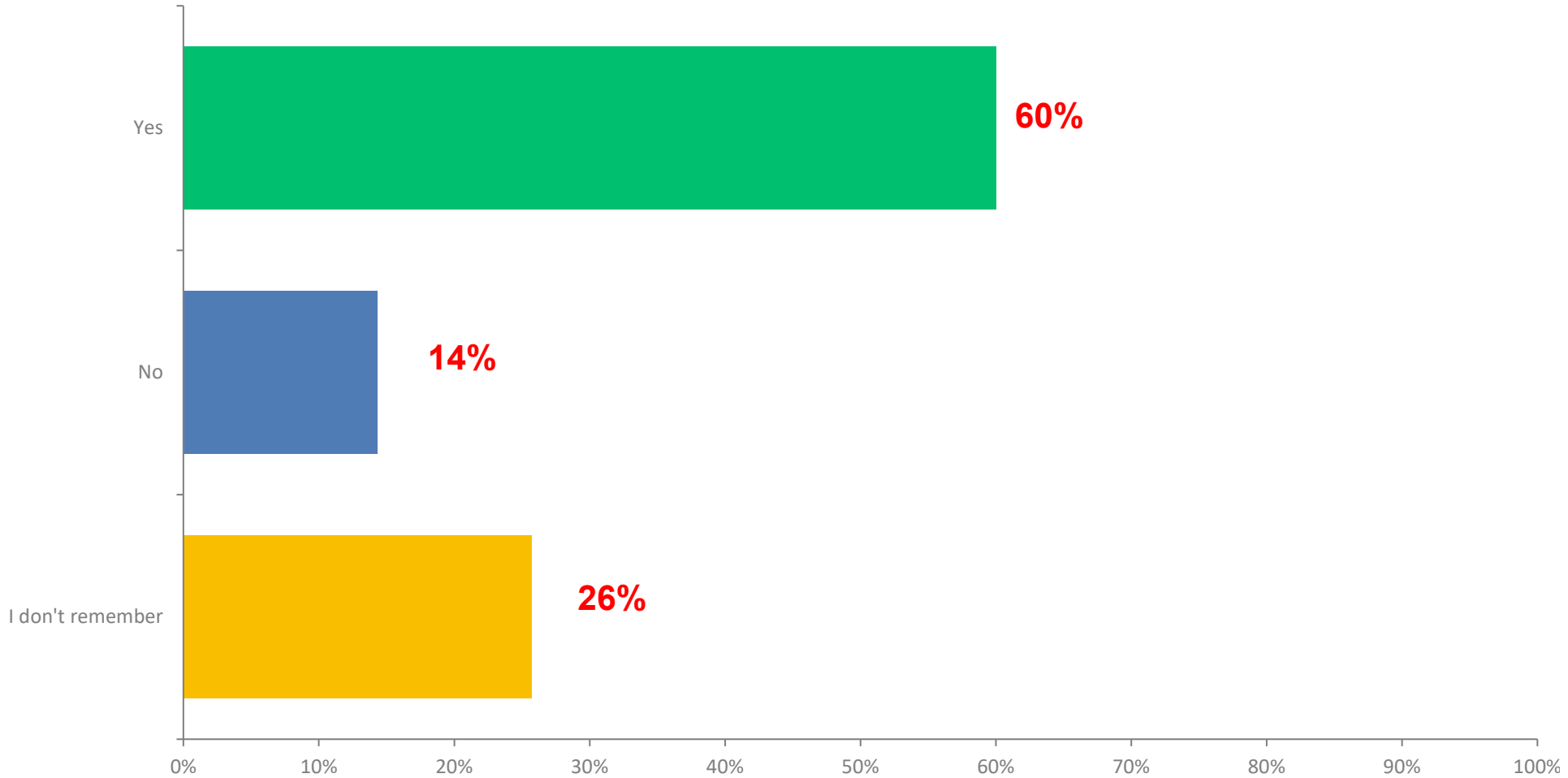
Presidents & Congress responded to patients, donors & allies:

2018: U.S. Secretary of Labor Alexander Acosta extends the Family Medical Leave Act (FMLA) to living organ donors to increase donation and reduce the waiting list – with bipartisan support.

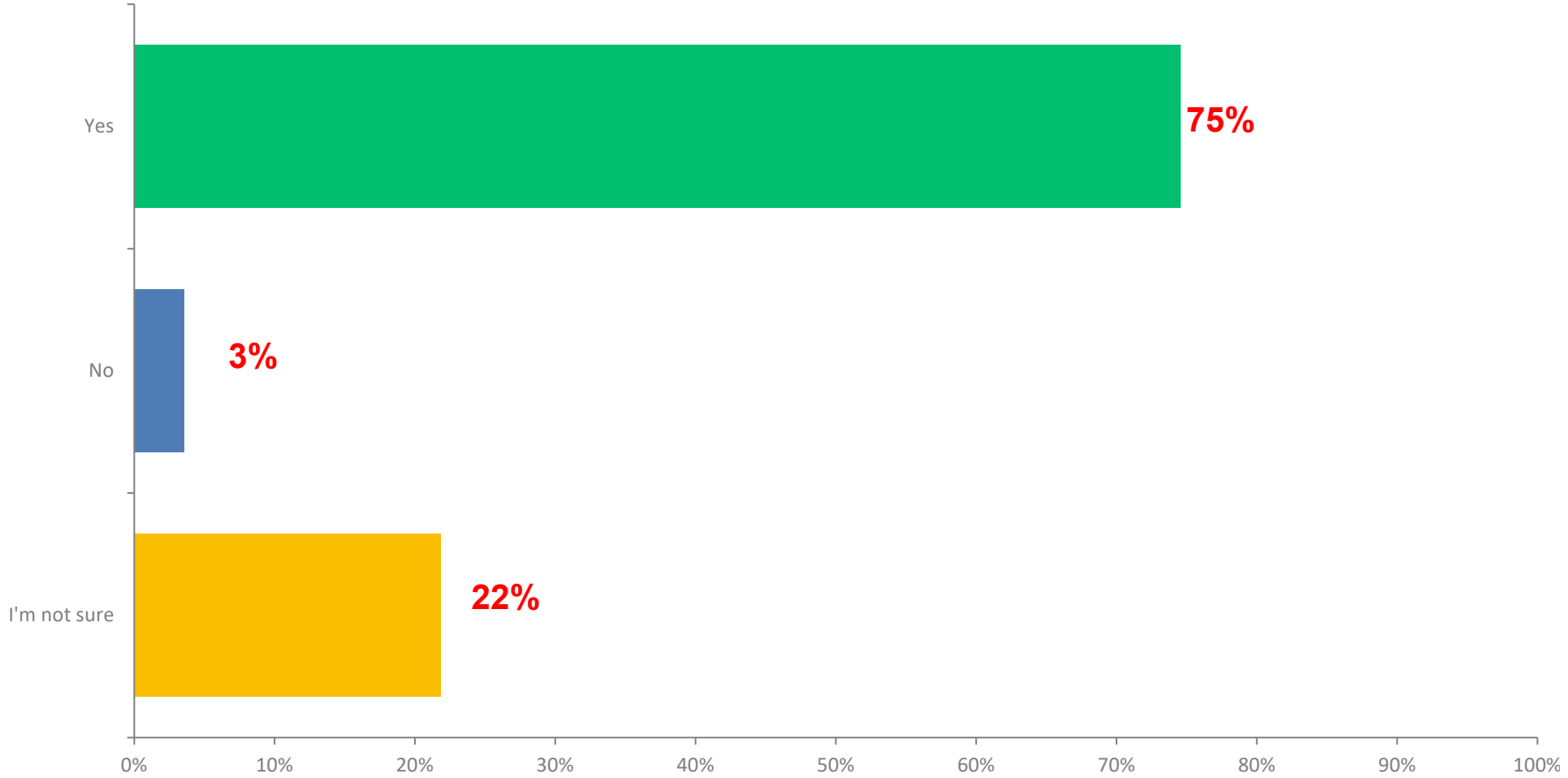
2016: President Barack Obama & The White House Office of Science & Technology host bipartisan *White House Organ Summit*, focusing on increasing organ donation, reducing waiting list and transplant survival.

2013: President Barack Obama signs bipartisan HOPE (HIV Organ Policy Equity) bill to address long-overdue inequities in transplantation for HIV positive patients.

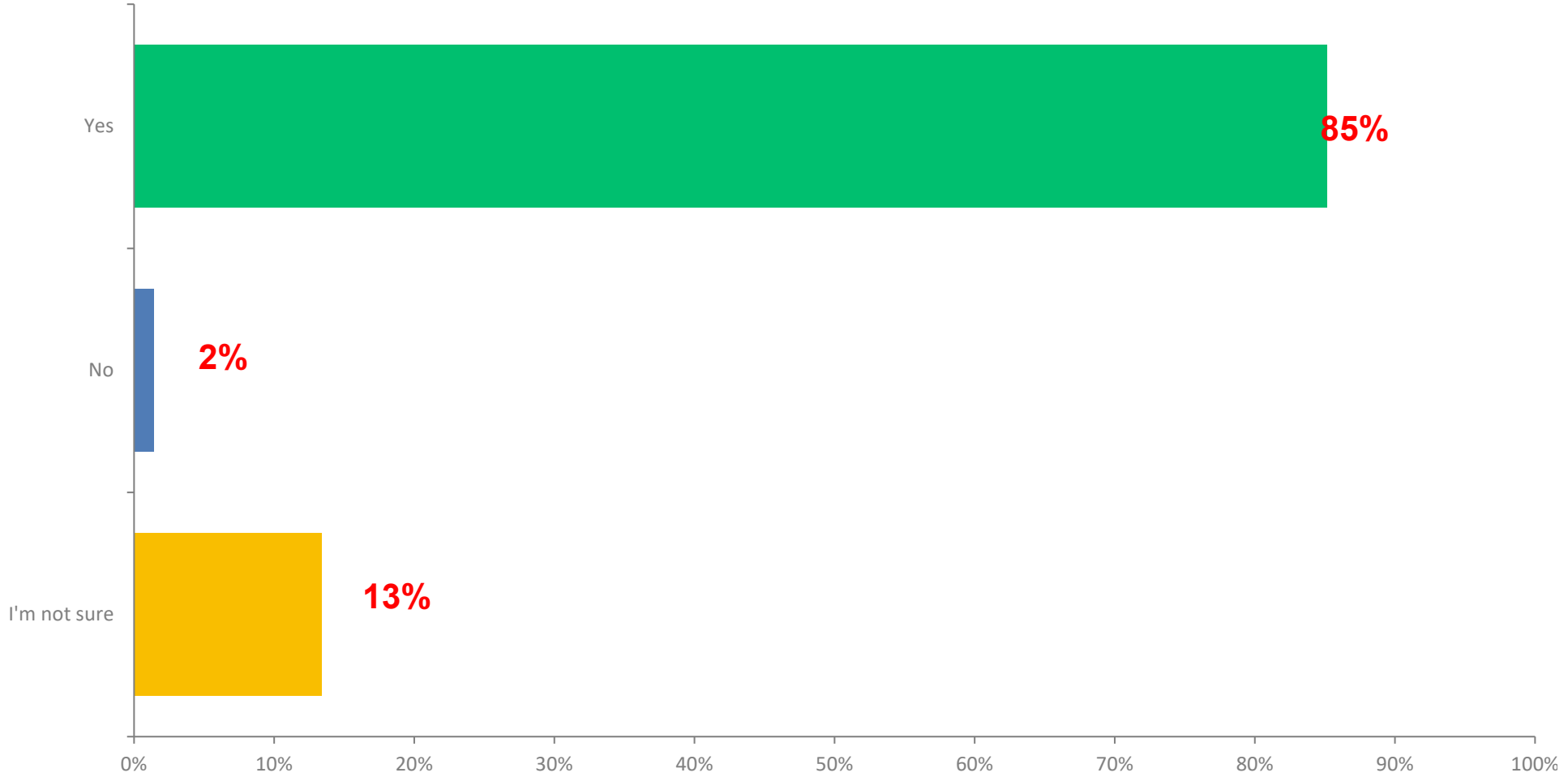
Q: When you first discussed donating a kidney as a potential treatment for a patient with kidney failure, was your medical team able to provide you with a general idea of how long your donated kidney might last for the transplant recipient?



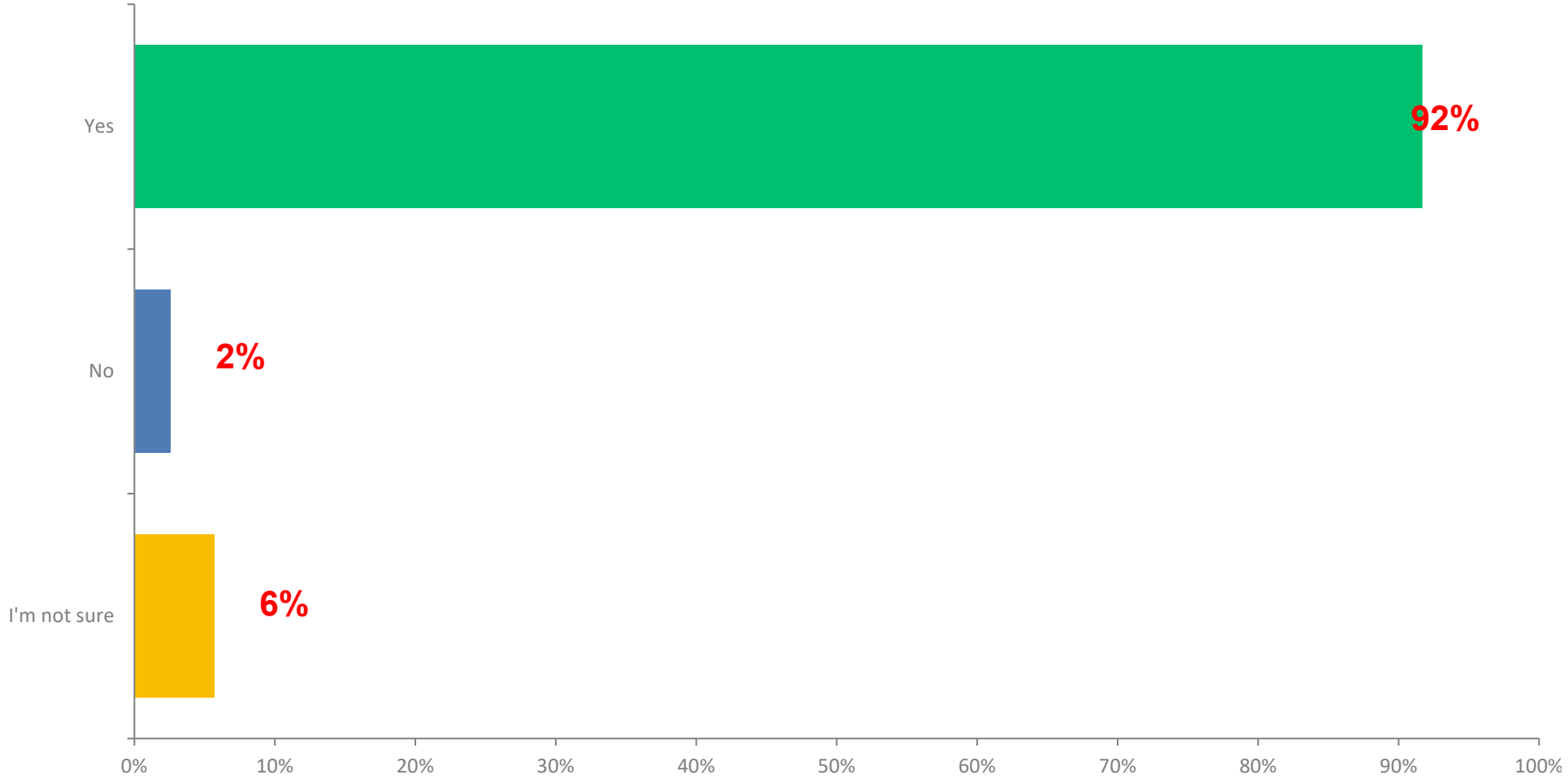
Q: If the U.S. Food and Drug Administration adopted a new primary or co-primary clinical endpoint that I could lead to innovations in transplant medicines that are better than current treatments and can improve the safety and prolong the survival of the transplanted organ, do you think living organ donors (family, loved ones, friend or anonymous people) would be more likely to donate a kidney to someone with kidney failure or on dialysis?



Q: If the U.S. Food and Drug Administration adopted a new primary or co-primary clinical endpoint that could lead to innovations in transplant medicines that are better than current treatments and can improve the safety and prolong the survival of the transplanted organ, do you think more individuals with kidney failure or on dialysis would consider getting a kidney transplant?



Q: If the U.S. Food and Drug Administration fails to adopt a new primary or co-primary clinical endpoint for the next generation of transplant drugs, private companies interested in developing new transplant therapies may abandon the kidney drug space completely, since there would be little incentive to create new therapies. For kidney patients and organ donors, that means it might take another 10 years or more before a new transplant drug is developed. Do you think that would be a setback for kidney transplantation?



True Impact of Kidney Disease

"These patients understood that kidney disease was not simply a medical issue. They saw it as both an economic and workforce issue. For many, their lives were a testament to the fact that kidney disease denies people the opportunity to pursue part-time or full-time work, the ability to care for their families and the chance to build a secure retirement."

"Earlier disease detection, faster interventions, improved dialysis technologies, greater opportunity for organ transplantation and new transplant drugs, and artificial and regenerative organs are now the future of kidney medicine."

The Honorable Alex Azar
Former U.S. Secretary of Health and Human Services
Remarks before the Global Summit on Kidney Disease Innovations
June, 2023

3 Questions FDA Must Answer

1.) Does today's meeting recognize ***known unmet*** patient and donor needs?

2.) Does today's meeting ***defend or excuse*** the status quo in transplant drugs?

3.) Does today's discussion ***advance*** pathways to spur innovation in transplant drugs ***within this decade***?

SESSION 1: EFFICACY ENDPOINTS FOR KIDNEY TRANSPLANT PROPHYLAXIS OF REJECTION TRIALS

FDA U.S. FOOD & DRUG ADMINISTRATION

CURRENT STATE OF PRIMARY ENDPOINTS IN KIDNEY TRANSPLANTATION TRIALS

Endpoints and Trial Designs to Advance Drug Development in Kidney Transplantation
Public Workshop
Nov. 9, 2023
Silver Spring, MD

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Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.

All information presented is publicly available.

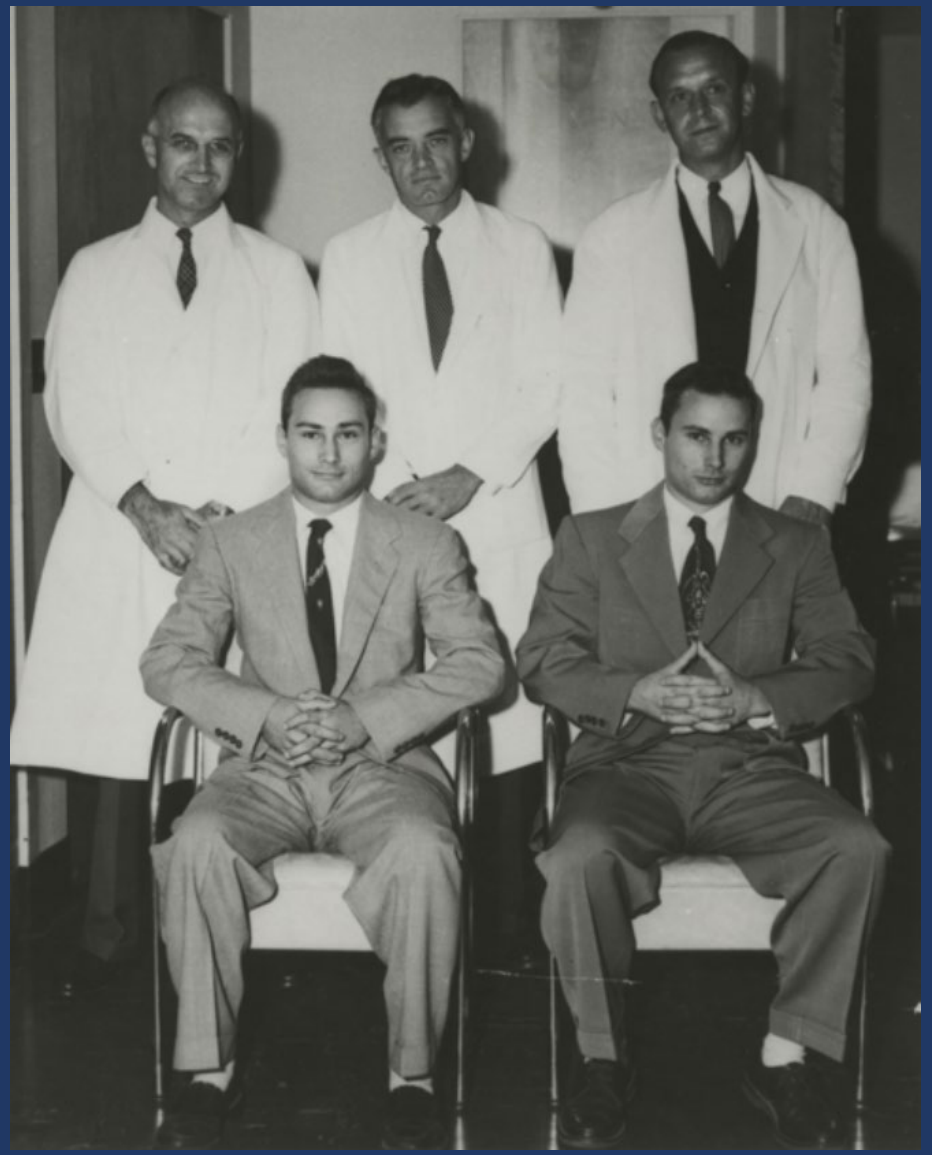
Disclosure

I have no financial relationship to disclose.

Brief History: How Progress was Made

1954

First successful kidney transplantation between monozygotic twins with long term graft survival (No immunosuppression needed)



SUBSEQUENT OUTCOMES "WITH" IMMUNOSUPPRESSION REQUIRING TRANSPLANTS

1963 HUMAN KIDNEY TRANSPLANT CONFERENCE IN DC

Bleak Picture:

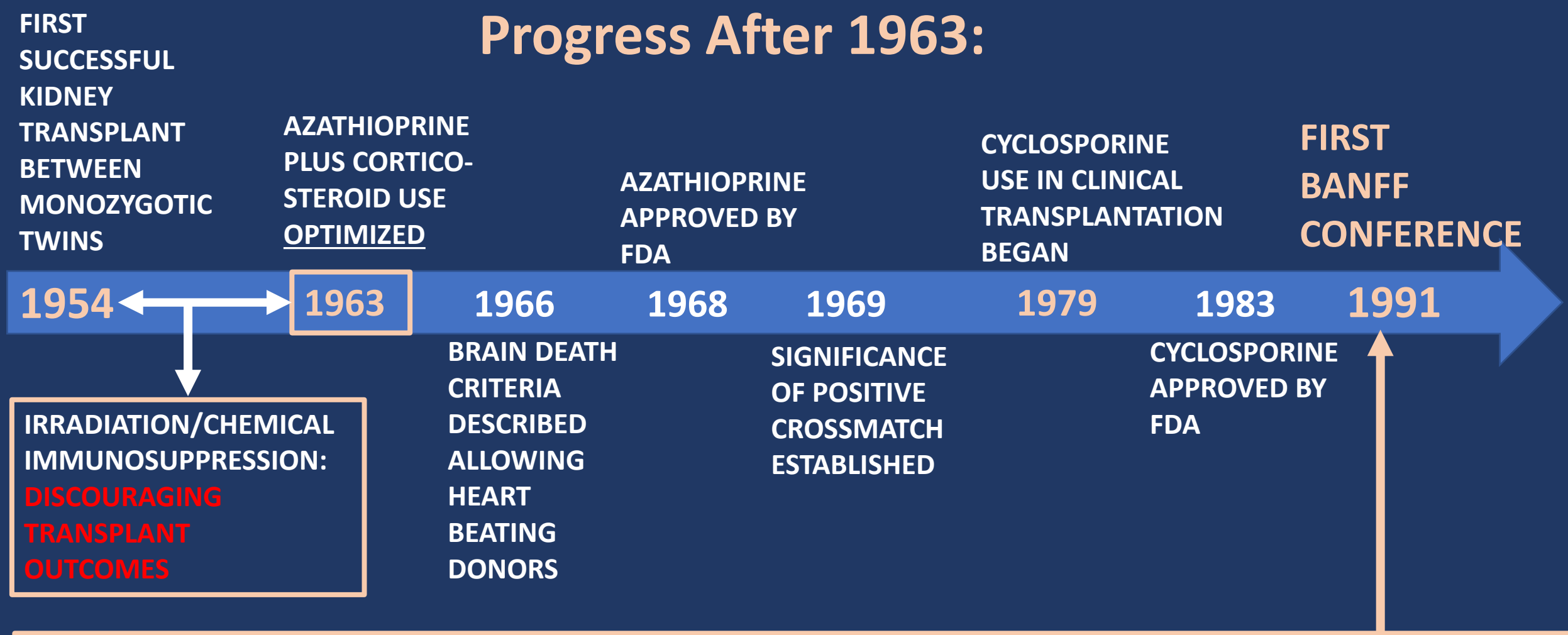
Out of 244 kidney transplantations performed until Sept. 1963, (majority from living donors) only 11 recipients had graft function beyond 12 months (*excluding 28 monozygotic twin transplants*)*

Overimmunosuppression was incriminated as the main cause of deaths

****Transplantation 2(1):p 147 (Table 1)***

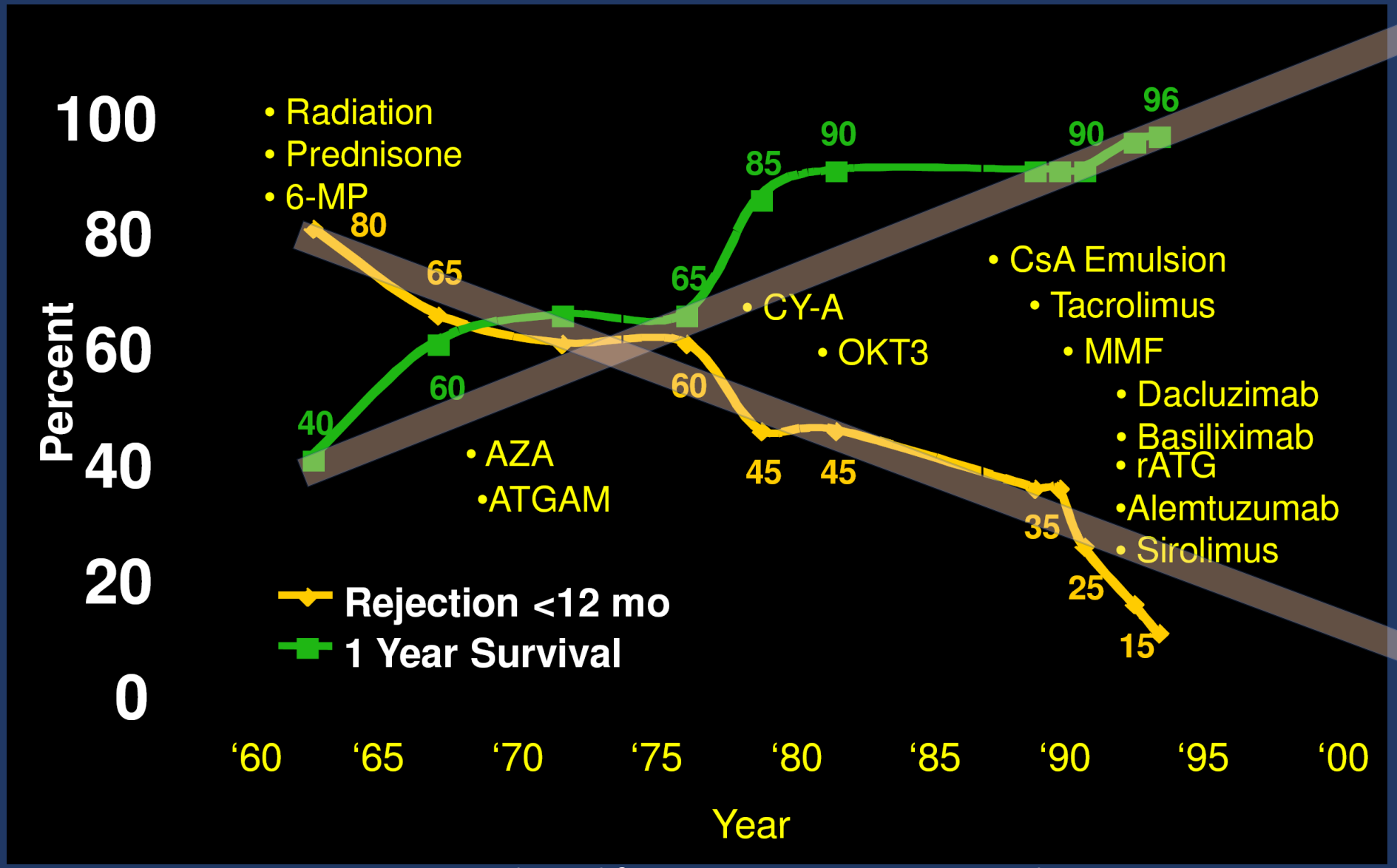
LANDMARKS IN KIDNEY TRANSPLANTATION HISTORY

Progress After 1963:



BANFF CONF. OBJECTIVE: STANDARDIZATION OF HISTOPATHOLOGIC CRITERIA TO GUIDE THERAPY AND TO ESTABLISH AN OBJECTIVE ENDPOINT IN CLINICAL TRIALS (*Solez et al. Kidney Int. 1993 Aug;44(2):411-22*)

Impact of Progress on Transplant Outcomes



SURVIVAL INCREASED

REJECTION DECREASED

Adapted from Stewart F, Organ Transplantation, 1999

EVOLUTION OF THE PRIMARY ENDPOINT
FOLLOWED
THE SCIENTIFIC PROGRESS:

SINCE ONE-YEAR SURVIVAL RATES IN KIDNEY TRANSPLANTATION APPROACHED 100%, PATIENT AND GRAFT SURVIVAL ENDPOINTS WERE REPLACED BY "ACUTE REJECTION" ENDPOINT

(***Deaths and graft loses are still imputed as events***)

First FDA Approved Immunosuppressant: Azathioprine, 1968

"**IMURAN®** is indicated as an adjunct for the **prevention of rejection** in renal homotransplantation. Experience with over 16,000 transplants shows a **5-year patient survival of 35% to 55%**, but this is dependent on donor, match for HLA antigens, anti-donor or anti-B-cell alloantigen antibody, and other variables. The effect of IMURAN on these variables has not been tested in controlled trials."

Basis for FDA Approval: summary information from transplant centers and registries which indicated relatively universal use with or without other immunosuppressants (**Real World Evidence**)

Anti-thymocyte Globulin (ATG equine) FDA (CBER) Approval 1981

"**ATGAM®** is indicated for the **management of allograft rejection** in renal transplant patients; when administered with conventional therapy at the time of rejection. ATGAM **increases the frequency of resolution of the acute rejection episode**"

Statistically significant differences in "rejection resolution" and "graft survival" were demonstrated in published randomized controlled trials (RCT)s

Cyclosporine FDA Approval 1983

(Cyclosporine had been released for limited clinical trials in 1979)

"**Sandimmune®** is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants.

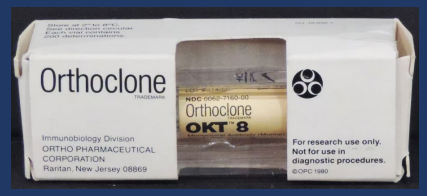
Basis for FDA approval:
Superiority of cyclosporine plus steroids with respect to **one year graft survival** compared to azathioprine plus steroids (Pittsburgh and Canadian RCTs)

Table I. Outcome of cadaveric renal allografts: CsA versus Aza therapy

		% Graft survival‡			% Patient survival‡	
*Group**	*n†*	*CsA*	*Aza*	*p*	*CsA*	*Aza*
Randomized trials						
Canadian	103	80	64	0.003	97	86
European	117	72	52	0.001	94	92
Najarian	53	83	76	NS	89	94
Concurrent trials						
Calne et al.[10]	79	77	62	NS	88	76
Starzl et al.[73]	191	81	50	0.01	91	85
Kahan et al.[35]	103	81	51	0.01	96	89

*Summary of published data.
†n is the number of patients treated with CsA.
‡Actuarial graft and patient 1-year survival rates in all series except the authors', which are actual survivals.

Kahan et al. Clinical and experimental studies with cyclosporine in renal transplantation. Surgery. ***1985*** *Feb;97(2):125-40.*



Muromonab-CD3 FDA Approval 1986

(First FDA approved monoclonal antibody)

"**ORTHOCLONE OKT3®** (*currently discontinued*) is indicated for the **treatment** of acute allograft rejection in renal transplant patients

In an RCT, ORTHOCLONE OKT3 **reversed 94%** of the rejections compared to a **75%** with corticosteroids (**p=0.006**). **One year KM graft survival rates** were 62% and 45% for ORTHOCLONE OKT3 and steroid-treated patients, respectively (**p=0.04**)

A Milestone Event :

1994 Biologic Response Modifiers Advisory Committee

The meeting was convened to provide guidance to sponsors

- Advisory Committee members were asked whether they agreed "a decrease in the proportion of patients experiencing a rejection episode in a set time interval" is an appropriate primary endpoint for approval of new agents

  - The committee agreed

MMF FDA Approval for Kidney Transplantation 1995

"**Cellcept®** [mycophenolate mofetil (MMF)] is indicated for the **prophylaxis of organ rejection**, … (kidney, heart or liver transplants)...

Primary efficacy endpoint: "treatment failure" defined as biopsy-proven acute rejection on treatment or the occurrence of death, graft loss or early termination from the study

Superiority (at 6 months) was demonstrated in three randomized double blind, de novo kidney transplantation studies

Tacrolimus FDA Approvals for Kidney Transplantation 1997 and 2009

Prograf® was previously approved for liver transplantation in 1994.

Kidney Transplantation Approvals:

1. **Prograf + AZA regimen approval (1997):**
   Supported by a randomized, open-label trial (Tacrolimus vs. CsA, both with ATG, azathioprine and corticosteroids). Approval was based on **similar one-year patient and graft survival** rates to CsA

2. **Prograf + MMF regimen approval (2009):**
   Supported by randomized, open-label, *de novo* trial (SYMPHONY ELITE). Tac/MMF/CS/Daclizumab **demonstrated superiority** to 3 other groups with respect to **"efficacy failure" (incidence of BPAR, graft loss, death or loss to follow-up at 12 Months)**

Daclizumab FDA Approval 1997

Zenapax® (*withdrawn*) is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplants

The primary endpoint was "proportion of patients who developed a biopsy-proven acute rejection (**BPAR**) episode within the first 6 months following transplantation." **Superiority** was demonstrated in two randomized, double-blind, placebo-controlled, multicenter trials

Basiliximab FDA Approval 1998

Simulect® is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplantation

The primary endpoint was superiority with respect to death, graft loss or biopsy-proven acute rejection (BPAR) at 6 and 12 months assessed in four randomized, double-blind, placebo-controlled clinical studies

Anti-thymocyte globulin (rabbit) FDA (CBER) Approvals:

THYMOGLOBULIN®

Treatment indication (1998):

Noninferiority with a 20% NI margin was demonstrated in a double-blind RCT in renal transplant patients with **biopsy-proven** Banff Grade II, Grade III, or steroid-resistant Grade I acute rejection episodes

Successful treatment was defined as those patients **whose serum creatinine levels (14 days from the diagnosis of rejection) returned to baseline** and whose graft was functioning on Day 30 after the end of therapy

Anti-thymocyte globulin (rabbit) FDA (CBER) Approvals: (cont.)

THYMOGLOBULIN®

Prophylaxis indication (2017):

FDA approval is supported by two open label RCTs, one demonstrating superiority and the other demonstrating noninferiority to the active comparator based on "treatment failure" defined as **BPAR (Banff Grade I-III), graft loss, death, or lost to follow-up** at one-year posttransplantation

Sirolimus FDA Approvals 1999 and 2003

Rapamune® is indicated for the prophylaxis of organ rejection in patients aged 13 years or older receiving renal transplants

1999: "Fixed Dose" with standard CsA + Steroids
Superiority with respect to incidence of efficacy failure (**BPAR**, graft loss, or death) at 6 months compared to controls was demonstrated in two double-blind RCTs

2003: Cyclosporine withdrawal at 2-4 months with subsequent sirolimus "therapeutic drug monitoring (TDM)"
The primary efficacy endpoint was **graft survival** at 12 months after transplantation which showed **similarity** across the study groups

Mycophenolate Sodium FDA Approval 2004

Myfortic® is indicated for the prophylaxis of organ rejection in patients receiving a kidney transplant

Treatment failure: **first occurrence of BPAR, graft loss, death or lost to follow-up at 6 months**

Similar incidence of treatment failure in MPA-Na and MMF treated patients at 6 and 12 months in combination with cyclosporine and corticosteroids were demonstrated in a) ***de novo*** and b) ***maintenance*** renal transplant patients in two double blind RCTs

Everolimus FDA Approval 2010

Zortress® is indicated for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant

Non-inferiority was met with respect to **efficacy failure (Treated BPAR, graft loss, death or loss to follow-up)** at 12 months (Everolimus with reduced dose CsA compared to MPA-Na with standard dose CsA)

Belatacept FDA Approval 2011

NULOJIX® is indicated for prophylaxis of organ rejection in adult patients receiving a kidney transplant

Two, open-label, randomized, active-controlled trials supported approval

- Study 1 - recipients of living donor and standard criteria deceased donor organs
- Study 2 - recipients of extended criteria donor organs

Non-inferiority with respect to composite endpoint of **BPAR**, graft loss, death or loss to follow-up was demonstrated. (*Am J Transplant. 2012 Mar;12(3):554-62.*)

Clinical Endpoints and Outcomes

A clinical trial's endpoints measure the outcomes in the trial. A clinical outcome assessment is a measure that describes or reflects how a patient feels, functions, or survives.*

Efficacy endpoints are measures intended to reflect the effects of a drug. They include assessments of clinical events, patient symptoms, measures of function, or surrogates of these events or symptoms.**

**Clinical Outcome Assessment (COA): Frequently Asked Questions*

***https://www.fda.gov/files/drugs/published/Multiple-Endpoints-in-Clinical-Trials-Guidance-for-Industry.pdf*

Biopsy-proven Acute Rejection
(Statistical Considerations)

- ❑ Clinically meaningful and sensitive endpoint
  - Makes calculation of an NI margin possible
- ❑ Intent to treat analysis
  - All patients are followed for outcome regardless of treatment compliance
  - Patients with death/graft loss are considered as having intercurrent events which are handled using the composite strategy. This means that these are also counted as events in the analysis.
  - Missing data (lost to follow-up) should be minimal. Initially imputed as failures but also assess results with different imputation methods

ICH E9(R1) Estimands and Sensitivity Analysis in Clinical Trials

Biopsy-proven Acute Rejection (Clinical Considerations)

- Acute rejection is a direct measure of “immunosuppressive efficacy” which is the main purpose of the treatment
- Diagnosis and treatment of acute rejection is associated with significant morbidity:
    - Graft biopsies (invasive and carry risks)
    - Hospitalization likely required during treatment
    - Rejection treatments are associated with increased risk of:
        - Infections
        - Malignancies
        - Cardiovascular events
        - Hyperglycemia/diabetes
        - Gastrointestinal complications
- Acute rejection, in addition to being a clinical endpoint, impacts long term graft and patient survival

ACUTE REJECTION TAKES A TOLL:
Death/Graft Loss in Belatacept Trials at Month 36 According to BPAR Status

STUDY			BELA MI	BELA LI	CsA
008 BENEFIT	BPAR	Death	10% (5/51)	12% (6/50)	6% (2/31)
		Graft Loss	10% (5/51)	10% (5/50)	6% (2/31)
		Death and/or Gr. Loss	**16%** (8/51)	**22%** (11/50)	**10%** (3/31)
	No BPAR	Death	2.5% (4/160)	2% (4/176)	7% (13/190)
		Graft Loss	3% (5/160)	2% (4/176)	4% (8/190)
		Death and/or Gr. Loss	**6%** (9/160)	**4%** (7/176)	**11%** (21/190)
027 BENEFIT-EXT	BPAR	Death	7% (3/41)	14% (6/42)	19% (8/42)
		Graft Loss	10% (4/41)	17% (7/42)	19% (8/42)
		Death and/or Gr. Loss	**17%** (7/41)	**24%** (10/42)	**31%** (13/42)
	No BPAR	Death	13% (19/143)	7% (9/133)	6% (9/142)
		Graft Loss	10% (14/143)	10.5% (14/133)	10.5% (15/142)
		Death and/or Gr. Loss	**20%** (29/143)	**16%** (21/133)	**16%** (23/142)

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125288Orig1s000MedR.pdf (Adopted from Table 27)

Additional Considerations on BPAR

Concern:

Despite the decrease in acute rejection rates and excellent one-year patient and graft survival in kidney transplantation, long-term outcomes are lagging behind

Consideration:

New data as presented by Poggio[1] and another similar published analysis by Hariharan et al.[2] show that the long-term outcomes continue to improve

[1] *Poggio ED, Augustine JJ, Arrigain S, Brennan DC, Schold JD. Long-term kidney transplant graft survival-Making progress when most needed. Am J Transplant. 2021 Aug;21(8):2824-2832.*

[2] *Hariharan S, Israni AK, Danovitch G. Long-Term Survival after Kidney Transplantation. N Engl J Med. 2021 Aug 19;385(8):729-743.*

Additional Considerations on BPAR (cont.)

Concern:

- The "7-year follow up data" from the belatacept trials that supported FDA approval, suggest that belatacept patients have better (or similar) long-term patient and graft survival (compared to the control arm) despite a higher rate of acute rejection with belatacept

Consideration:

- Over 30% of the originally randomized patients were not enrolled in the 7-year follow-up long-term extension (LTE) studies, precluding a meaningful assessment of comparative efficacy

- Belatacept PI states: "Although initially designed as three-year studies, Studies 1 and 2 were subsequently extended to seven years to provide descriptive long-term safety and efficacy data.."*

*https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125288s070lbl.pdf

Summary

- Effective prevention of acute rejection enabled successful transplantation
- BPAR continues to be clinically relevant and BPAR at one year can establish clinical benefit
- Given the great success on lowering the BPAR rates at one year and acknowledging the room for improvement in long-term graft survival rates, additional endpoints may further inform the potential of a therapeutic intervention for long-term graft survival, if supported by adequate data

U.S. FOOD & DRUG ADMINISTRATION

Surrogate Endpoints and Biomarkers

Jeffrey Siegel, MD

Director, Office of Drug Evaluation Sciences (ODES)

OND / CDER / FDA

Endpoints and Trial Designs to Advance Drug Development in Kidney Transplantation

November 9, 2023

University of Manitoba

Disclaimers

- Views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position

Overview

- Types of biomarkers

- Considerations for Surrogate Endpoints

BEST Resource: Biomarkers, EndpointS, and Other Tools

- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- Created by the NIH-FDA Biomarker Working Group
- Publicly available at http://www.ncbi.nlm.nih.gov/books/NBK326791/
- BEST harmonizes terms and definitions and addresses nuances of usage and interpretation among various stakeholders, including:

- Biomedical scientists
- Translational and clinical researchers
- Medical product developers
- Patient/disease advocacy groups
- Government officials
- Clinicians

BEST (Biomarkers, EndpointS, and other Tools) Classification: Range of Biomarker Types

- **Susceptibility / risk biomarker**
- **Diagnostic biomarker**
- **Prognostic biomarker**
- **Monitoring biomarker**

Measures of disease presence and status

- **Predictive biomarker**
- **Pharmacodynamic/Response biomarker – including surrogate endpoints**
- **Safety biomarker**

Measure aspects of response to treatment

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Measures of disease presence and status

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- **Safety biomarker**

Measure aspects of response to treatment

Considerations for Biomarker Utility

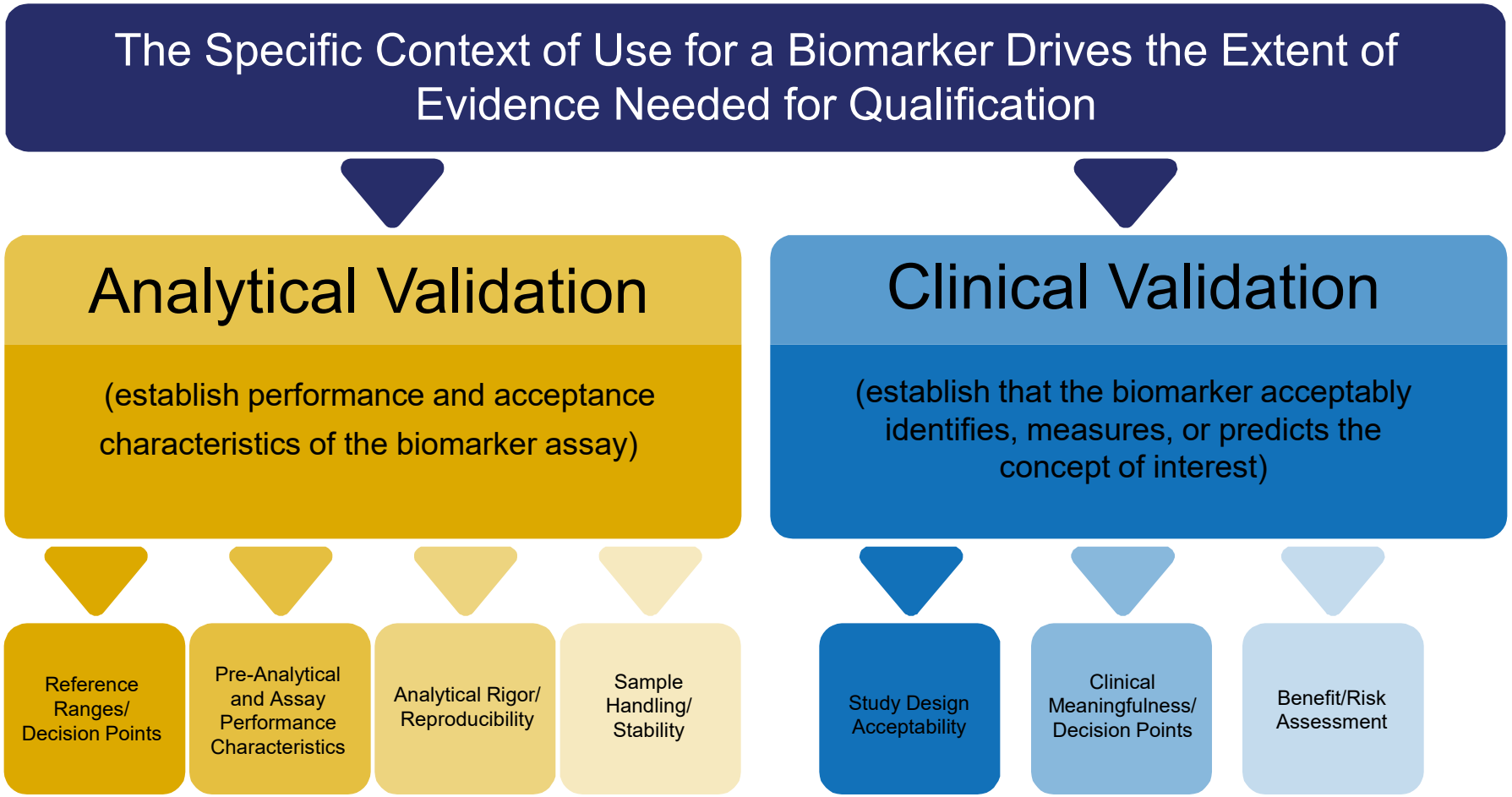
Context of Use (COU): 1) BEST biomarker category and 2) how the biomarker impacts the clinical trial or drug development program

What question is the biomarker intended to address. Examples include:

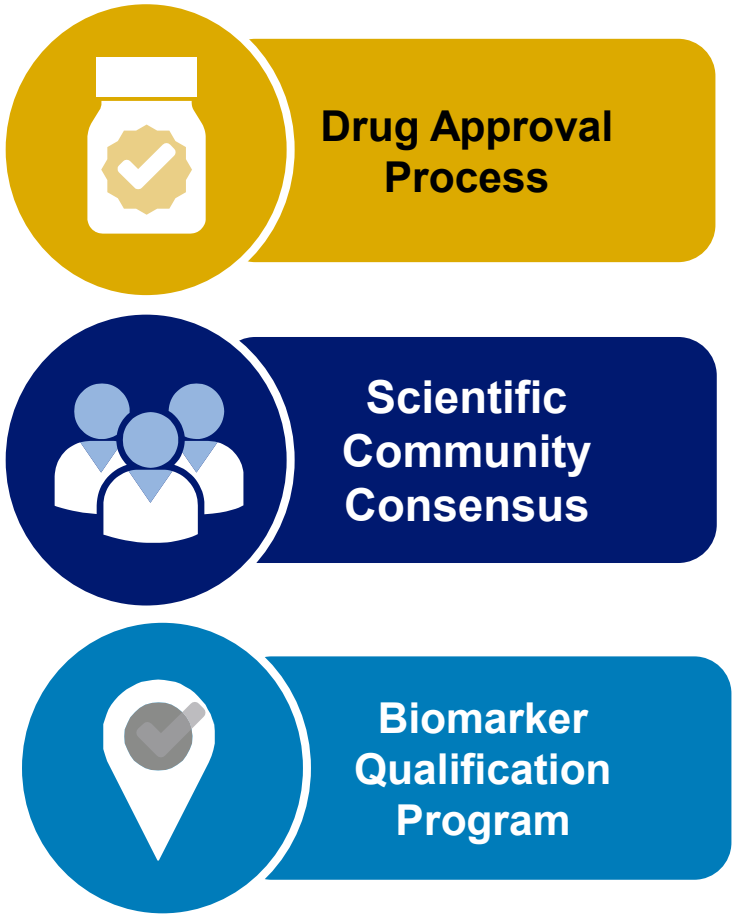
- Inclusion/exclusion criteria for prognostic or predictive enrichment?
- Alter treatment allocation based on biomarker status?
- Result in cessation of a patient's participation in a clinical trial because of safety concern?
- Support dose selection for first in human or Phase 3 studies?
- Evaluate treatment response (e.g. pharmacodynamic effect)?
- **Support regulatory acceptability of a surrogate endpoint for accelerated or traditional approval?**

[1] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458483.pdf

Analytical Assay and clinical Validation considerations in biomarker Qualification



BIOMARKER INTEGRATION INTO DRUG DEVELOPMENT



Note: These pathways do not exist in isolation and many times parallel efforts are underway within or between pathways. All share common core concepts, are data-driven, and involve regulatory assessment and outcomes based on the available data.

Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration; Published June 2016, Duke-Margolis Center for Health Policy

BEST (Biomarkers, EndpointS, and other Tools)
Classification: *Pharmacodynamic / Response BMs*

To support approval, FDA expects substantial evidence of effectiveness – that shows that a drug improves meaningful clinical outcomes: how a patient ***feels, functions, or survives***

- A **validated surrogate endpoint**: accepted by FDA that the effect on the biomarker *predicts* a specific clinical outcome. Validated endpoints have strong and diverse evidence supporting the relationship of the BM and the outcome. Used to support traditional approval.

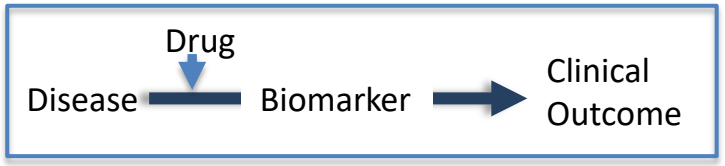
- A **"reasonably likely" surrogate endpoint**: an endpoint supported by strong mechanistic and/or epidemiologic rationale such that an effect on the surrogate endpoint is *expected* to be correlated with a clinical benefit, but not yet reaching the standard for validation. Used for accelerated approval for product intended to treat a serious or life-threatening disease or condition.

The limitations of surrogate endpoints

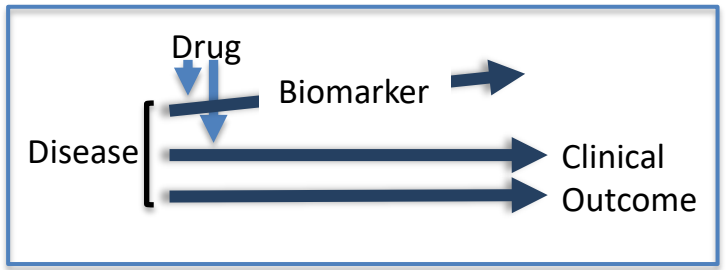
- Not a direct measure of how a patient *feels, functions or survives*
- Intended to reflect and predict clinical benefit not measure the outcome
- With a surrogate endpoint, the benefit / risk assessment therefore must be based upon *assumptions / predictions of benefit*
  - And biomarkers may *fail* to predict clinical benefit
- For a surrogate endpoint that is reasonably likely to predict a clinical benefit and is relied upon to support accelerated approval, post-marketing confirmatory trials are required to verify the clinical benefit

The limitations of surrogate endpoints

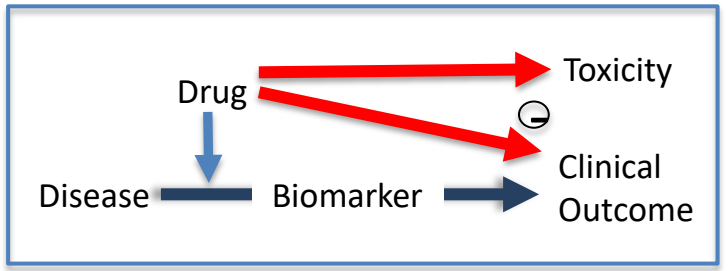
Surrogate on **causal pathway** modulated by drug



Surrogate ***not*** **on causal pathway** by which drug leads to benefit, or **multiple pathways of leading to clinical outcome,** BM *may or may* not reflect key pathways



Drug may induce **adverse effects on desired clinical outcome** through a pathway *not reflected* by BM, or may lead to other toxicities = BM does not reflect benefit (or risk)



After Fleming Statistics in Medicine 2012

Types of pharmacodynamic biomarkers or surrogates

Causal Biomarker

Reflecting causal factor

- **Environmental exposure**
- **Toxin or overdose**
- **Microbiologic**

- Sputum culture
- HIV or HCV RNA
- Bacterial culture
- Serology (e.g., Chagas)
- Lead or other toxin level (e.g., lead concentration)
- Drug concentration (e.g., dig)

Target Engagement

Target binding or activity

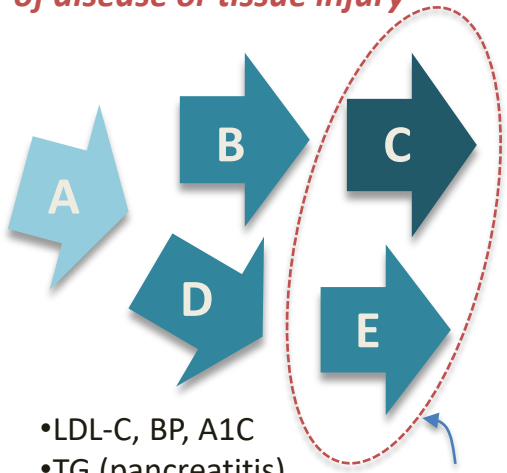
- Receptor binding, activation or inhibition
- Activation or inhibition of signal transduction
- Enzyme or channel inhibition or activation

Responses to TE:

- Change in circulating precursor or substrate
- Tissue or blood cell gene expression profile
- Change in circulating factor reflecting receptor modulation

Pathway or mediator biomarker

Mediates OR reflects mediator of disease or tissue injury



- LDL-C, BP, A1C
- TG (pancreatitis)
- Uric acid (gout)
- Tumor volume (e.g., ORR)
- GL3 inclusions (Fabry's)
- Liver iron (overload)
- Urinary cystine (cystinuria)
- Amyloid plaque (AD)
- Vitamin or electrolyte level (deficiencies)

Genetic (e.g., single gene, or polygenetic)

Organ dysfunction (e.g., pancreatic, renal, liver)

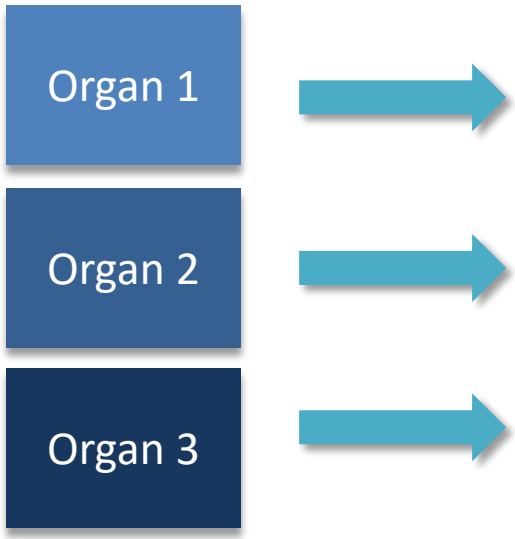
Cancer: genomic mutation

Multifactorial (genetic, dietary, environmental)

Organ injury or organ function biomarker

Reflecting tissue injury

Sites of Injury



Tissue injury biomarkers

- Alk phos (PBC)
- CPK (polymyositis, MI)
- Urinary kidney injury BMs
- Urinary microalbumin
- Liver bx (NAS, fibrosis) NASH
- BMD (osteoporosis)
- Neurofilament light chain (ALS SOD1)
- ALT (hepatocellular injury)

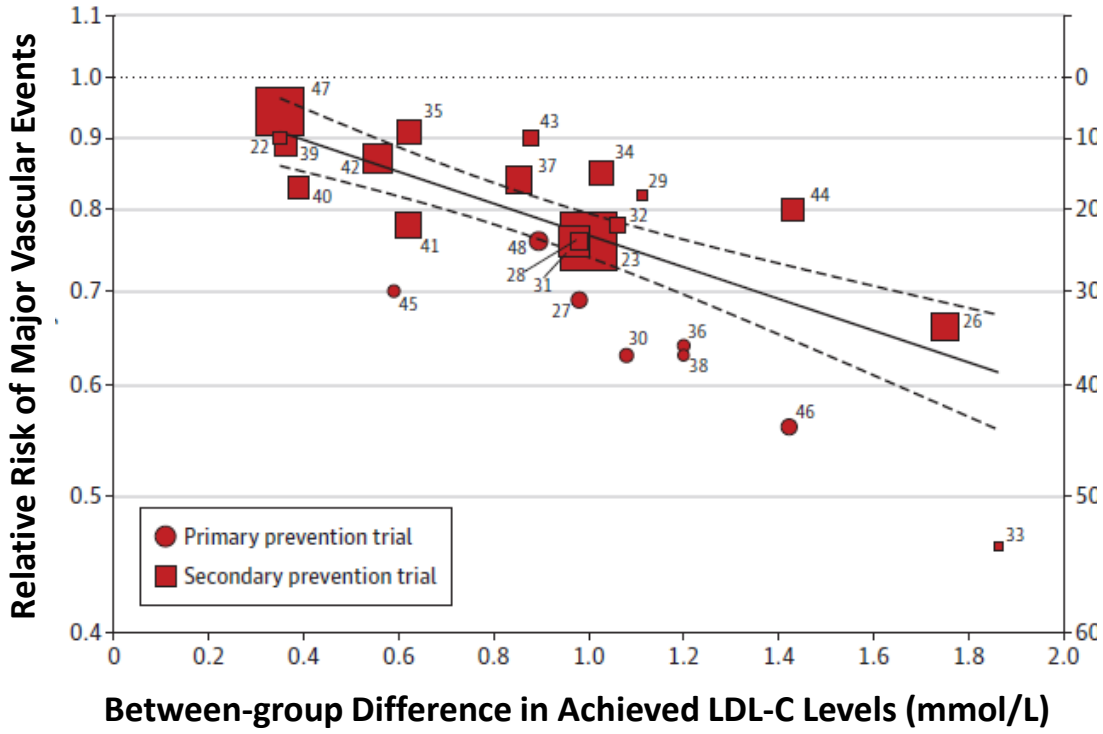
Measure organ function

- 6 MWT
- FEV1
- eGFR
- Dynamometry
- Cardiac ECHO
- Neurocognitive function testing
- Liver function: bili, PT, etc.
- Hgb, WBC, plts (BM function)
- UMA (glomerular disease)

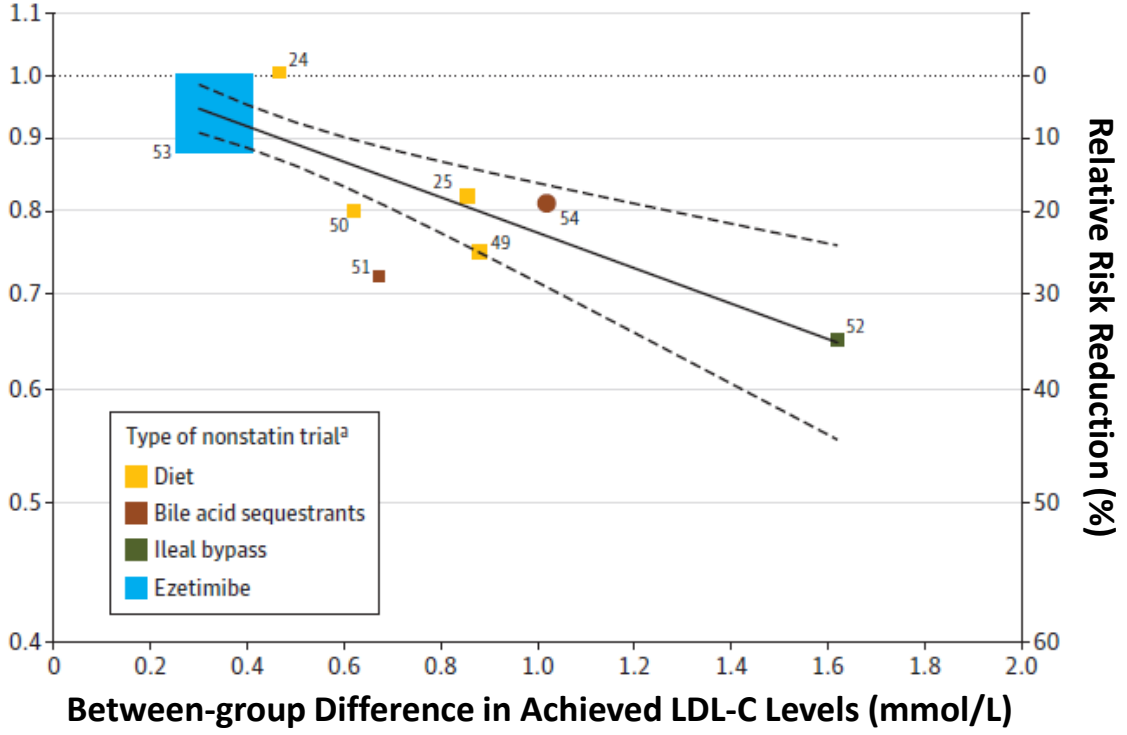
Clinical Endpoints

LDL-C as a surrogate: validation with multiple LDL-C lowering mechanisms

Twenty-five Statin Trials



Eight Non-statin Trials



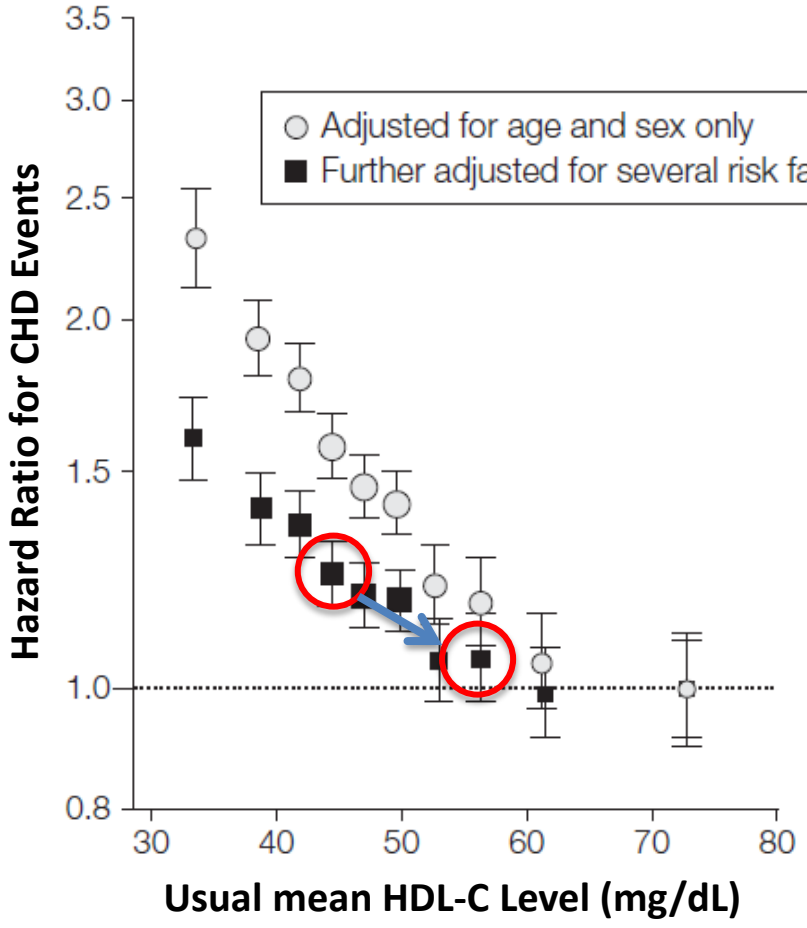
plus

- Strong evidence from epidemiological studies
- Strong mechanistic / biological evidence
- Animal model evidence

Silverman et al. JAMA 316: 1289-1297, 2016

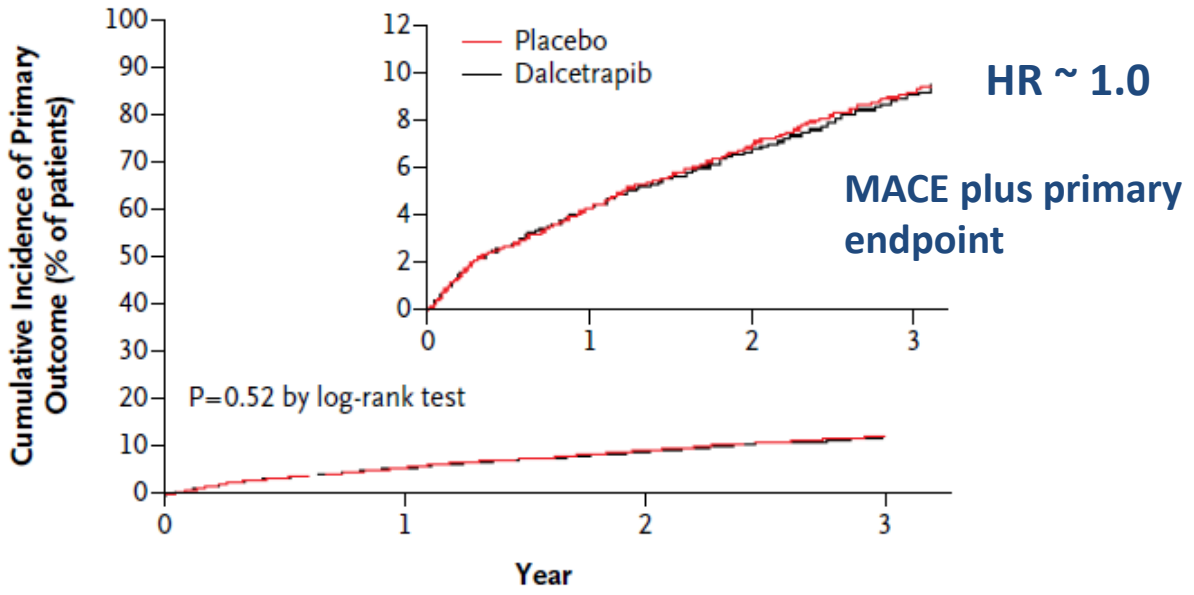
HDL-C as a surrogate: epidemiology and interventional changes have divergent outcomes

HDL-C Levels and CHD Events



Emerging Lipid Collaborators JAMA 2009

Effects of Dalcetribid (CETP-inhibitor) on HDL-C and CV Outcomes in patients with ACS



HR ~ 1.0

MACE plus primary endpoint

HDL-C: ↑ by 31-40% with dalcetrabid vs 4-11% in placebo group, from ~ 57 mg/dL vs ~ 44 mg/dL
LDL-C: no between group difference
SBP: +0.6 mm increase vs placebo

Schwartz et al. NEJM 367: 2089-99, 2012

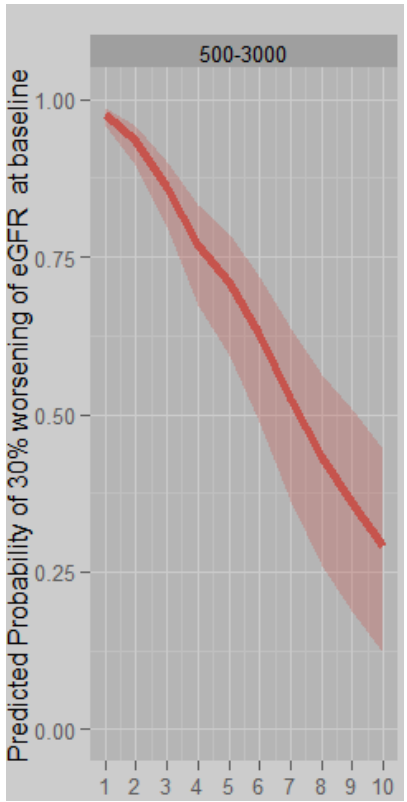
Potential sources of data to support a surrogate

- Randomized clinical trial **treatment-group level** data evaluating relationship between change in surrogate and change in clinical endpoint
- **Individual patient-level** data from intervention trials
  - May or may not be a correlation; interpretation and limitations if present or not present
- **Observational data**
  - Natural history study / cohort data (e.g., registry)
  - Epidemiological data
- **Mechanistic data** showing the role of proposed surrogate in disease pathogenesis
- **Human drug pharmacodynamic studies** showing changes in surrogate leading to modulation of putative causative pathways
- **Human genetic data**
- **Translational animal models**

Step-wise process may be useful for biomarker validation: Example of AD-PKD

- Consortium developed model relating total kidney volume (TKV) to progression of renal disease in autosomal dominant PKD (AD-PKD):
  - TKV progression model (continuous model endpoint over time)
  - Survival model (time-varying probability of reaching a 30% decline in eGFR)
  - Including covariates such as baseline eGFR and age

Age	TKV	Follow-Up Period	1-Probability of 30% Worsening of eGFR		
			Median	Lower	Upper
Baseline age=30yrs	Baseline TKV 1.7L	1	0.98	0.96	0.99
		2	0.93	0.90	0.96
		3	**0.86**	0.80	0.90
		4	0.77	0.67	0.83
		5	0.71	0.59	0.79
		6	0.63	0.49	0.72
		7	0.52	0.36	0.64
		8	0.43	0.26	0.56
		9	0.36	0.19	0.51
		10	0.29	0.12	0.45



Adapted with permission from Critical Path Institute

Progression of TKV biomarker for PKD

- Initially qualified as prognostic biomarker based on modeling results
- Subsequently applied in individual drug development programs
- Data supported acceptance by FDA review division as reasonable likely SE for accelerated approval

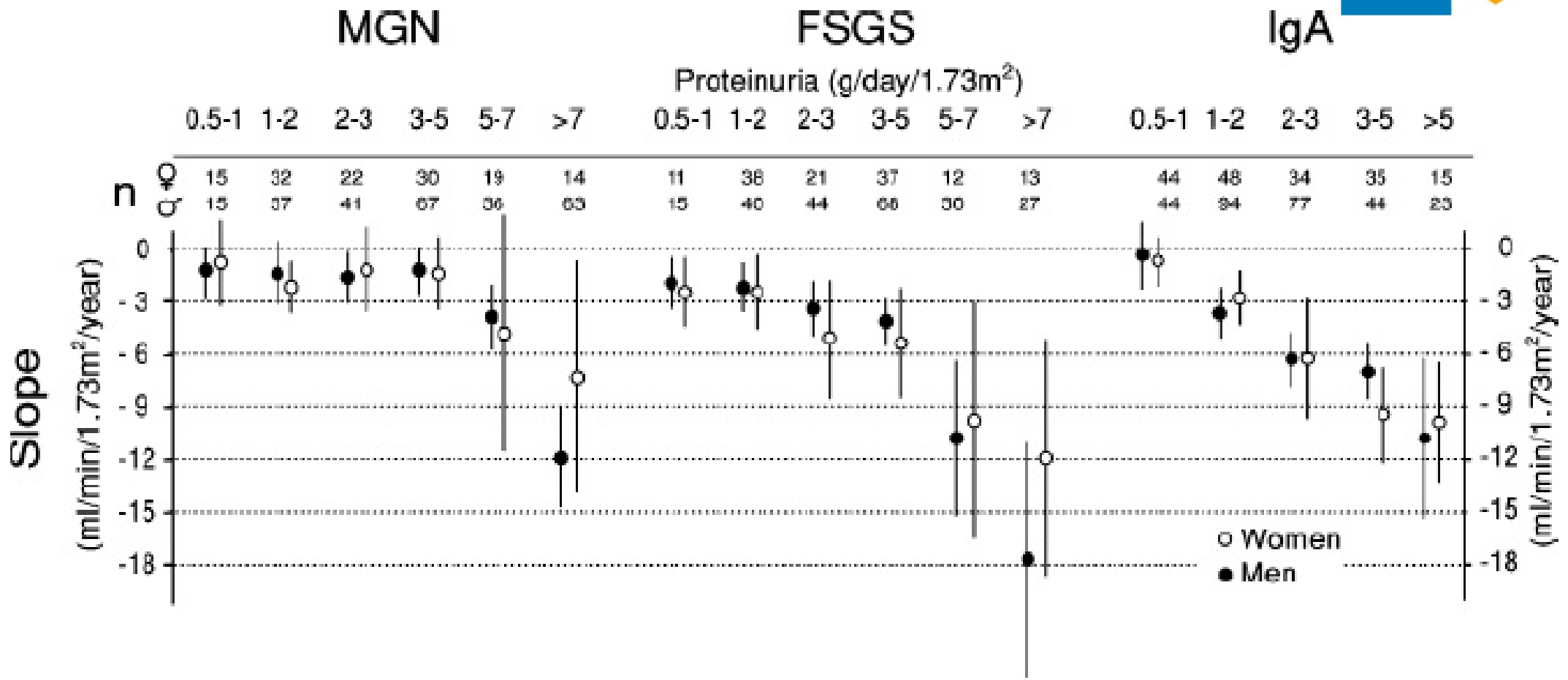
Example 2: Proteinuria for IgA nephropathy

Mechanistic data tying urine protein to kidney damage

Epidemiologic studies showing consistent association between severity/duration of proteinuria and loss of kidney function

Interventional trials: Association between change in proteinuria & COs

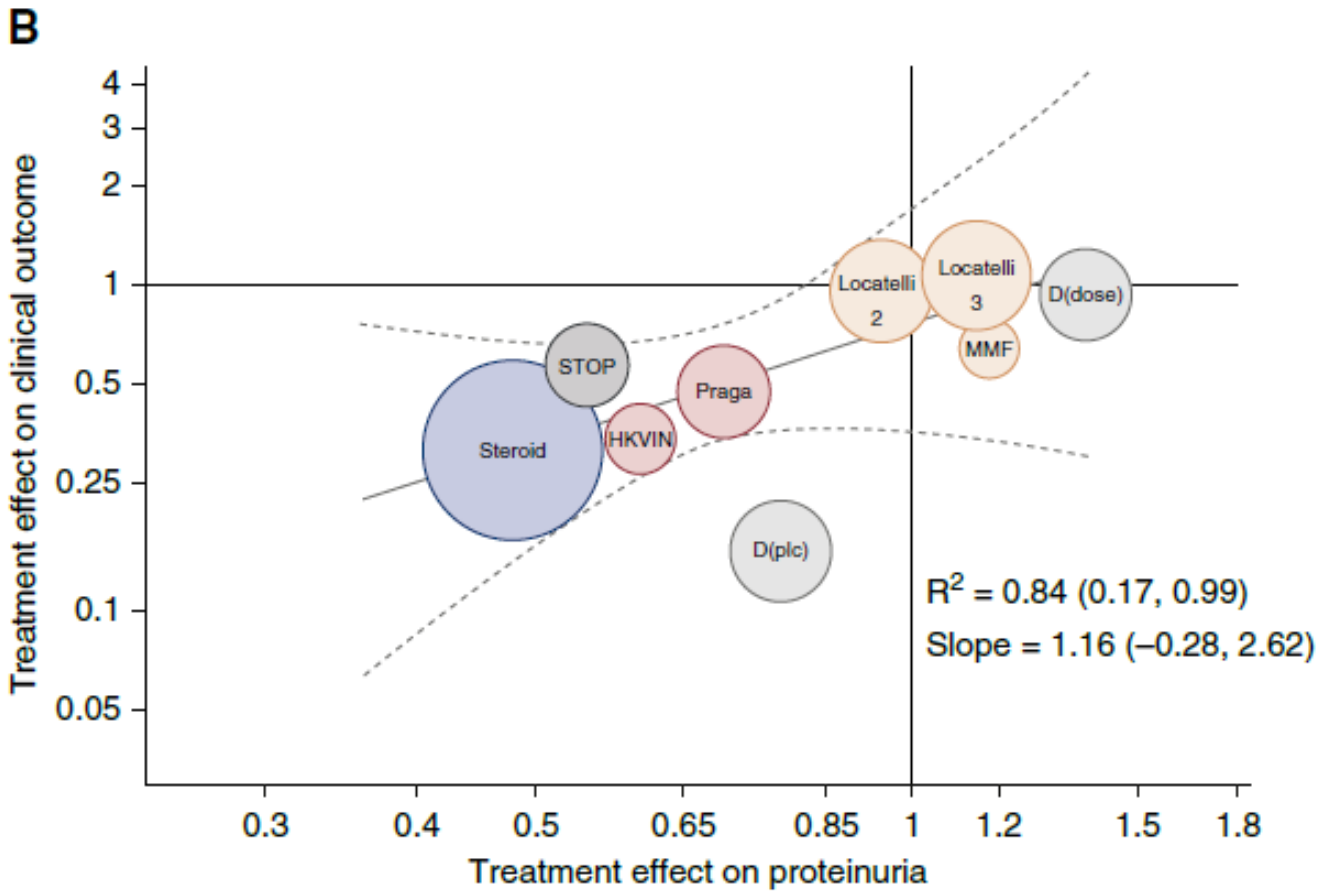
Epimiologic studies show association between level of proteinuria and rate of loss of kidney function



Cattran DC et al. Nephrol Dial Transplant 2008;23:2247-53

IgAN: Treatment effect on proteinuria vs clinical outcomes

Thompson A et al. Clin J Am Soc Nephrol 14:469-81, 2019



Supporting a surrogate: getting to acceptance

- Context dependent – e.g., rare/serious disease/unmet need vs other settings
- Impact of accepting the surrogate – “risks” of approval
- Different level of evidence (and often type of evidence) needed for a validated surrogate vs a reasonably-likely surrogate
- Multiple sources of evidence – biological plausibility supported by varying extent of clinical pharmacology and clinical trial evidence
- “Convergence of evidence” approach

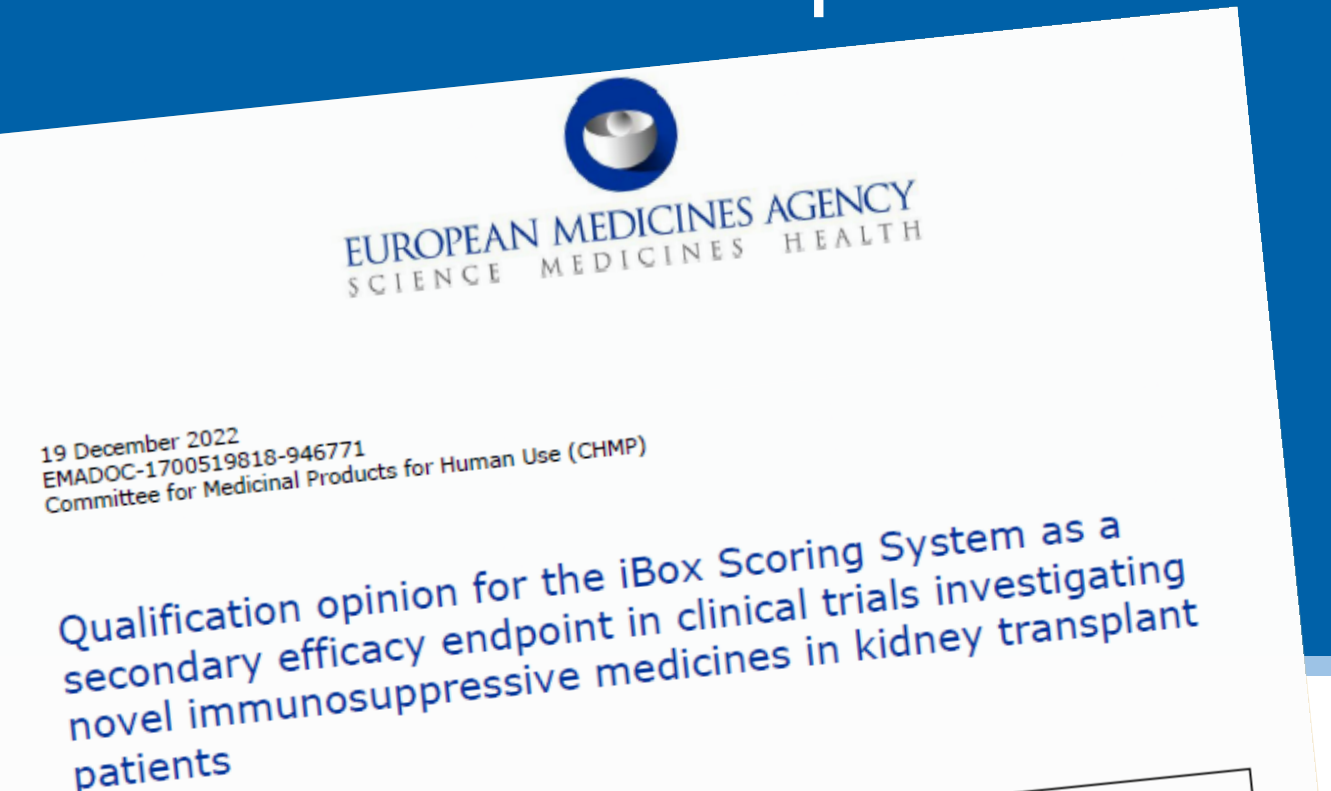

FDA
U.S. FOOD & DRUG
ADMINISTRATION

Lyfjastofnun
Icelandic Medicines Agency

FDA University of Manitoba

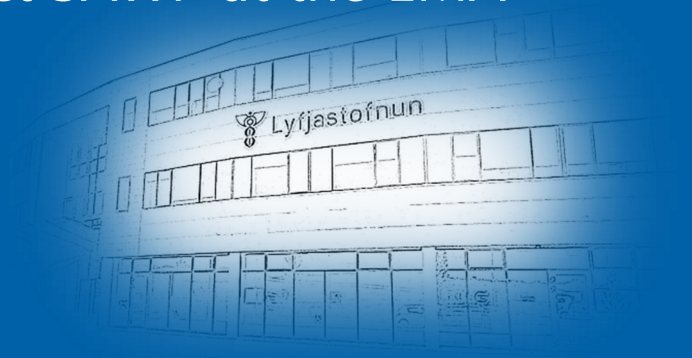
iBox as an endpoint – EMA perspective

Hrefna Guðmundsdóttir, IMA
Member of CHMP & SAWP at the EMA

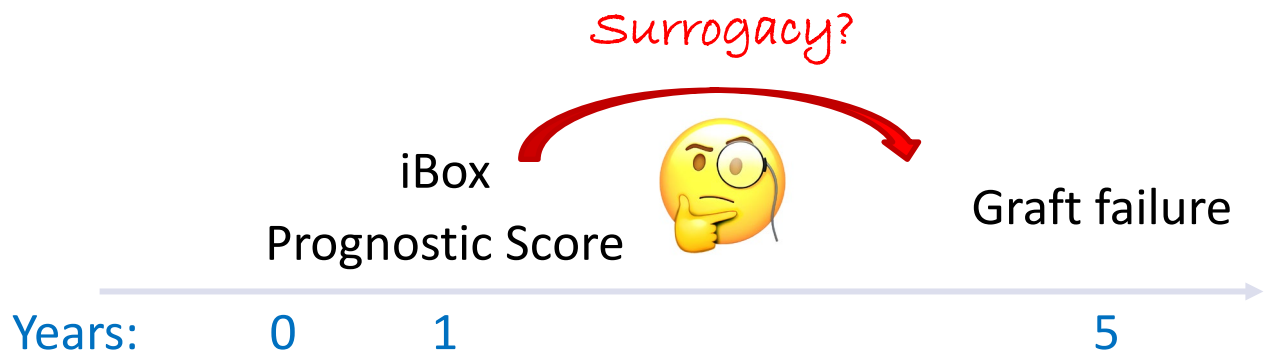

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

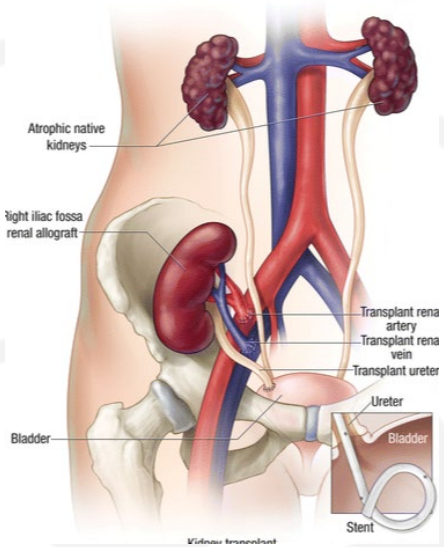
19 December 2022
EMADOC-1700519818-946771
Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion for the iBox Scoring System as a secondary efficacy endpoint in clinical trials investigating novel immunosuppressive medicines in kidney transplant patients



iBox QO as surrogate for kidney graft survival





4.2 Context-of-use

Proposed context-of-use statement

The iBox Scoring System (Composite Biomarker Panel) used at one-year post-transplant is a surrogate endpoint for the five-year risk of death-censored allograft loss (allograft failure) in kidney transplant recipients for use in clinical trials to support evaluation of novel IST applications via CMA.

General area:

Surrogate endpoint for the five-year risk of death-censored allograft loss (allograft failure) in kidney transplant subjects for use in clinical trials to support evaluation of novel IST applications.

Target population for use of the biomarker:

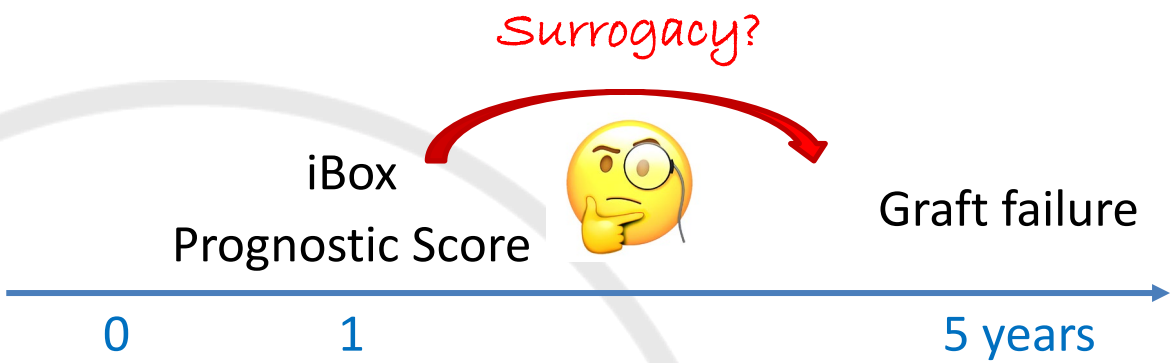
Adult *de novo* kidney only transplant recipients from a living or deceased donor.

The Datasets

	Data name	Data type	Geography	Median follow-up (years)	Full iBox (n)	Abbreviated iBox (n)
Derivation	**Loupy et al., 2019**	Transplant centers	Europe	7.0	3,941	4,000
Validation	**Mayo Clinic Rochester**	Transplant center	North America	7.6	483	497
	Helsinki U. Hospital	Transplant center	Europe	8.5	344	344
	BENEFIT	RCT	International	7.0	416	515
	BENEFIT-EXT	RCT	International	7.0	260	357
	Total				**1,503**	**1,713**

iBOX: Results

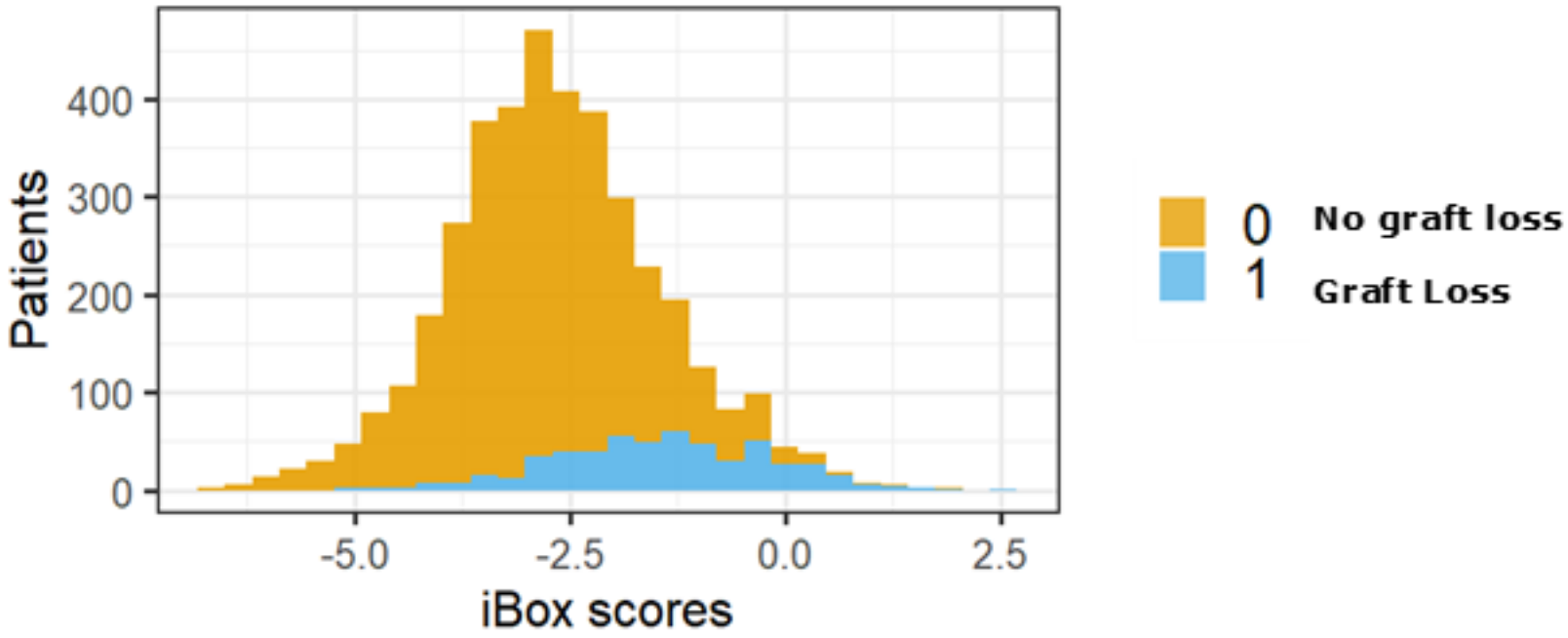
$$iBox_i = \sum_{j=1}^{J} \hat{\beta}_j X_{ij}$$



	Factor	HR (exp[$\hat{\beta}_j$]) (95% C.I.)*	P-value
	Time from transplant to evaluation (years)	1.08 (1.03 - 1.14)	0.0032
Abbreviated iBox	eGFR (mL/min/1.73 m²)	0.96 (0.95 - 0.96)	<0.0001
	Log (UPCR, g/g)	1.5 (1.39 - 1.62)	<0.0001
	DSA MFI		
	< 1400	1	
	≥ 1400	1.84 (1.44 - 2.34)	<0.001
Full iBox	Interstitial fibrosis/tubular atrophy (IFTA score):		
	0-1	1	
	2	1.14 (0.92 - 1.43)	0.2256
	3	1.41 (1.1 - 1.8)	0.0059
	Microcirculation inflammation (g score and ptc score):		
	0-2	1	
	3-4	1.43 (1.11 - 1.85)	0.0057
	5-6	1.84 (1.25 to 2.7)	0.0019
	Interstitial inflammation and tubulitis (i score and t score):		
	0-2	1	
	≥ 3	1.33 (1.06 - 1.68)	0.0141
	Transplant glomerulopathy (cg score)		
	0	1	
	≥ 1	1.47 (1.14 - 1.9)	0.0033

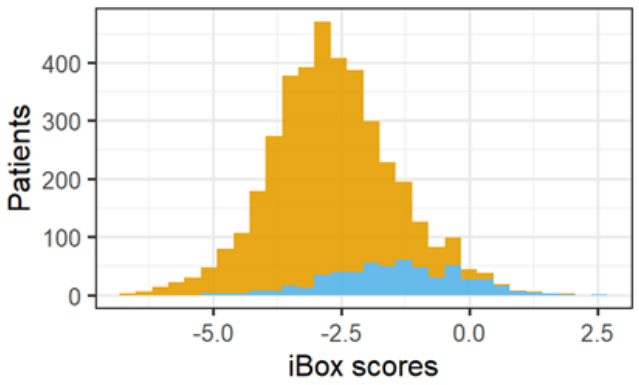
Distribution of iBOX scores

Derivation Dataset



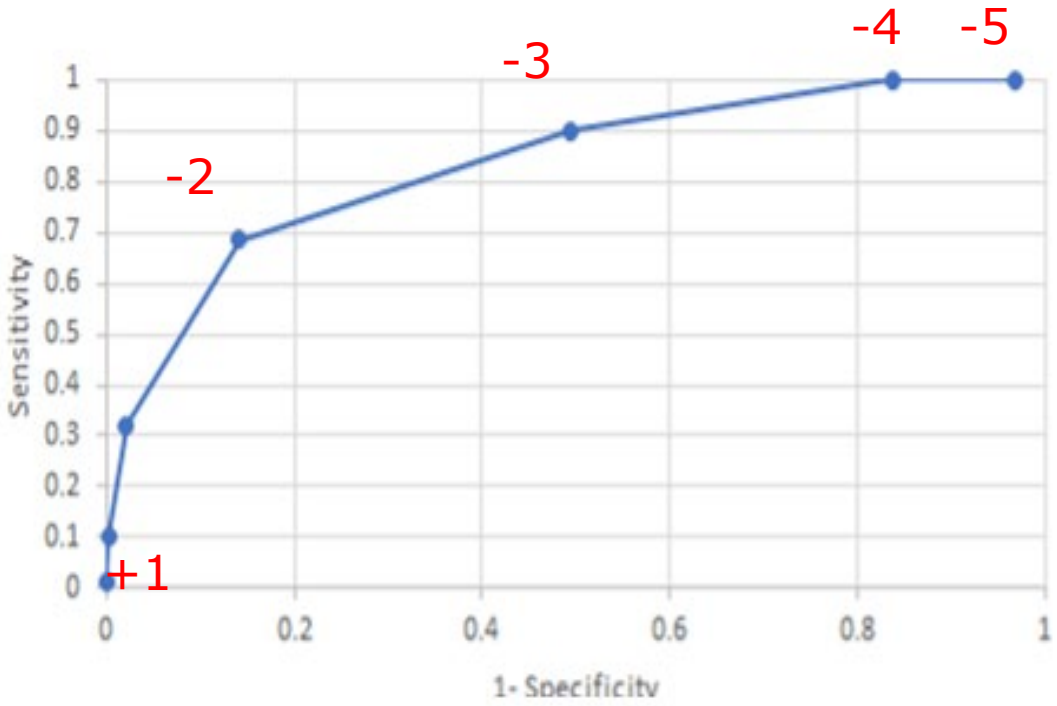
Lower iBox score indicates lower risk

ROC Curve for iBox



ROC Curve for iBox cutoff (X)
Qualification derivation dataset

True positive



True negative

Conclusion:
Modest Performance

The Validation Datasets

	Data name	Data type	Geography	Median follow-up (years)	Full iBox (n)	Abbreviated iBox (n)
Derivation	**Loupy et al., 2019**	Transplant centers	Europe	7.0	3,941	4,000
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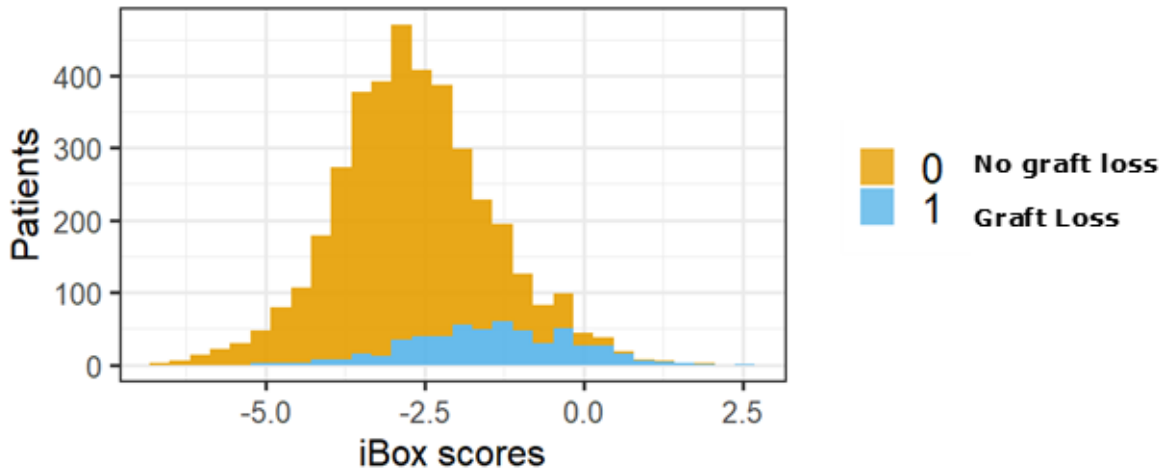
	BENEFIT	RCT	International	7.0	416	515
	BENEFIT-EXT	RCT	International	7.0	260	357
	Total				**1,503**	**1,713**

Translating clinical parameter into iBOX score

$$iBox_i = \sum_{j=1}^{J} \hat{\beta}_j X_{ij}$$



Parameter difference		Magnitude of iBox score difference
eGFR (ml/min/1.73m^2) difference		
5		0.23
8		0.37
10		0.46
Dipstick proteinuria difference	**UPCR proteinuria (log g/g) difference**	
Negative vs. Trace	0.05	0.02
Negative vs. +	0.24	0.10
Negative vs. ++	0.96	0.39
Negative vs. +++	3.11	1.27
DSA MFI difference		
<1400 vs. ≥ 1400		0.61
IFTA score difference		
< 2 vs. 2		0.14
< 2 vs. 3 or more		0.34
g and ptc score difference		
< 3 vs. 3-4		0.36
< 3 vs. 5 or more		0.61
cg score difference		
0 vs. 1 or more		0.38

Imputed

Poisson calibration results for the full iBox Scoring System.

Z-scores and p-values were calculated from a Poisson regression model

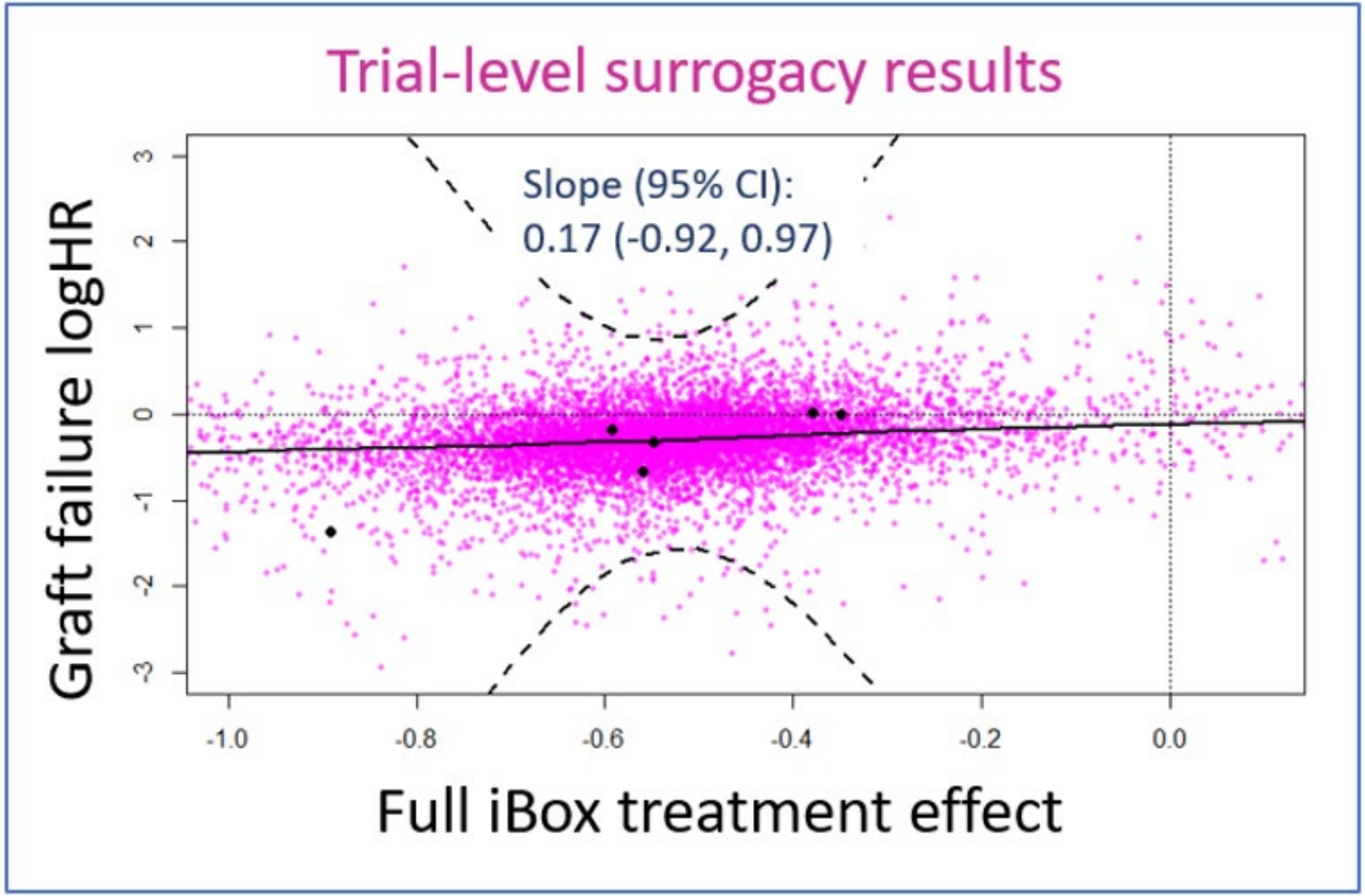
Validation Dataset	No. of subjects	Observed # of graft loss events	Predicted # of graft loss events	Observed /Predicted	z score for Observed /Predicted	P-value
Combined observational	827	39	38.74	1.01	0.04	0.97
Helsinki University Hospital	344	21	14.40	1.46	1.73	0.08
Mayo Clinic Rochester	483	18	24.34	0.74	-1.28	0.20
Combined RCTs	676	24	29.49	0.81	-1.01	0.31
BENEFIT RCT	416	12	14.52	0.83	-0.66	0.51
BENEFIT-EXT RCT	260	12	14.97	0.80	-0.77	0.44

iBox QO: Full- vs Abbreviated iBox Scoring System

External validation

Dataset	C-statistic for full iBox Scoring System (SE)	C-statistic for abbreviated iBox Scoring System (SE)
Mayo Clinic Rochester	0.93 (0.03)	0.84 (0.05)
Helsinki University Hospital	0.78 (0.06)	0.77 (0.06)
BENEFIT RCT	0.70 (0.09)	0.70 (0.08)
BENEFIT-EXT RCT	0.81 (0.07)	0.78 (0.06)

iBox QO: Trial level analysis



QO Conclusion iBox Scoring System

Key points

The need for reliable surrogate(s) for transplant studies investigating new immunosuppressive therapies is agreed

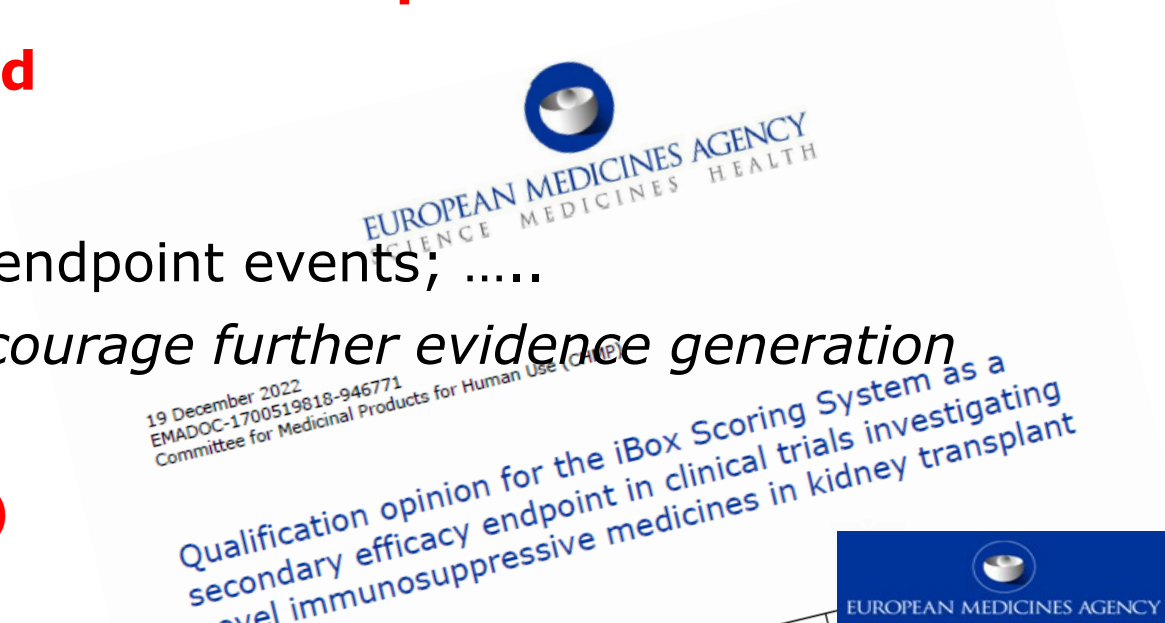
The overall validation approach was endorsed, with detailed comments on future options to further extent the work with a view to qualifying the iBox as surrogate endpoint in the future.

QO as surrogate/primary efficacy endpoint is not possible as trial-level surrogacy of iBox has not been demonstrated

The COU was modified and refined:

- Database still limited: size; low number of endpoint events; …..
- *iBox as secondary endpoint intended to encourage further evidence generation*

(for details see: EMADOC-1700519818-946771)



CRITICAL PATH INSTITUTE

iBOX as an endpoint
C-Path/TTC perspective

Amanda Klein, PharmD, on behalf of the Transplant Therapeutics Consortium (TTC)

Executive Director, TTC, Critical Path Institute

Tucson, Arizona, USA

November 9, 2023

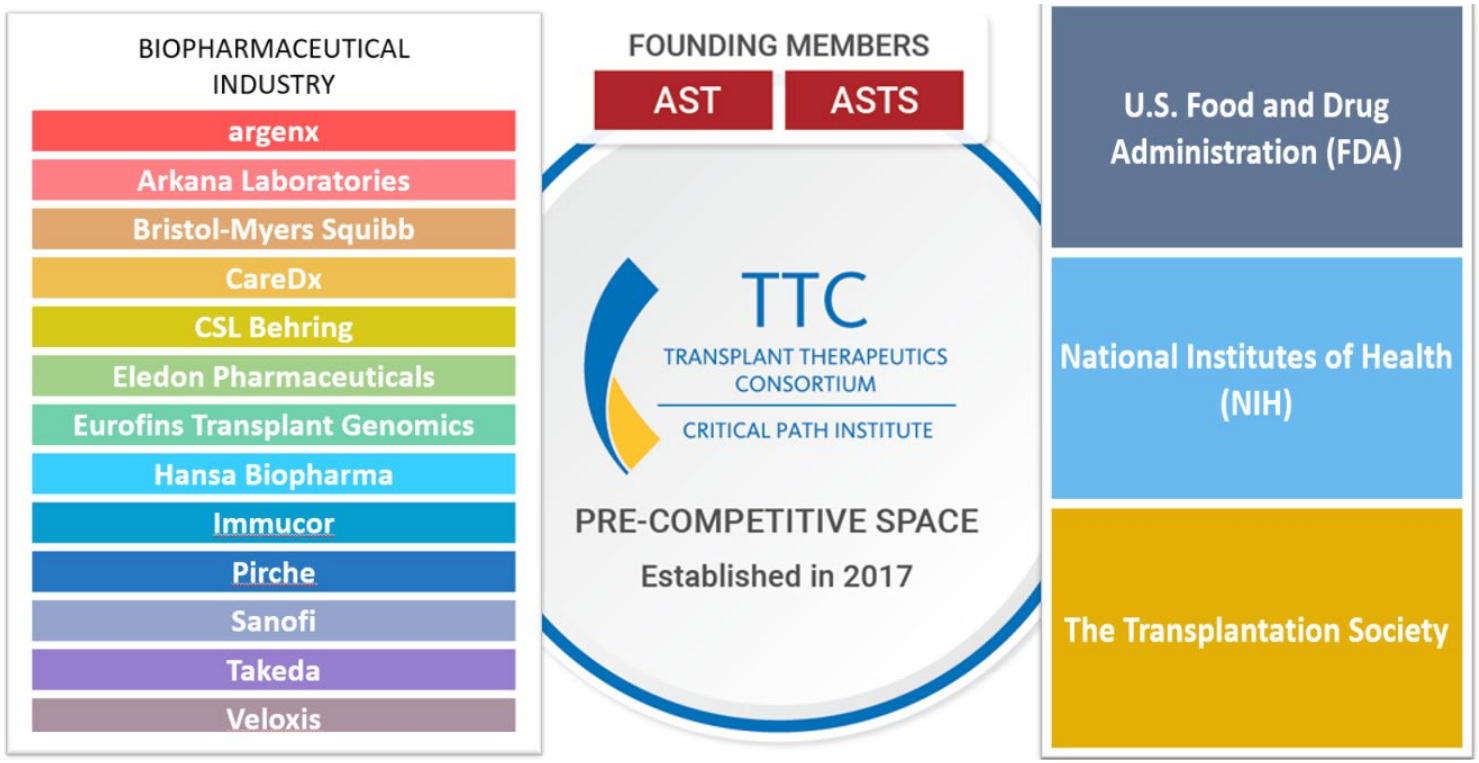
Disclosures

TTC is supported by funds from the transplant community, including the biopharmaceutical and diagnostic industries, professional societies, and regulatory agencies.

My presentation includes investigating a novel endpoint for qualification with FDA.

Transplant Therapeutics Consortium (TTC)

- **Only community-based group** dedicated to advancing the **regulatory science needs of transplant**.
- **1-year graft survival** after kidney transplantation is **excellent.**
- **Unmet need** for **improved long-term** graft survival.
- **Primary effort:** To qualify **iBOX** as a **reasonably likely surrogate endpoint** for long-term graft survival after **kidney transplantation.**



Stifled new IST development in transplantation

Transplant Regulatory Framework:

- No therapy is approved for preventing long-term graft loss.
- All currently approved ISTs are indicated for the prophylaxis of organ rejection.
- Biopsy-proven acute rejection (BPAR) is correlated with long-term graft survival
  - but is neither prognostic nor predictive of long-term graft survival.
- In transplant, traditional approval of ISTs has required 2 phase 3 RCTs.

Impact on ISTs for Transplant:

- **No new IST** demonstrating improved efficacy has been developed over 2 decades.
- **No new IST** has been approved for the prevention of organ rejection for more than a decade.
- **No new IST** is currently in phase 3 clinical trials.

Fitzsimmons & Naesens, 2023; Naesens & Thaunat, 2016; Nulojix PI: BMS.

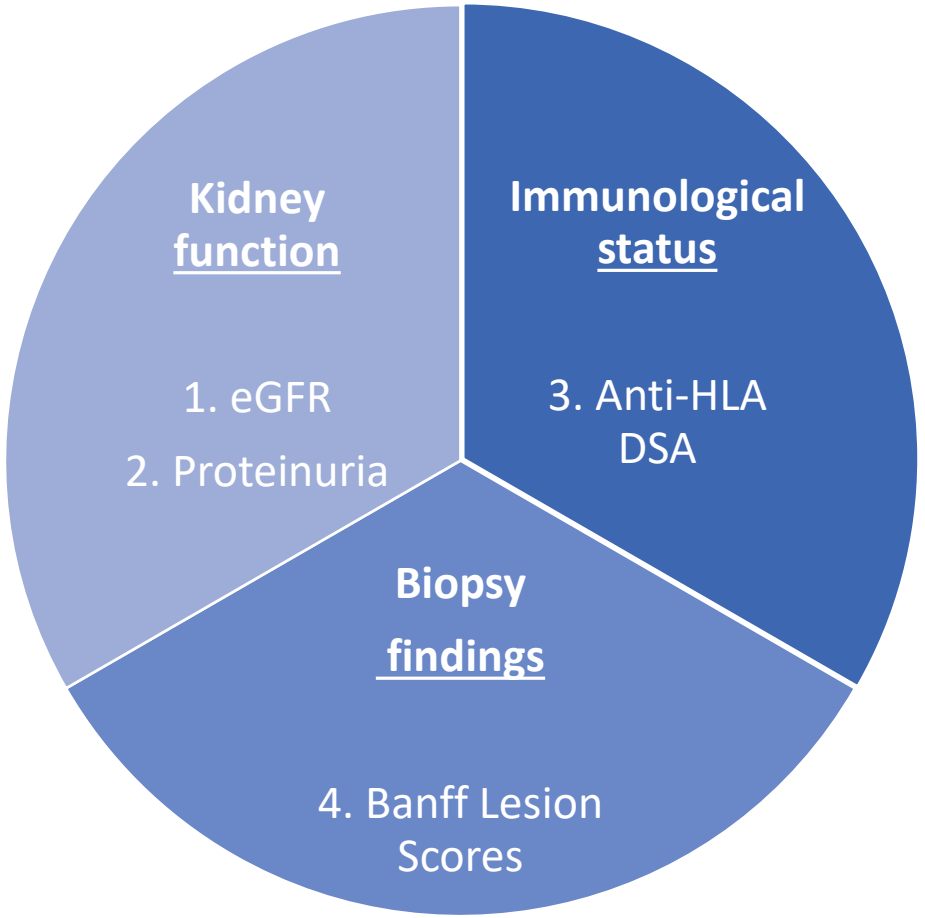
Inability to improve upon the current efficacy failure endpoint,

And lack of endpoint prognostic for long-term graft survival,

Has stifled new IST development in transplantation.

iBOX – best surrogate for late graft failure

- iBOX, Loupy et al., 2019, led by the Paris Transplant Group
- Extensive epidemiologic and prognostic data (n = 4,000)
- Strong mechanistic data for each component
- Comprehensive assessment of kidney graft health
- 2 iBOX versions:
  - Full (with biopsy)
  - Abbreviated (without biopsy)



iBOX meets criteria for a RLSE

	FDA US[1]	EMA Europe[2]
Validated Surrogate Endpoint	"An endpoint supported by a clear mechanistic rationale and **clinical data providing strong evidence that an effect on the surrogate endpoint predicts a specific clinical benefit**."	• Biological plausibility of the relationship • Demonstration in epidemiological studies of the prognostic value of the surrogate for clinical outcome • **Evidence from clinical trials that treatment effects on the surrogate correspond to effects on the clinical outcome**
Reasonably Likely Surrogate Endpoint (RLSE)	"An endpoint supported by **strong mechanistic and/or epidemiologic rationale** such that an effect on the surrogate endpoint is expected to be correlated with an endpoint intended to assess clinical benefit in clinical trials, but **without sufficient clinical data to show that it is a validated surrogate endpoint**. Such endpoints may be used for **accelerated approval** for drugs." (next slide)	**Non-existent**

[1] https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development [2] Naesens M, Budde K, Hilbrands L, Oberbauer R, Bellini MI, Glotz D, et al. Surrogate Endpoints for Late Kidney Transplantation Failure. Transpl Int [Internet]. 2022 [cited 2022 Aug 17];0. Available from: https://www.frontierspartnerships.org/articles/10.3389/ti.2022.10136/full

iBOX meets ALL criteria for FDA Accelerated Approval

- ✓ Treats a serious condition
  - Graft loss

- ✓ Provides a meaningful advantage over available therapies
  - Allows superiority of a new therapy and a new indication

- ✓ Demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible mortality or morbidity
  - iBOX as a RLSE at 1 year for 5-year graft survival

https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review

Qualifying iBOX as a RLSE with FDA

- June 1, 2020: iBOX accepted into FDA Biomarker Qualification Program
  - **FDA Suggested COU as a RLSE for 5-year risk of allograft loss for use in the Accelerated Approval Program.**

- July 31, 2023: Context-of-use modified to include co-primary with efficacy failure; currently under review by the Agency

Does not compromise FDA's current standard,

and in fact,

held to higher standards than current efficacy failure endpoint while providing sponsors a pathway to accelerated approval

https://www.fda.gov/media/139300/download

Prognostic ability of iBOX is superior to BPAR

- Prognostic performance of iBOX (continuous and binary) is superior to BPAR (binary) for long-term graft survival

- Demonstrated in discrimination and calibration analyses
  - N = 2,708 kidney transplant recipients with 1-year iBOX assessments

  - iBOX had significantly ($p < 0.01$) higher c-statistic values in 4 of 5 datasets. c-statistics ranged from 0.71-0.92 for iBOX vs. 0.52-0.65 for BPAR

  - In 4 of 5 datasets, the expected number of events from iBOX was not significantly different from the observed events but was significantly ($p < 0.01$) different for BPAR

- BPAR is not predictive of a treatment effect on graft survival (Fitzsimmons and Naessens, 2023)

Potential labeling. Indication and Usage for accelerated approval

Example for kidney transplant:

- [NEW DRUG] is a [MECHANISM OF ACTION] indicated for the **prophylaxis of organ rejection** and **improvement in the iBOX in kidney transplant**.

- This indication is **approved under accelerated approval** based on an improvement in the iBOX observed in patients treated with [NEW DRUG]. It has not been established whether [NEW DRUG] will improve long-term survival of the kidney graft. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

Note: This is for demonstration only; any labeling is determined between FDA and the sponsor.

Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway Guidance for Industry. January 2019. Labeling.
https://www.fda.gov/media/119755/download

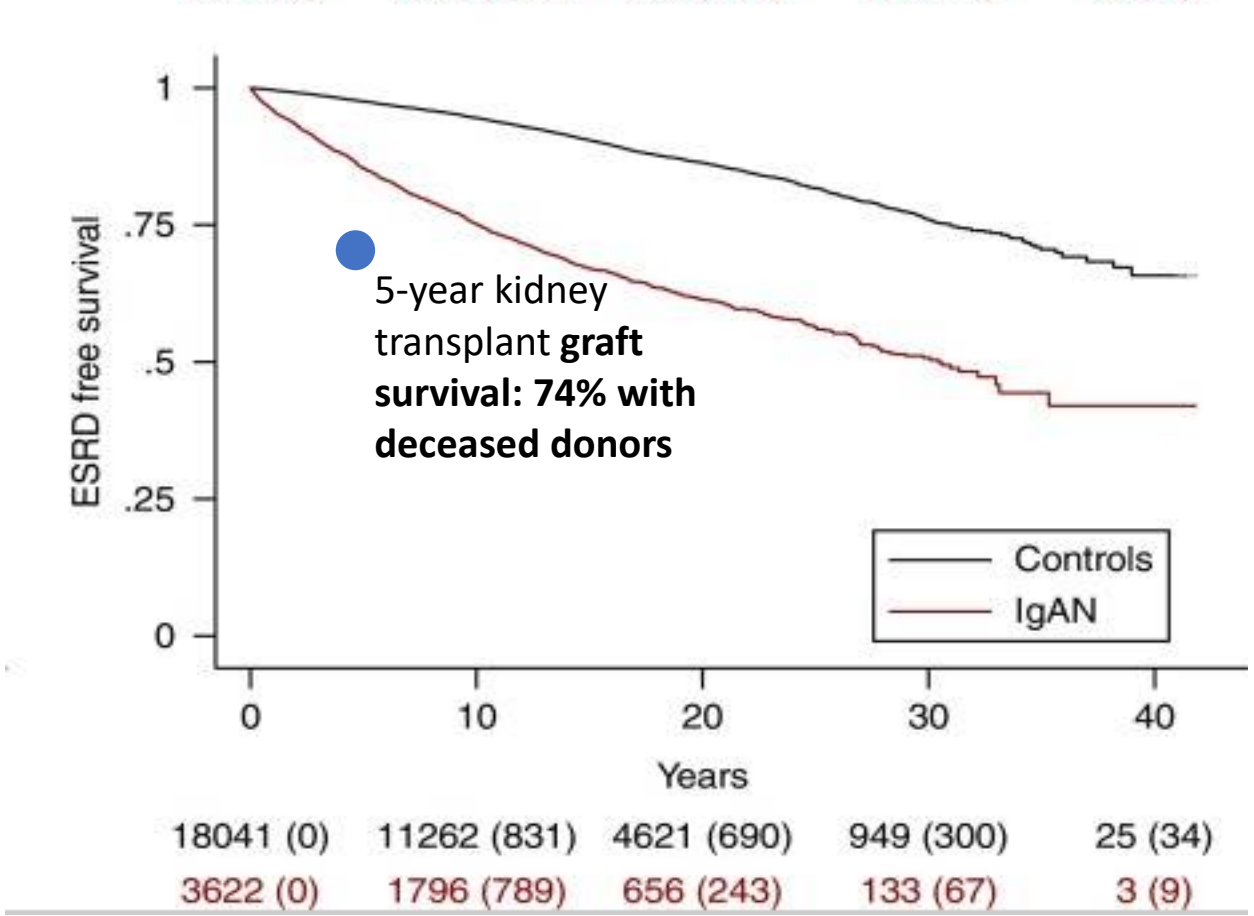
Impact of surrogate endpoints

- Integral to accelerating the availability of new treatments in:
  - Oncology
  - HIV
  - Alzheimer's disease
  - Sickle cell disease
  - Fabry disease
  - IgA nephropathy
    - ➢ 2020: no approved therapies
    - ➢ 2023: Two accelerated approvals: Filspari™ (2023) and Tarpeyo™ (2021)
    - ➢ Present: 5 therapies in phase 3 development

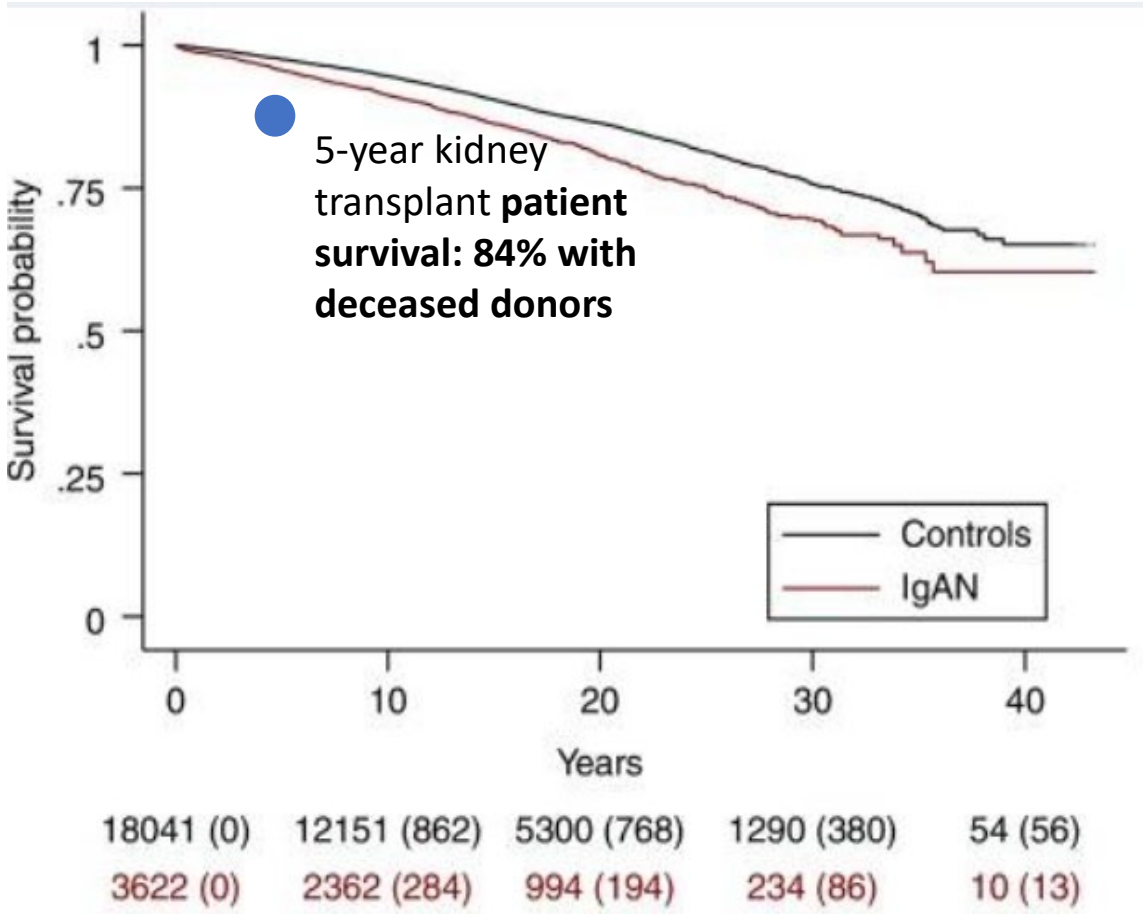
- All prior accelerated review approvals have been based on **1 pivotal trial**.

CDER Drug and Biologic Accelerated Approvals Based on a Surrogate Endpoint", 2023; Clinical Trials (igan.org) October 2023; NCT04573478

Outcomes - IgA nephropathy and kidney transplant



5-year kidney transplant **graft survival: 74% with deceased donors**



5-year kidney transplant **patient survival: 84% with deceased donors**

Hastings MC, Bursac Z, Julian BA, et al. Life Expectancy for Patients From the Southeastern United States With IgA Nephropathy. *Kidney Int Rep*. 2017;3(1):99-104. Published 2017 Aug 24. doi:10.1016/j.ekir.2017.08.008; Jarrick S, Lundberg S, Welander A, et al. Mortality in IgA Nephropathy: A Nationwide Population-Based Cohort Study. J Am Soc Nephrol. 2019;30(5):866-876. doi:10.1681/ASN.2018101017; UNOS. September 2023.

iBOX is our best option

1. Only endpoint in FDA Biomarker Qualification Program addressing patient, regulatory, and clinician needs.

2. Best prognostic endpoint for long-term graft survival.

3. Allows for superiority of a new therapy and a new indication.

4. Does not preclude traditional approval on efficacy failure if iBOX fails but meets non-inferiority on efficacy failure.

5. Current efficacy failure/BPAR remains.

6. Opportunity to incentivize the introduction of innovative graft-preserving therapies through accelerated approval compared to traditional approval.

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Estimated GFR (eGFR) as a Surrogate Endpoint: FDA perspective

FDA-Univ of Manitoba Workshop on Endpoints and Trial Designs to Advance Drug Development in Kidney Transplantation

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US Food and Drug Administration
Division of Rheumatology and Transplant Medicine
November 9, 2023

Disclaimer and disclosure

- This presentation is not intended to convey official US FDA policy or views.
- The materials presented are available in the public domain.
- I do not have any financial interest or conflict of interest to disclose.

Outline of Presentation

- Defining kidney function as a surrogate endpoint (SE)
- eGFR as a SE: The CKD example
- Reversible hemodynamic effect of calcineurin inhibitors (CNI) as a confounder of an eGFR SE
- eGFR as a potential SE in kidney transplant trials

Defining kidney function as a SE

- Large change in creatinine (i.e., doubling of serum creatinine)
- Reduction in rate of GFR decline (e.g., slope-based endpoint)

→

- Confounded by non-GFR determinants
- Confounded by medication effect / other mechanisms of allograft injury

→

- Also confounded by reversible medication effect
- Examples of use in kidney transplant trials

Maggiore U, Leventhal J, Cravedi P. Rethinking clinical endpoints in kidney transplant trials. Curr Opin Organ Transplant 2020; 25:1-7.

eGFR as a SE: The CKD Example

Reference endpoints in CKD	
End stage kidney disease / Kidney failure (treatment with dialysis, transplantation, eGFR<15 ml/min/1.73m^2)	Clinical endpoint
Doubling of serum creatinine (Serum Cr) / 57% decline in eGFR	Accepted surrogate endpoint

2012 NKF-FDA Workshop	
≥ 40% decline in GFR (confirmed)	Validated surrogate endpoint

2018 NKF-FDA-EMA Workshop	
GFR slope reduction measured over an adequate period of time	Validated surrogate endpoint

Reversible effects of the treatment on GFR may complicate interpretation of treatment effect and trial design

Source: Table adapted from Table 8, Levey A, Gansevoort R, Coresh J, et al. Change in Albuminuria and GFR as Endpoints for Clinical Trials in Early Stages of CKD: A Scientific Workshop Sponsored by the National Kidney Foundation in Collaboration with the US Food and Drug Administration and European Medicines Agency. 2020; 75(1): 84-104.

Reversible hemodynamic effect of CNIs as a confounder of an eGFR SE

- Definition: Acute, functional, dose-dependent, and generally reversible acute decline in kidney function
- Associated with: Higher tacrolimus levels (i.e., C_0>20 ng/ml)
- Mechanism: Alterations of intrarenal hemodynamics leading to reduced GFR
- Diagnosis: Often presents with an increase in plasma creatinine concentration
- May be more pronounced in the setting of volume depletion and concomitant meds (e.g., diuretics, NSAIDs)

This hemodynamic effect on an eGFR based endpoint may complicate interpretation of treatment effect and trial design

Farouk S, Rein J. The many faces of Calcineurin Inhibitor Toxicity- What the FK? Adv Chronic Kidney Dis. 2020 January; 27(1): 56-66.

eGFR as a SE in Kidney Transplantation

1. **The Relationship Between Kidney Function and Long-term Graft Survival After Kidney Transplant.** Kasiske B, Israni A, Snyder J, et al on behalf of Patient Outcomes in Renal Transplantation (PORT) Investigators. Am J Kid Dis **2011**; 57 (3):466-475.

Background: Whether chronic kidney disease (CKD) staging provides a useful framework for predicting outcomes after kidney transplant is unclear.

Study Design: Retrospective cohort study.

Setting & Participants: We used data from the Patient Outcomes in Renal Transplantation (PORT) Study, including 13,671 transplants from 12 centers during 10 years of follow-up.

Predictor: Estimated glomerular filtration rate (eGFR; in milliliters per minute per 1.73 m^2) at 12 months posttransplant.

Outcomes: All-cause graft failure (a composite end point consisting of return to dialysis therapy, pre-emptive retransplant, or death with function), death-censored graft failure, and death with a functioning graft.

Measurements: The relationship between 12-month eGFR and subsequent graft outcomes through 10 years posttransplant was assessed using Cox proportional hazards analyses.

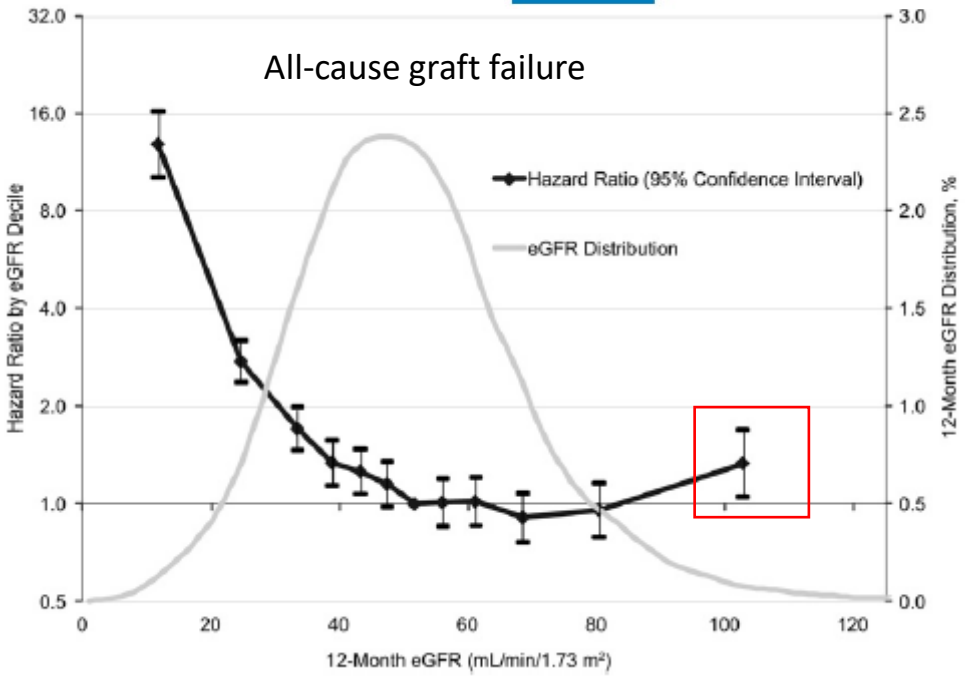
eGFR as a SE in Kidney Transplantation

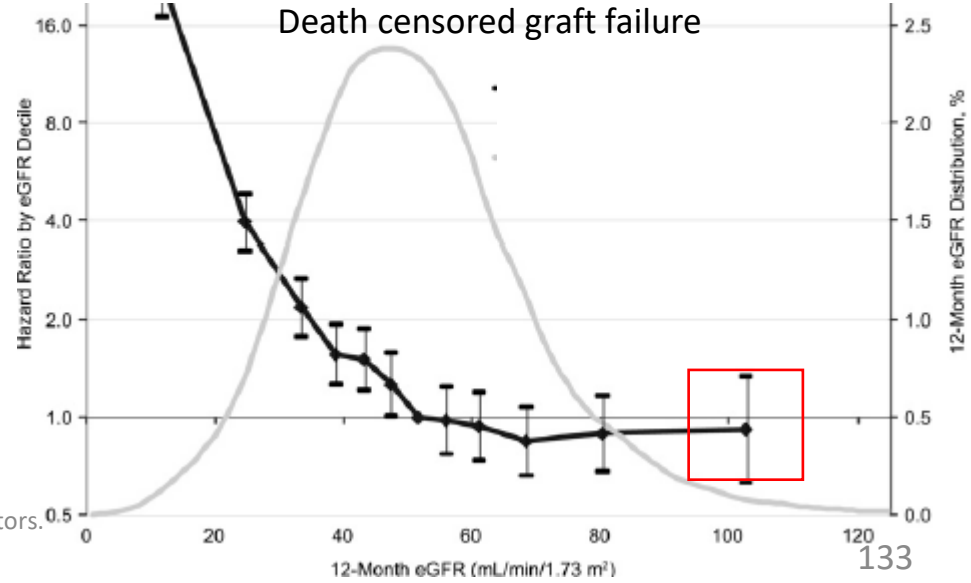
Table 3. Relationship Between CKD Stage at 12 Months Posttransplant and Subsequent Graft and Patient Survival

		HR (95% CI); *P*		
CKD Stage (eGFR)	%[a]	Graft Failure	Death-Censored	Death With Function
1 (≥90 mL/min/1.73 m^2)	3	1.41 (1.13-1.75); 0.002	1.04 (0.73-1.48); 0.8	1.61 (1.22-2.14); <0.001
2 (60-89 mL/min/1.73 m^2)	24	1.00 (reference)	1.00 (reference)	1.00 (reference)
3a (45-59 mL/min/1.73 m^2)	34	1.13 (1.02-1.25); 0.03	1.25 (1.08-1.44); 0.003	0.98 (0.84-1.13); 0.8
3b (30-44 mL/min/1.73 m^2)	29	1.53 (1.38-1.69); <0.001	2.01 (1.75-2.32); <0.001	1.07 (0.92-1.25); 0.4
4 (15-29 mL/min/1.73 m^2)	9	2.97 (2.63-3.35); <0.001	4.63 (3.95-5.44); <0.001	1.58 (1.30-1.91); <0.001
5 (<15 mL/min/1.73 m^2)	1	14.11 (11.35-17.54); <0.001	26.69 (20.85-34.18); <0.001	2.80 (1.51-5.17); 0.001

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
[a]Percentage of the study population at each CKD stage.

"Although results show that lower kidney function is associated with worse outcomes, it is not possible to infer that specific measures that alter function will necessarily alter outcomes. In particular, we cannot determine whether different immunosuppressive medication regimens can alter function and thereby outcomes; only randomized trials can do this."





Source: Table 3, Figure 1, Figure 2. Kasiske B, Israni A, Snyder et al on behalf of Patient Outcomes in Renal Transplantation (PORT) Investigators. The Relationship Between Kidney Function and Long-term Graft Survival After Kidney Transplant. Am J Kid Dis 2011; 57 (3):466-475.

eGFR as a SE in Kidney Transplantation

2. Relationship between eGFR Decline and Hard Outcomes after Kidney Transplants. Clayton P, Lim W, Wong G et al. JASN 2016 (27): 3440-3446.

ABSTRACT

Trials designed to assess the effect of interventions on death and graft failure in kidney transplant recipients are not feasible, because these are predominantly late events. Here, we examined the potential of percentage decline in eGFR as a surrogate for hard outcomes. We obtained deidentified data from the Australia and New Zealand Dialysis and Transplant Registry and studied 7949 transplants performed from 1995 to 2009, including 71,845 patient-years of follow-up, 1121 graft losses, and 1192 deaths. We used adjusted Cox proportional hazards models to determine risks of death or death–censored graft failure related to percentage change in eGFR between years 1 and 3 after transplant. Percentage change in eGFR was modeled as a restricted cubic spline. Rate of eGFR decline associated with exponentially increased risks of graft failure and death. Compared with stable eGFR, a ≥30% decline in eGFR, detected in 10% of patients, strongly associated with subsequent death (hazard ratio, 2.20; 95% confidence interval, 1.87 to 2.60) and death–censored graft failure (hazard ratio, 5.14; 95% confidence interval, 4.44 to 5.95). Decline in eGFR was superior to other surrogates, including acute rejection, doubling of serum creatinine level, and eGFR at year 1 or year 2. We conclude that 30% decline in eGFR between years 1 and 3 after kidney transplant is common and strongly associated with risks of subsequent death and death–censored graft failure, which mirrors findings in CKD. Percentage decline in eGFR should be considered for use as a surrogate outcome in kidney transplant trials.

J Am Soc Nephrol 27: 3440–3446, 2016. doi: 10.1681/ASN.2015050524

eGFR as a SE in Kidney Transplantation

Table 3. Relationships between percentage eGFR decline between years 1 and 3 post-transplant and outcome

eGFR Decline	Prevalence, %	Graft Failure		Patient Death	
		HR (95% CI)	*c* Statistic	HR (95% CI)	*c* Statistic
≥10%	33	2.09 (1.91 to 2.29)	0.68	1.52 (1.35 to 1.71)	0.75
≥20%	19	2.50 (2.26 to 2.77)	0.69	1.84 (1.62 to 2.10)	0.75
≥30%	10	3.58 (3.16 to 4.05)	0.70	2.20 (1.87 to 2.60)	0.75
≥40%	5	5.24 (4.43 to 6.20)	0.69	2.57 (2.04 to 3.22)	0.75
≥50%	3	7.90 (6.21 to 10.06)	0.67	2.96 (2.17 to 4.04)	0.75

Table 4. Associations between different eGFR–based surrogate outcomes and hard outcomes

Outcome	Prevalence, %	Graft Failure		Death–Censored Graft Failure		Patient Death	
		HR (95% CI)	*c* Statistic	HR (95% CI)	*c* Statistic	HR (95% CI)	*c* Statistic
≥30% decline eGFR 1–3 yr	9.9	3.58 (3.16 to 4.05)	0.70	5.14 (4.44 to 5.95)	0.75	2.20 (1.87 to 2.60)	0.75
≥30% decline eGFR 1–2 yr	6.1	3.51 (3.01 to 4.09)	0.68	4.69 (3.92 to 5.61)	0.72	2.33 (1.91 to 2.86)	0.75
≥30% decline eGFR 6 mo to 2 yr	8.7	2.94 (2.59 to 3.35)	0.68	4.16 (3.59 to 4.83)	0.73	1.99 (1.68 to 2.36)	0.75
eGFR at 1 yr <45 ml/min per 1.73 m^2	32.3	1.85 (1.69 to 2.02)	0.67	2.60 (2.31 to 2.93)	0.73	1.39 (1.24 to 1.56)	0.74
eGFR at 2 yr <45 ml/min per 1.73 m^2	33.7	2.21 (2.01 to 2.42)	0.68	3.16 (2.78 to 3.58)	0.74	1.68 (1.49 to 1.89)	0.75
Rejection first 6 mo	24.4	1.34 (1.21 to 1.47)	0.66	1.37 (1.21 to 1.55)	0.69	1.27 (1.12 to 1.44)	0.75
Double creatinine 1–3 yr	1.9	9.87 (7.27 to 13.42)	0.66	15.20 (11.18 to 20.67)	0.70	2.81 (1.84 to 4.29)	0.75
ΔeGFR 1–3 yr <−15 ml/min per 1.73 m^2	12.0	2.48 (2.20 to 2.81)	0.68	3.28 (2.84 to 3.80)	0.72	1.77 (1.50 to 2.09)	0.75

All models are adjusted for age at transplant, sex, race, primary disease, diabetes, coronary artery disease, peripheral vascular disease, cerebrovascular disease, chronic lung disease, donor type, prior transplant, donor age, HLA mismatch, peak panel–reactive antibodies, and era.

Source: Tables abstracted from Clayton P, Lim W, Wong G et al. Relationship between eGFR Decline and Hard Outcomes after Kidney Transplants. JASN 2016 (27): 3440-3446.

eGFR as a SE in Kidney Transplantation

3. **Allograft Function as Endpoint for Clinical Trials in Kidney Transplantation.** Hilbrands L, Budde K, Bellini M, et al. Transplant International 2022; 35:1-11.

- The CHMP agreed that conceptual approaches used to assess efficacy endpoints for dysfunction can be extrapolated to kidney transplantation, as far as the concomitant medications and diseases are comparable
- The impact of additional nephrotoxicity (e.g., in cases of CNI or viral nephropathy due to over immunosuppression) should be delineated from lower potential to preserve functional efficacy"
- Choice of GFR-based endpoint will depend on baseline rate of GFR decline, feasibility issues (e.g., disease prevalence, estimated efficacy of the medicinal product)
- Clinically relevant magnitude of effect size. Clinical significance of the proposed difference in slope progressions between treatment arms (active or placebo) should be defined for the specific development
- Annualized loss of GFR does not meet all criteria for a valid surrogate endpoint, but (properly defined) is considered as a valuable measure of efficacy in addition to the currently accepted hard clinical endpoints (incidence of ESRD and renal/overall survival)
- Efficacy should be supported by other clinical measures (e.g., second study or other endpoints, most often standard renal endpoints)

Takeaways

- Reversible hemodynamic effects of CNIs will need to be considered and accounted for in kidney transplant trials, if eGFR is proposed as a SE
- Late graft failure is more complex than renal failure resultant from native kidney disease because of competing risks involved at different time points
- For kidney transplantation, a quantifiable proposed change in eGFR as a SE will need to show a clinically meaningful and statistically significant effect on clinical endpoints in kidney transplantation (i.e., graft failure/survival)

Acknowledgements

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Thank You!

eGFR as an Endpoint: An Academic Perspective

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Steering Committee: CSL-Behring Imagine Trial
Other: Deputy Editor | Am Jnl Transplant; Trustee | Banff Foundation

AND

My presentation **does not** include discussion of off-label or investigational use.

The Challenge is Late Allograft Failure

- Long term graft survival is **still** the challenge we face.
  - Includes both non-immunologic and immunologic entities,[1] the latter of which have no approved therapies (CA-TCMR; CA-AMBR).[2]
- Current management decisions of induction and maintenance IST focuses on **early outcomes—***the status quo*.
- Therapeutic development of new agents **lacks** any regulatory pathway to assess long term impact.
- To develop new agents to address these unmet needs, we need methodology that informs us whether a therapy **may improve** long term outcomes.

[1]Langewisch E, Mannon RB. *CJASN* 2021; 16:1723. [2]Kim, Brennan. *Front Pharmacol* 2021; 12:651222

Endpoints for Clinical Trials: Many Meetings, Little Change

- Discussed in FDA workshops of 2012 (Silver Spring) and 2015 (Arlington) and 2018 (Silver Spring)[1]
  - TTS post FDA workshop 2015[2]
- "Surrogate endpoints at one year that correlate with subsequent graft loss will further enhance trial feasibility"[1,2]
  - eGFR and proteinuria are clearly *prognostic* of late graft loss.
  - Other biological markers include biopsy histology and HLA DSA are *predictive*.
  - **"Combining both of these types of markers can uniquely inform about the graft outcomes."**

[1]Mannon et al. *Am Jnl Transplant* 2020; 20: 1495.
[2]O'Connell, Kuypers, Mannon et. al. *Transplantation* 2017; 101:1527.

Objectives

- eGFR as a proxy of kidney/allograft function.
  - Impact of tacrolimus, the standard of care CNI, on eGFR.
  - Understanding the dissociation between eGFR and specific treatments.
  - Potential for iBOX to improve eGFR prognostic ability.
- eGFR slope in the first transplant year
  - eGFR slope beyond 1 year in transplantation

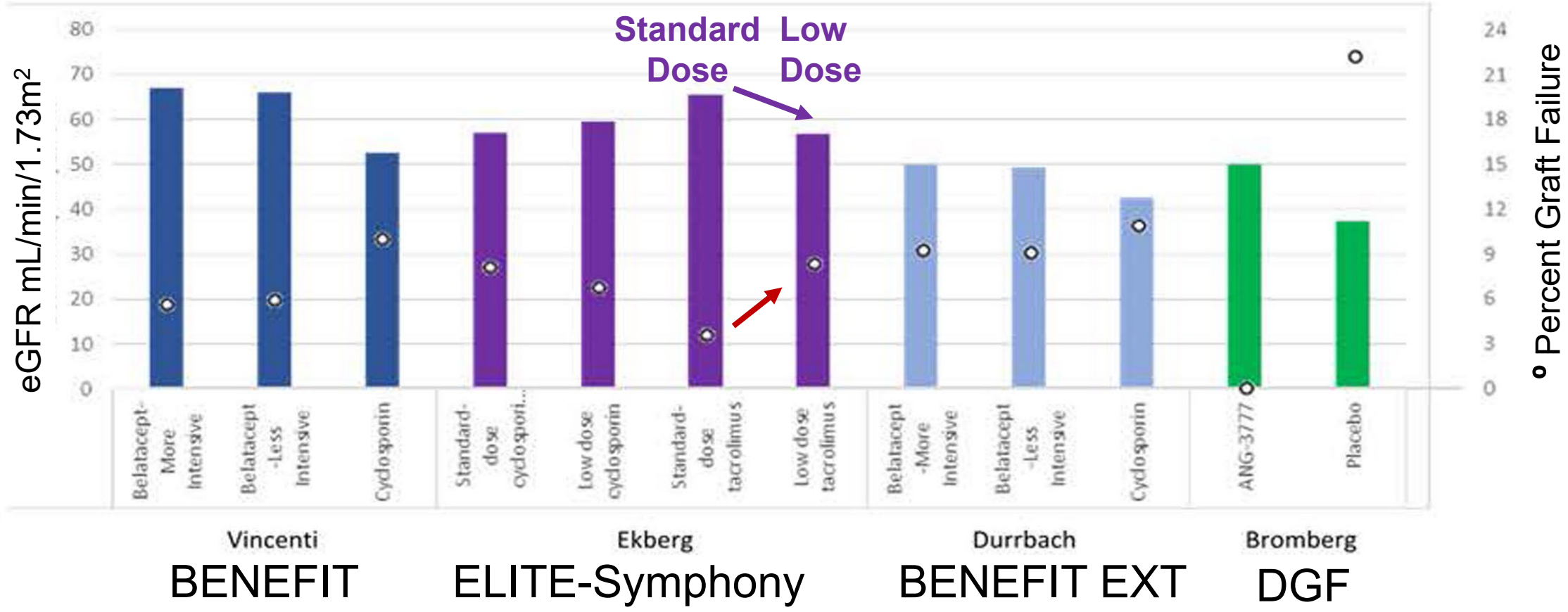
General Comments about GFR in Kidney Transplantation

- GFR is clinically important and strongly associated with graft failure.[1,2]
  - However, eGFR is not reasonable to utilize alone as a surrogate for graft loss.[3]
- Clinical monitoring uses serum creatinine (not cystatin C in adults).
- Multiple equations have been developed from native kidneys, larger studies, primarily of North Americans.
  - Performance in KTRs suboptimal but accepted in practice and regulation.[4,5]
  - MDRD Equation (1999) | CKD-EPI Equation (2009) | Creatinine/cystatin equation (2012) | RF KTS equation (2023)[6]

[1]Loupy A, et al. *BMJ* 2019 Sep 17:366:l4923. [2]Mayne et al. Clin Transplant 2021; 35:e14326 [3]Kaplan et al. Am Jnl Transplant 2003; 3:1560; [4]Murata K.*CJASN;* 2011; 8:1963 [5]Masson I et. al. *Transplantation* 2013;l 95(10):1211 [6]Raynaud M et al. *BMJ* 2023;381:e073654

eGFR at 1 Year is Inversely Related to DCGL….Usually

Mayne et al. Clin Transplant 2021; 35:e14326



Hemodynamic Impacts of Calcineurin Inhibitor Therapy: Tac is not CsA

- Acute infusion studies in anesthetized rats show CsA renal vasoconstrictive effect (mitigated by ARB or ET1 blockade) with absent with Tac.[1]
- Similar findings using po treatment in health humans for 2 weeks.[2]

	Baseline	Cyclosporine	Tacrolimus
Body weight (kg)	76.9±13.1	77.7±12.8[b]	76.7±13.0
Mean arterial pressure (mmHg)	93±8	108±10[b]	96±11
Plasma creatinine (μmol/L)	100±11	105±15	97±13[d]
ERPF (ml/min/1.73 m^2)	597±108	438±84[c]	588±103
GFR (ml/min/1.73 m^2)	98±9	85±10[c]	93±7
RBF (ml/min/1.73 m^2)	1088±204	819±156[c]	1085±149
RVR (mmHg*min/l/1.73 m^2)	87±19	144±45[c]	89±20

- Resistive Index and MAP was significantly lower in KTR treated with Tac compared to CsA (n=48).[3]

[1]Gardiner SM. *Brit Jnl Pharm* 2004; 141:634 [2]Klein I. *Transplant* 2022; 73:732 [3]Radermacher J. *Transplant Int* 1998; 11:3.

Bela and Tac Arms Have Similar 1-year eGFR

- In a series of Belatacept trials comparing to Tac, Adams (Emory; n=745)[1], Woodle (BEST; N=316)[2], and Kumar (meta-analysis)[3] all demonstrate that 1-year eGFR is similar in BELA vs. Tac regimens.
  - Mean eGFR ranged 55.9±8.9 – 63.8± 18.0 mL/min/1.73m^2
- Grinyo et al. (conversion study) demonstrated no significant difference in eGFR between Tac and BELA for the 1st year *after* conversion, unlike the CsA vs. BELA groups where there were differences in eGFR.[4]

[1]Adams AB, et al. *Am J Transplant*. 2017;17(11):2922. doi:10.1111/ajt.14353.
[2]Woodle ES, et al. *Am J Transplant*. 2020;20(4):1039. doi:10.1111/ajt.15688.
[3]Kumar J, et al. *World J Transplant*. 2021;11(3):70. doi:10.5500/wjt.v11.i3.70
[4]Grinyo J, et al. *Transpl Int*. 2012;25(10):1059. doi:10.1111/j.1432-2277.2012.01535.x

CNI Avoidance with mTORi: Less IFTA | eGFR is Similar

TABLE 3. Histologic features of 1-year surveillance biopsies of kidney transplant recipients managed continuously with tacrolimus- or sirolimus-based immunosuppression

Histologic index	Tacrolimus (n=57)	Sirolimus (n=38)	*P*
Number of glomeruli (mean±SD/%≤6)	14.2±6.8/8%	13.1±6.4/14%	0.4
% Sclerotic glomeruli (mean±SD/%≥20%)	6.9±11.6/7%	13.1±6.4/13%	0.3
g (mean±SD/%≥1)	0.23±0.50/19%	0.13±0.34/13%	0.3
cg (mean±SD/%≥1)	0.05±0.23/3%	0.05±0.32/5%	1.0
mm (mean±SD/%≥1)	0.09±0.29/5%	0.05±0.23/9%	0.5
i (mean±SD/%≥1)	0.23±0.54/18%	0.16±49/11%	0.5
t (mean±SD/%≥1)	0.40±0.73/28%	0.32±0.62/24%	0.5
i+t (mean±SD/%≥2)	0.63±1.20/14%	0.47±1.06/11%	0.5
v (mean±SD/%≥1)	0/0%	0/0%	—
ah (mean±SD/%≥1)	0.35±0.48/35%	0.39±0.50/39%	0.7
ci (mean±SD/%≥2)	0.86±0.79/21%	0.53±0.60/5%	0.03
ct (mean±SD/%≥2)	1.26±0.55/25%	1.03±0.37/8%	0.02
ci+ct (mean±SD/%≥3)	2.12±1.27/25%	1.55±0.86/5%	0.02
cv (mean±SD/%≥2)	0.68±0.66/11%	0.63±0.63/8%	0.7
ci+ct+cv (mean±SD/%≥4)	2.81±1.51/30%	2.18±1.33/11%	0.04
% interstitial fibrosis (mean±SD/%≥20%)	11.0±11.5/30%	6.9±7.8/11%	0.06

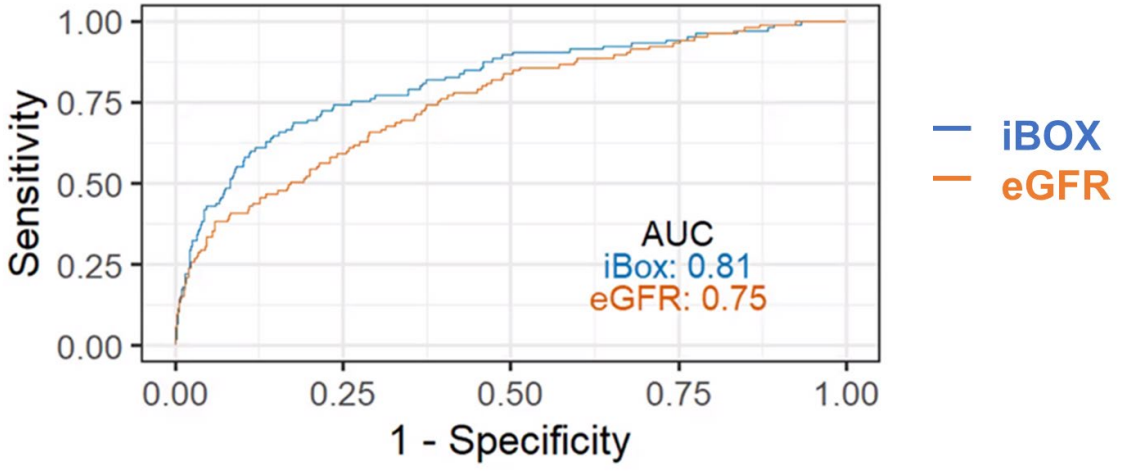
TABLE 2. Characteristics of patients from the two treatment groups that were eligible for inclusion in the histologic analysis study

	Tacrolimus (n=57)	Sirolimus (n=38)	*P*
Recipient age (mean±SD)	47±16 yr	50±14 yr	0.27
Recipient gender (M:F)	29:28	21:16	0.57
Primary transplant	47 (82%)	34 (89%)	0.39
Living donor transplant	51 (89%)	34 (89%)	0.99
Donor age (mean±SD)	43±13 yr	42±10 yr	0.57
Acute rejection (clinical or subclinical) during first year	6/57 (11%)	3/38 (8%)	0.74
GFR 1 mo after transplant (mean±SD)	56±15 mL/min/SA	62±19 mL/min/SA	0.11
GFR 1 yr after transplant (mean±SD)	55±16 mL/min/SA	57±16 mL/min/SA	0.7

Dean PG…Stegall M. *Transplant* 2008; 85:1212

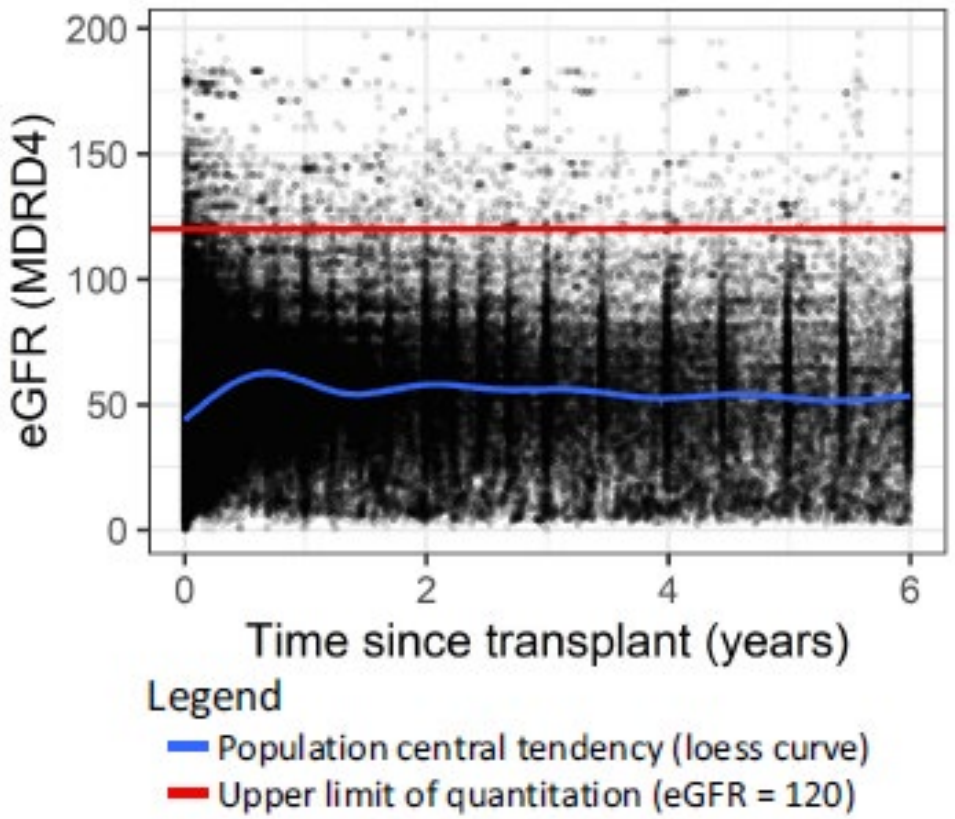
Improvement of the Prognostic Ability of eGFR on Long-Term Graft Survival: Multicomponent Biomarker

Dataset	Full iBOX c-statistic (SE)	eGFR c-statistic (SE)
PTG Derivation N = 1174	0.83 (0.02)	0.77 (0.02)
Helsinki University Hospital N = 344	0.77 (0.06)	0.73 (0.07)
Mayo Clinic Rochester N = 483	0.92 (0.03)	0.86 (0.04)
BENEFIT RCT N = 435	0.71 (0.09)	0.63 (0.09)
BENEFIT-EXT RCT N = 272	0.83 (0.07)	0.82 (0.07)



Trajectory of eGFR in 1st Post-Transplant Year

- GFR in the first post-transplant year is subject to early changes associated with organ procurement, implantation and reperfusion, donor quality, followed by recipient factors such as medications (TMP, h2 blockers) and immune responses.
  - Tac vs. BELA regimens demonstrate that eGFR even on Tac gradually increases, not decreases, over the first year.[1]
- C-Path's longitudinal eGFR model demonstrates that eGFR trajectories, in 1st year post-transplant, are **nonlinear and highly individualized** in kidney transplant patients.[2]
  - This creates additional challenges for applying a linear slope or % change-based method for evaluating kidney function between groups of transplant recipients, while a single, 12-month-based measurement offers a practical method of comparison.



[1]Adams AB, et al. *Am J Transplant*. 2017;17(11):2922. doi:10.1111/ajt.14353.
[2]Kosinski L et al. .Clin Transl Sci. 2023; DOI: 10.1111/cts.13579

Trajectory Based Assessment of eGFR and Risk of Graft Failure after First Year: Tool for Entity Specific Interventions

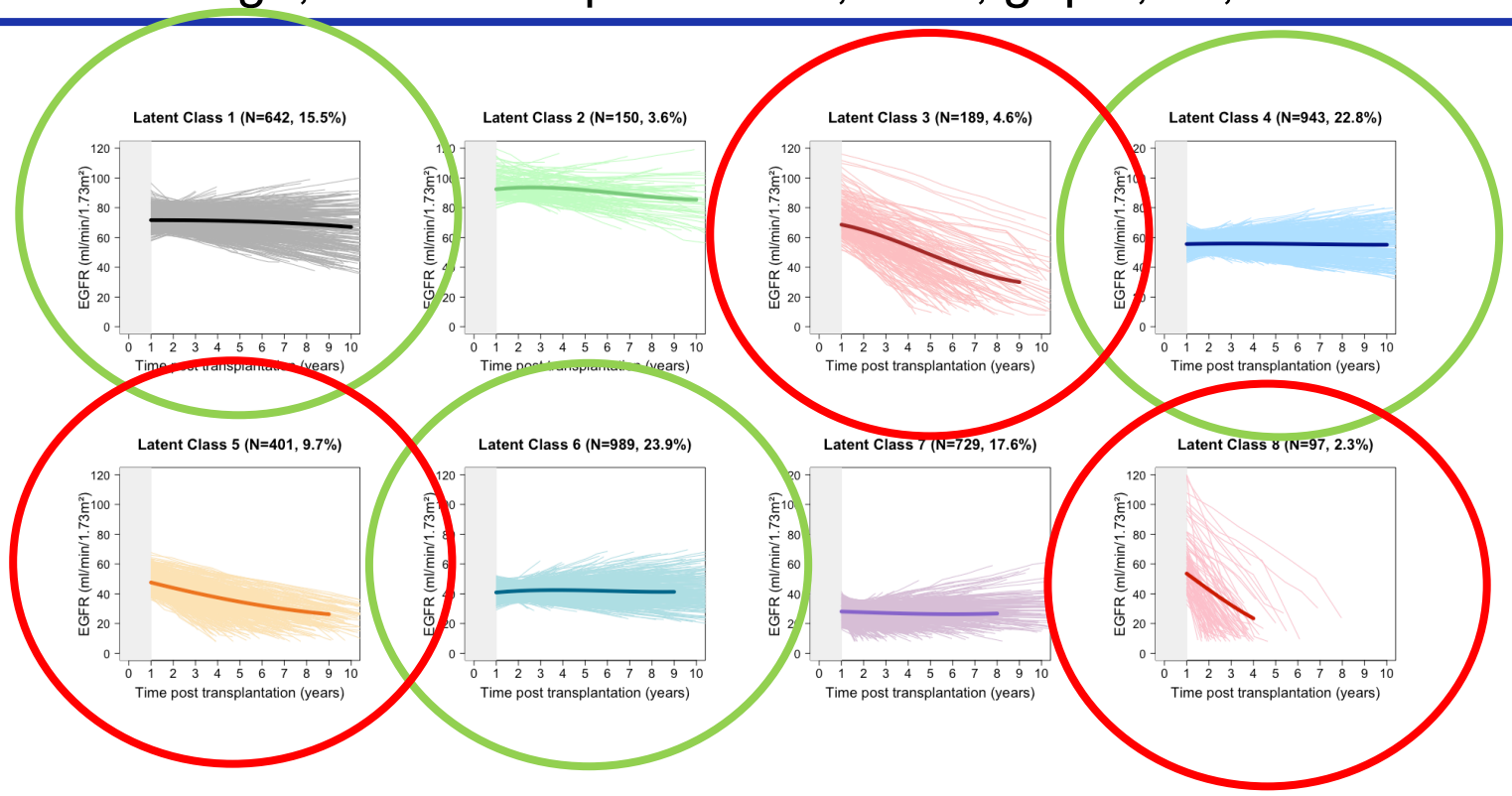
Cohort: 14,132 Kidney transplant recipients

15 transplant centers, Europe and US, 2001-2016

At least 2 eGFR measurements after 1y post-transplant

Independent Determinants of eGFR Trajectory

Donor age, eGFR and proteinuria, IFTA, g+ptc, i+t, HLA DSA



Latent class	eGFR baseline	eGFR slope per year	Functional correspondence
#1	**71.6** (10.4)	**-0.75** (3.10)	High baseline, stable
#2	**91.6** (11.4)	**-1.04** (3.37)	Very high baseline, slightly decreasing
#3	**70.1** (15.9)	**-8.88** (3.44)	High baseline, fast declining
#4	**55.6** (8.11)	**-0.13** (2.51)	Middle baseline, stable
#5	**48.2** (10.3)	**-5.38** (2.46)	Low baseline, decreasing
#6	**41.0** (7.1)	**0.12** (2.40)	Low baseline, stable
#7	**28.4** (6.4)	**-2.97** (6.00)	Very low baseline, slow decreasing
#8	**58.0** (18.5)	**-23.9** (8.76)	Middle baseline, fast declining

Raynaud et al. *Kidney Int* 2021; 99: 186-197

Summary

- eGFR is an important prognostic factor of kidney allograft with caveats.
- The change from CsA-based control arms to tacrolimus as standard of care has affected one-year eGFR comparisons with Bela (as an example).
  - Regardless, this change does not provide any information of how new agents may perform relative to Tac.
- Addition of features in iBOX multi-composite significantly improves the prognostic performance of eGFR (proteinuria, DSA, histology)
- First-year slope of eGFR post-transplant is limited in its utility.
  - However, slopes of eGFR (and proteinuria) have value for interventions later post transplant.

SESSION 2: BIOPSY PROVEN ACUTE REJECTION (BPAR) EFFICACY FAILURE

Defining BPAR – past, present, future?

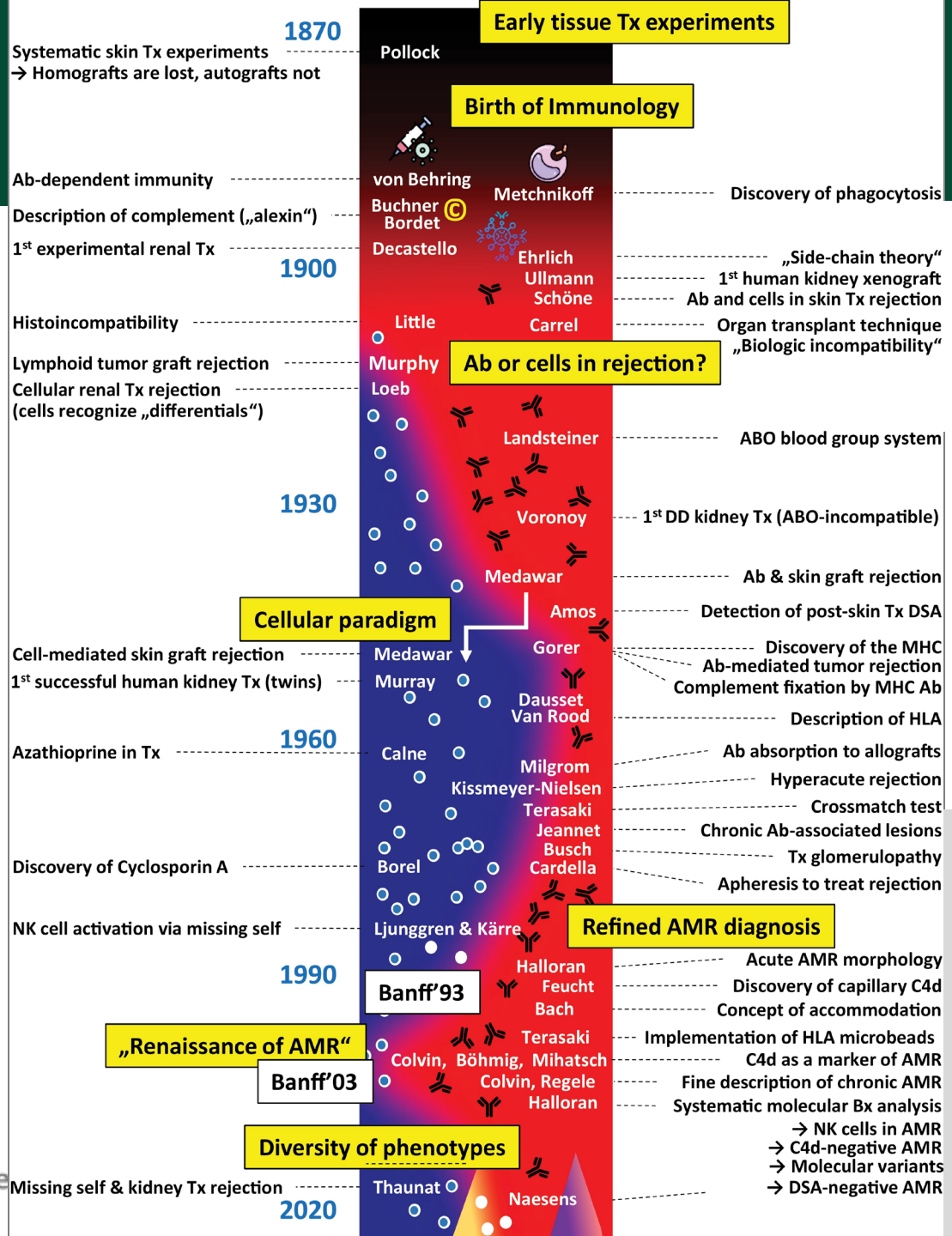
Michael Mengel

University of Alberta, Edmonton, Canada

Disclosures

- Honorarium: CSL Behring, DEKA Inc.
- Associate Editor American Journal of Transplantation
- Chairman, Board of Trustees, Banff Foundation For Allograft Pathology

I will not discuss the off label use of drugs/medication



On a Long and Winding Road: Alloantibodies in Organ Transplantation

Böhmig, Georg A.; Halloran, Philip F.; Feucht, Helmut E.

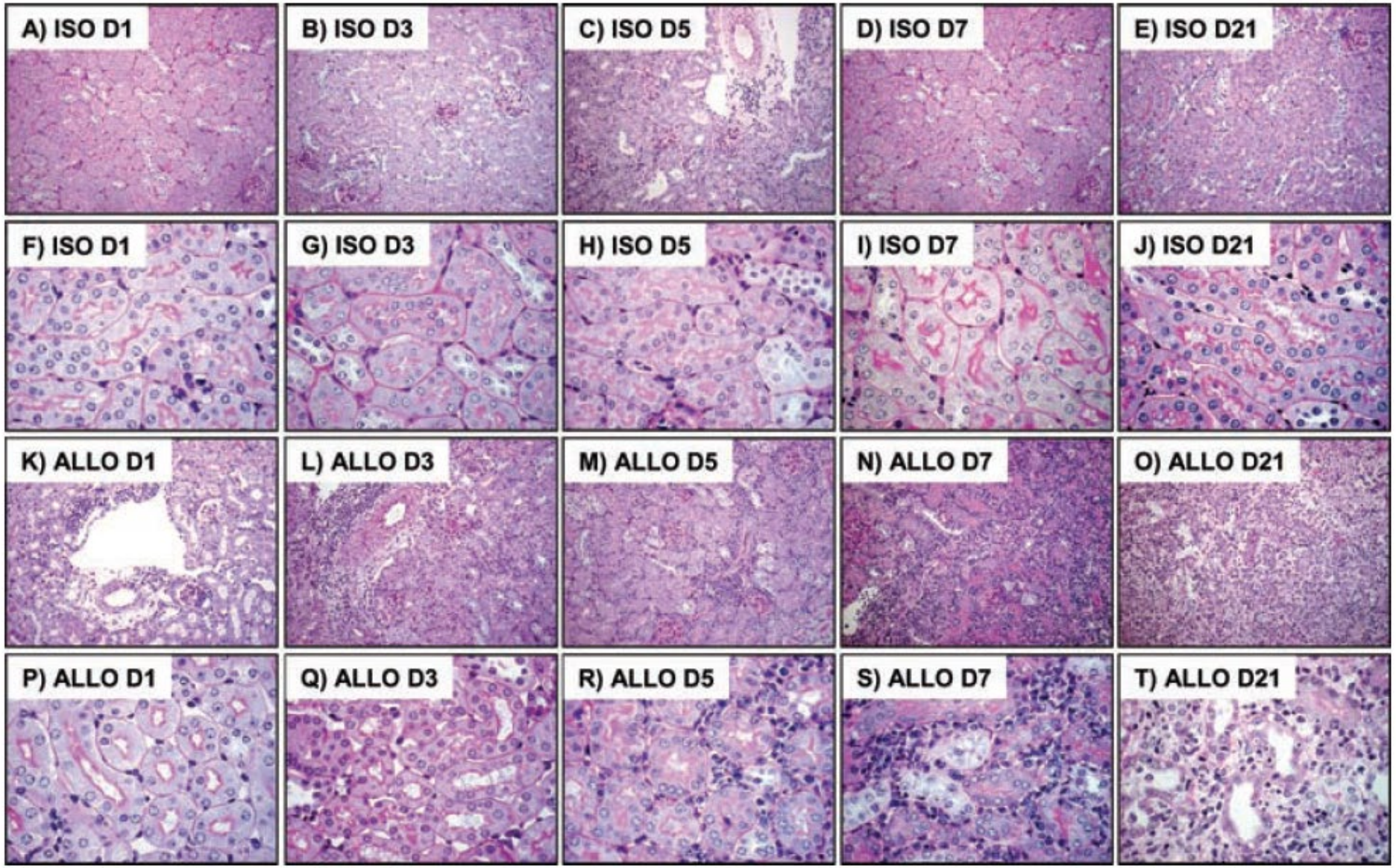
Transplantation : March 22, 2023

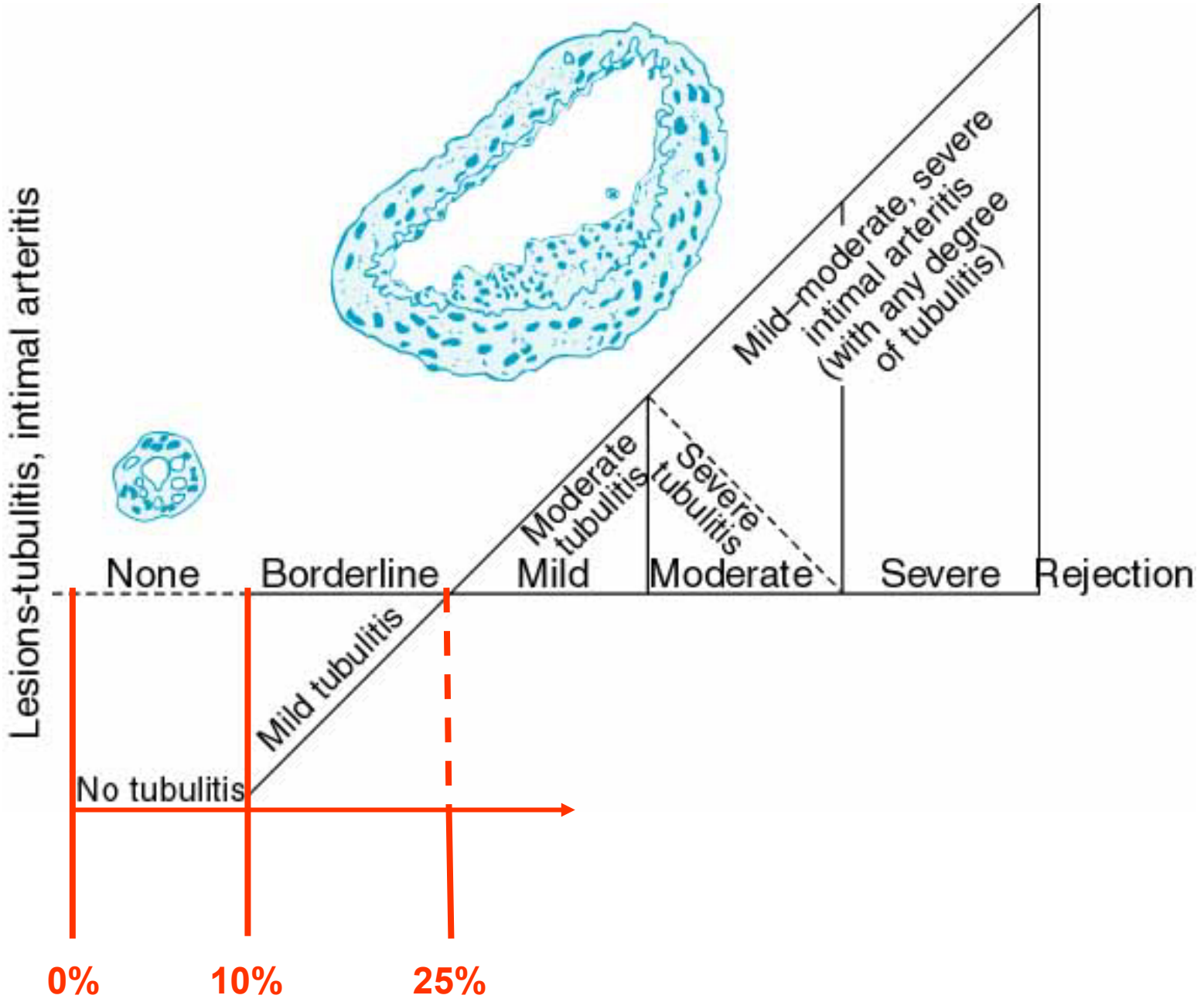
doi: 10.1097/TP.0000000000004550

Discoveries contributing to our understanding of cellular-mediated rejection versus AMR. The scheme provides a selection of discoveries and researchers that have contributed to our understanding of rejection. Ab, antibody; AMR, antibody-mediated rejection; DD, deceased donor; DSA, donor-specific antibody; MHC, major histocompatibility complex; NK cell, natural killer cell; Tx, transplantation.

Time course of TCMR in fully mismatched, untreated mice

images courtesy by Gunilla Einecke, PhD thesis work

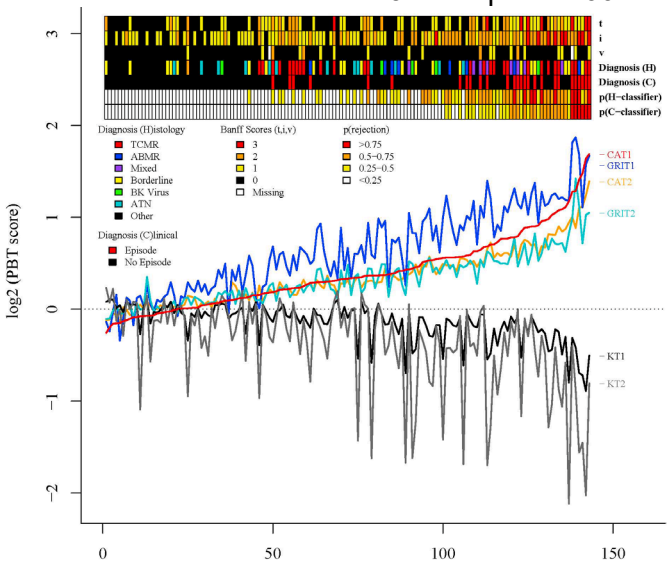




by Lorraine Racusen & Kim Solez 1991

Microarray analysis of rejection in human kidney transplants using pathogenesis-based transcript sets.

Mueller TF, Einecke G, Reeve J, Sis B, Mengel M, Jhangri GS, Bunnag S, Cruz J, Wishart D, Meng C, Broderick G, Kaplan B, Halloran PF.
Am J Transplant. 2007 Dec;7(12):2712-22.



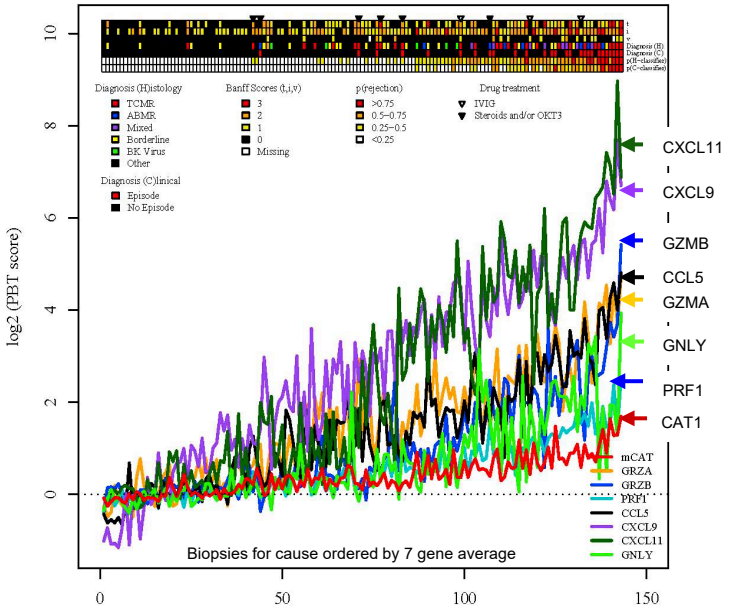


TABLE 4. Probability of upregulation of genes in pathogenesis based transcripts sets, compared by C4d staining status

Groups*	KT	IRIT	GRIT	QCAT	CMAT	AMA	BAT	NKST	IGT	ENDAT
G2–G1	0.34	0.30	0.70	0.64	0.67	0.40	0.26	0.18	0.35	0.44
G2–G6	0.73	0.16	**0.02	**0.05	**0.05	0.07	0.07	0.06	**0.01	**0.04
G1–G3	0.38	0.48	**0.005	**0.02	**0.002	0.23	0.27	0.62	**0.007	0.11
G1–G4	0.86	0.25	**<0.001	**0.004	**0.002	0.16	0.12	0.52	**0.04	**0.03
G1–G5	0.76	0.40	**<0.001	**0.02	**0.01	0.20	0.31	0.43	0.09	0.13
G1–G6	0.91	0.36	**<0.001	**0.03	**0.01	0.17	0.20	0.44	**0.048	0.09
G3–G5	0.81	0.40	0.1	0.51	0.59	0.37	0.58	0.22	0.57	0.47
G4–G6	0.52	0.31	0.14	0.19	0.20	0.42	0.17	0.55	0.59	0.10

*Comparison made on the ratio of the first group to the second.
**P value for significance, <0.05.
KT, kidney transcripts; IRIT, injury and repair-induced transcripts; GRIT, gamma-interferon and rejection-induced transcripts; QCAT, quantitative cytotoxic T cell–associated transcripts; CMAT, quantitative constitutive macrophage-associated transcripts; AMA, alternative macrophage activation transcripts; BAT, B cell–associated transcripts; NKST, natural killer cell selective transcripts; IGT, immunoglobulin transcripts; ENDAT, endothelial cell–associated transcripts.

G1. Focal or diffuse PTC C4d+ (N=13)
G2. Minimal PTC C4d+ (N=4)
G3. Isolated glomerular C4d+ with glomerular disease (N=13)
G4. Isolated glomerular C4d+ staining without glomerular disease (N=15)
G5. C4d negative with glomerular disease (N=12)
G6. C4d negative biopsies without evidence of glomerular disease (N=25)

Hayde N, Bao Y, Pullman J, Ye B, Calder BR, Chung M, Schwartz D, Alansari A, de Boccardo G, Ling M, Akalin E. Transplantation. 2013 27;95(4):580-8.

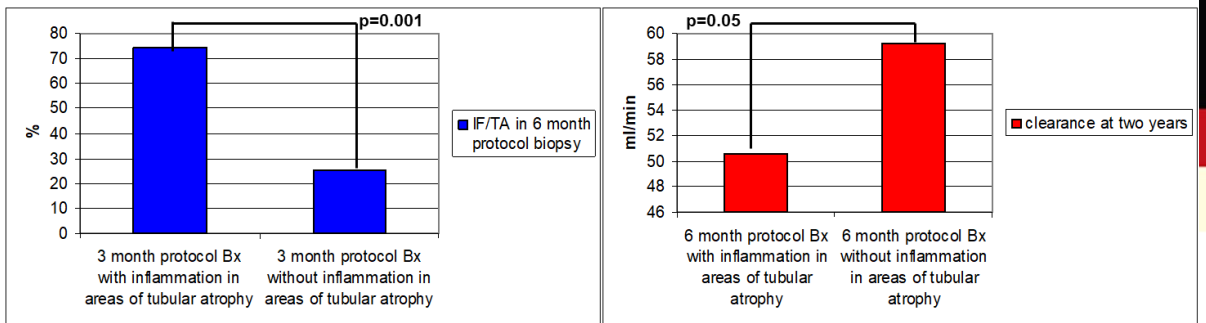
Inflammation in renal allografts

Mengel et al. AJT 2007; 7: 356-365

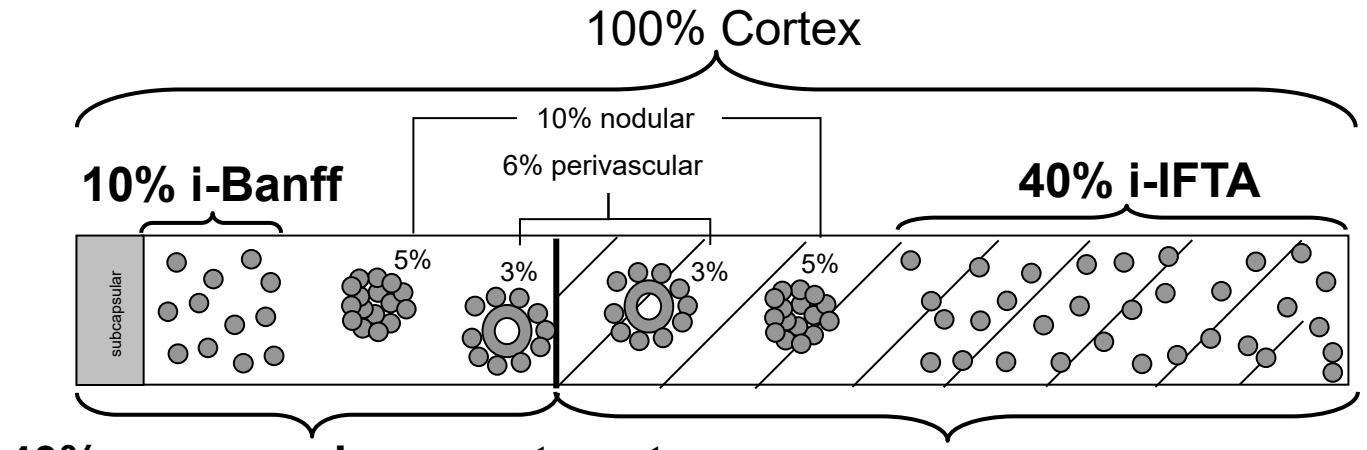
Table 1: Infiltrate pattern and type in protocol and indication biopsies

Infiltrate	Protocol biopsies (n = 833)	Indication biopsies (n = 306)	p-value
Infiltrate present	86.8%	87.3%	ns
Focal	13.2%	9.5%	ns
Multifocal	73.6%	77.8%	ns
Diffuse	11.8%	25.2%	0.001
Nodular	29.1%	17.0%	0.001
Raggedly	64.8%	67.6%	ns
Atrophic	58.8%	56.5%	ns

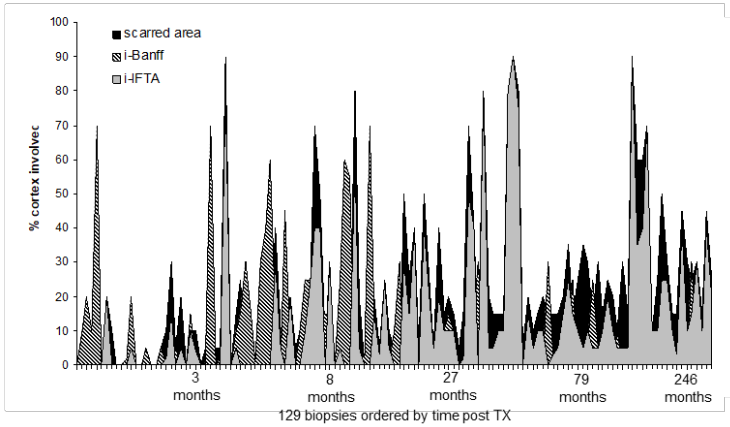
ns = not significant.



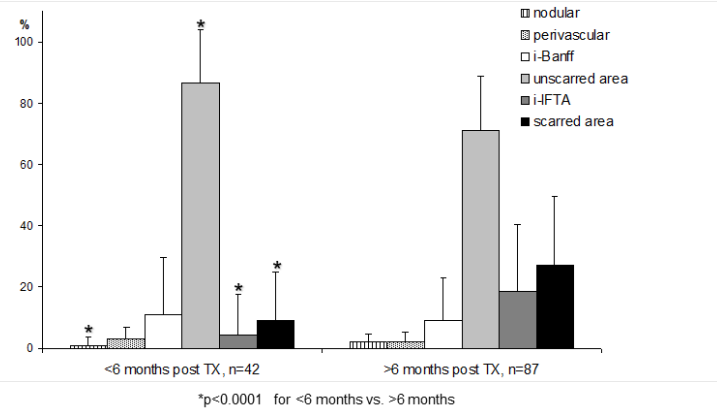
Scoring inflammation in renal allograft biopsies and gene expression studies from whole needle cores



A



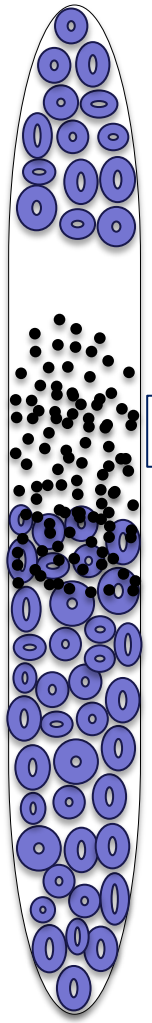
B



Mengel et al. Am J Transplant. 2009 Jan;9(1):169-78

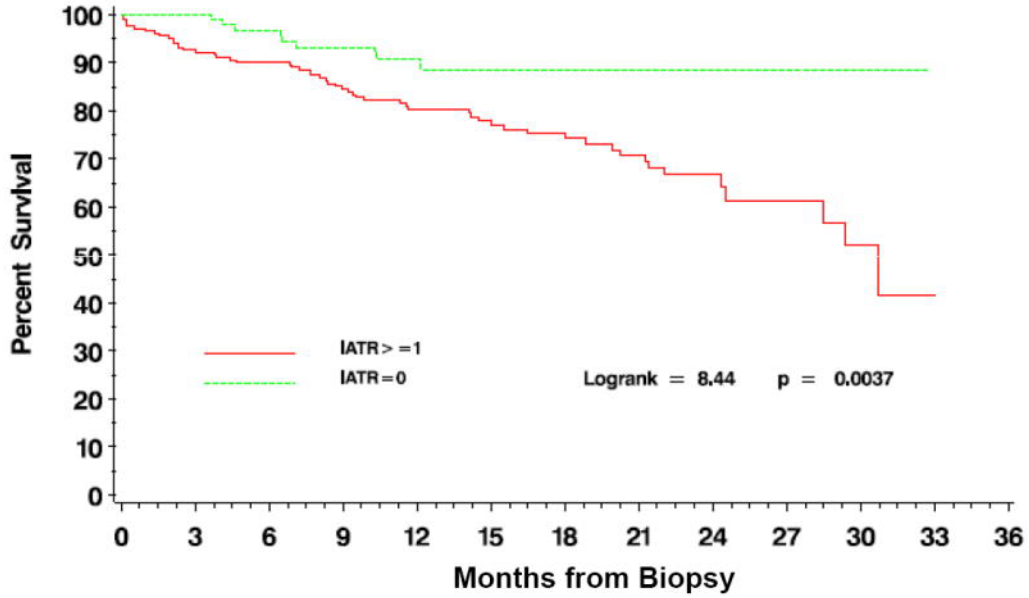
INFLAMMATION IN SCARRED AREAS

Negative prognostic impact of i-IFTA confirmed by Multiple Studies



Inflammation in Areas of Tubular Atrophy in Kidney Allograft Biopsies: A Potent Predictor of Allograft Failure

R. B. Mannon *American Journal of Transplantation 2010; 10: 2066–2073*



1. Mengel/Halloran: Am J Transplant 2009: 9: 1859
2. Mannon/Rush: Am J Transplant 2010: 10:2066
3. Cosio/Stegall: J Am Soc Nephrol 2010:21:1987
4. Cosio/Stagall: Am J Tx 2012: 12: 1199
5. Naesens: Am J Transplant 2013: 13; 86 & Kid Int 2011: 80: 1364
6. Batal/Chandrakar: J Am Soc Nephrol 2015: 26; 3102

No controversy that i-IFTA = PROGNOSTIC parameter

Distribution of individual interstitial infiltrates grades according to histopathological diagnosis and allograft failure* in late biopsies.

Diagnoses	Late biopsies (>1yr)						
	N (failure)	i-Banff0	i-Banff>0	i-total0	i-total>0	i-IFTA0	i-IFTA>0
C4d positive ABMR	**21 *(10)***	11 *(5)*	10 *(5)*	2	19 *(10)*	3 *(1)*	18 *(9)*
C4d negative ABMR	**43 *(15)***	34 *(11)*	9 *(4)*	11 *(4)*	*32 (11)*	17 *(5)*	26 *(10)*
Mixed TCMR plus ABMR	**1 *(1)***	0	1 *(1)*	0	1 *(1)*	0	1 *(1)*
TCMR	**5 *(2)*[a]**	1 *(1)*	3 *(1)*	0	5 *(2)*	2	3 *(2)*
Borderline	**23 *(5)*[b]**	14 *(4)*	9 *(1)*	4 *(2)*	19 *(3)*	7 *(2)*	16 *(3)*
Glomerulonephritis	**23 *(8)***	18 *(4)*	5 *(4)*	3	20 *(8)*	6	17 *(8)*
Polyoma virus nephropathy	**2**	2	0	1	1	1	1
Transplant glomerulopathy	**6 *(2)***	6 *(2)*	0	0	6 *(2)*	0	6 *(2)*
Calcineurin inhibitor toxicity	**28 *(3)***	28 *(3)*	0	16 *(1)*	12 *(2)*	19 *(1)*	9 *(2)*
Interstitial fibrosis and tubular atrophy NOS	**20 *(3)***	20 *(3)*	0	10 *(1)*	10 *(2)*	12 *(1)*	8 *(2)*
Others	**13[c] *(1)***	8	5 *(1)*	7	6 *(1)*	8	5 *(1)*
Total	**185 *(50)***	142 *(33)*	43 *(17)*	54 *(8)*	131 *(42)*	75 *(10)*	110 *(40)*
% of failures	27%	23.2%	39.5%	18.4%	32%	13.3%	36.3%

Table 5: Findings in the latest biopsy of kidneys with no histologic diagnosis of rejection (group 5) that subsequently failed: impact of scarring, inflammation and AKI signal

Scoring only inflammation in fibrotic areas	Distribution of failures by inflammation, scarring and AKI signal		
	Bottom tertile of the AKI signal (four failures)	Middle tertile of the AKI signal (five failures)	Top tertile of the AKI signal (22 failures)
ci = 0 i-IFTA = 0	2	1	1
ci > 0 i-IFTA = 0	0	0	1
ci > 0 i-IFTA > 0[1]	2	4	20

[1]Significant difference in the distribution among the AKI tertiles by a chi-square test (p-value < 0.05). Only one (last) biopsy per patient was analyzed.

n=185 late cases

Uni

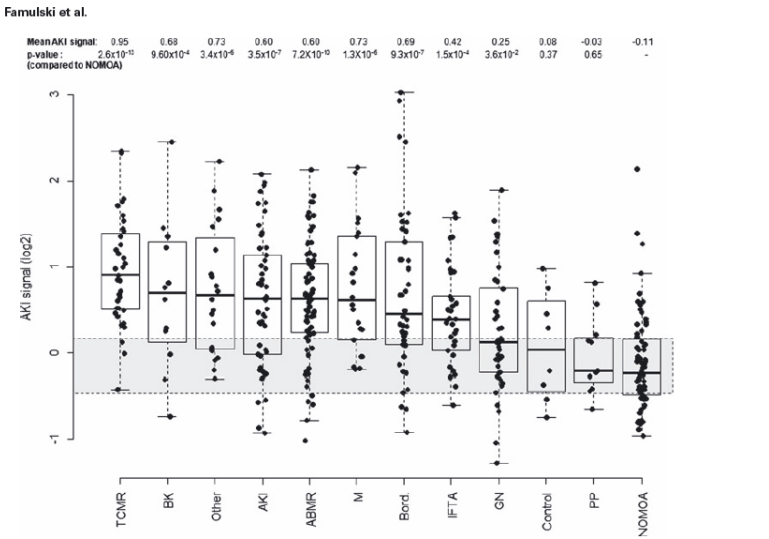
Feature	HR	p-value
i-IFTA	1.8 (1.35-2.39)	<0.001
i-Total	1.95 (1.4-2.7)	<0.001
i-Banff	1.702 (1.13-2.54)	0.01
ci	1.93 (1.38-2.71)	<0.001
t	1.59 (1.2-2)	0.001
Progressive diseases	2.55(1.4-4.6)	0.002
v	1.24 (0.6-2.5)	0.55

Multi

Feature	HR	p-value
ci	1.7 (1.03 – 2.55)	0.03
Progressive diseases	2.1 (1.1-3.9)	0.02

Progressive diseases: AMR + Mixed + GN

Sellares et al. Am J Transplant. 2011 Mar;11(3):489-99



Famulski et al. Am J Transplant. 2013 Mar;13(3):634-44.

FACULTY OF MEDICINE & DENTISTRY UNIVERSITY OF ALBERTA

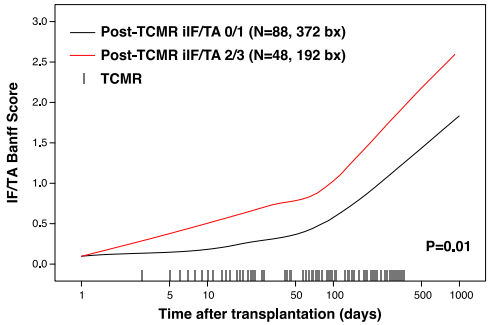
Association between i-IFTA and T-Cell Mediated Rejection

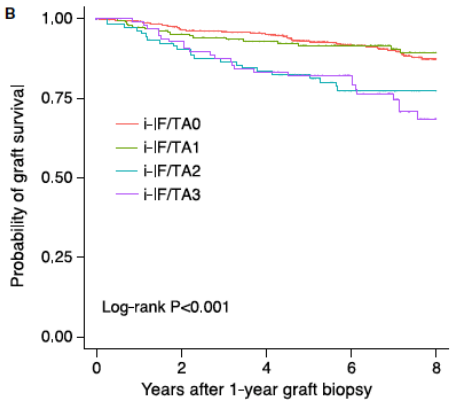
Patients with TCMR in the first year and i-IFTA on a one year post transplant protocol follow-up biopsy showed accelerated progression of IFTA and decreased long term allograft survival

TABLE 4 Determinants of i-IF/TA at 1 year after transplantation: multivariable model

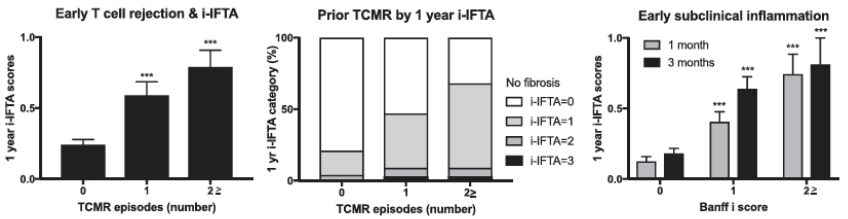
	Number of patients	Number of events	OR	95% CI	P
First-y T cell–mediated rejection					
No	798	306	1	-	
Yes	142	85	2.73	[1.87-3.97]	<.001
First-y BK virus–associated nephropathy					
No	914	373	1	-	
Yes	26	18	3.25	[1.38-7.67]	.007
Six-mo steroid therapy					
No	103	50	1	-	
Yes	837	341	0.64	[0.42-0.98]	.039
Six-mo calcineurin inhibitor therapy					
No	51	29	1	-	
Yes	889	362	0.47	[0.26-0.84]	.011
Six-mo IMPDHi therapy					
No	50	29	1	-	
Yes	890	362	0.46	[0.25-0.84]	.011
HLA-B mismatch (per 1-unit increment)	940	391	1.29	[1.06-1.59]	.012
HLA-DR mismatch (per 1-unit increment)	940	391	1.23	[1.01-1.50]	.044

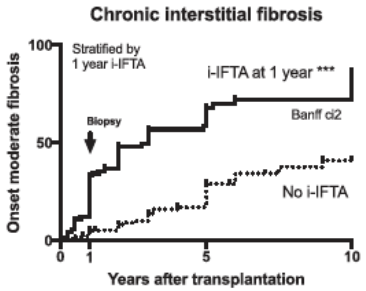
CI, confidence interval; HLA, human leukocyte antigen; i-IF/TA, inflammation in fibrosis areas; IMPDHi, inosine-5′-monophosphate dehydrogenase inhibitor; OR, odds ratio; TCMR, T cell–mediated rejection.



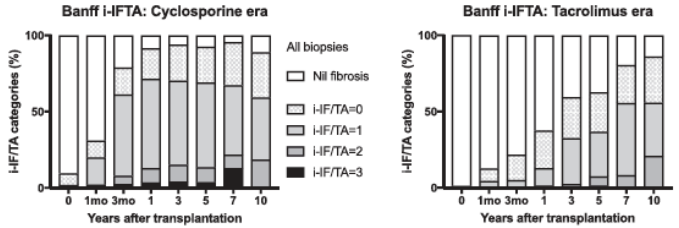


Lefaucheur et al.AJT 2018, 18:377-390





Risk factor	HR	95% CI	P value
Peak PRA (%)	1.020	1.012-1.028	<.001
Current PRA (%)	1.018	1.006-1.029	.002
Solid state DSAs present	1.548	1.120-2.138	.008
DSA "strength" (MFI)	1.000	Incalculable	.717
Late de novo DSAs (any)	0.763	0.461-1.262	.293
HLA mismatch (of 6)	0.970	0.871-1.081	.568
Anastomosis time (min)	1.014	0.999-1.029	.064
Total ischemic time (min)	1.001	1.000-1.002	.005
Transfusions (number)	1.257	1.199-1.317	<.001
Retransplantation	2.214	0.700-7.010	.176
Recipient hypertension	1.447	1.089-1.924	.011
Tacrolimus-era therapy (vs cyclosporine)			
At transplantation	0.178	0.132-0.240	<.001
3 months posttransplantation	0.220	0.164-0.294	<.001
Early T cell rejection	2.708	2.049-3.578	<.001
Early vascular rejection	2.230	1.530-3.250	<.001
Early antibody rejection	2.606	1.809-3.756	<.001
Antilymphocyte required	2.895	2.156-3.889	<.001
Multivariable model 1	**HR**	**95% CI**	***P* value**
Early T cell rejection	1.464	1.062-2.017	.020
Early vascular rejection	1.660	1.129-2.442	.010
Tacrolimus era (vs cyclosporine)	0.219	0.157-0.306	<.001



Nankivell et al.AJT 2018, 18:364-376

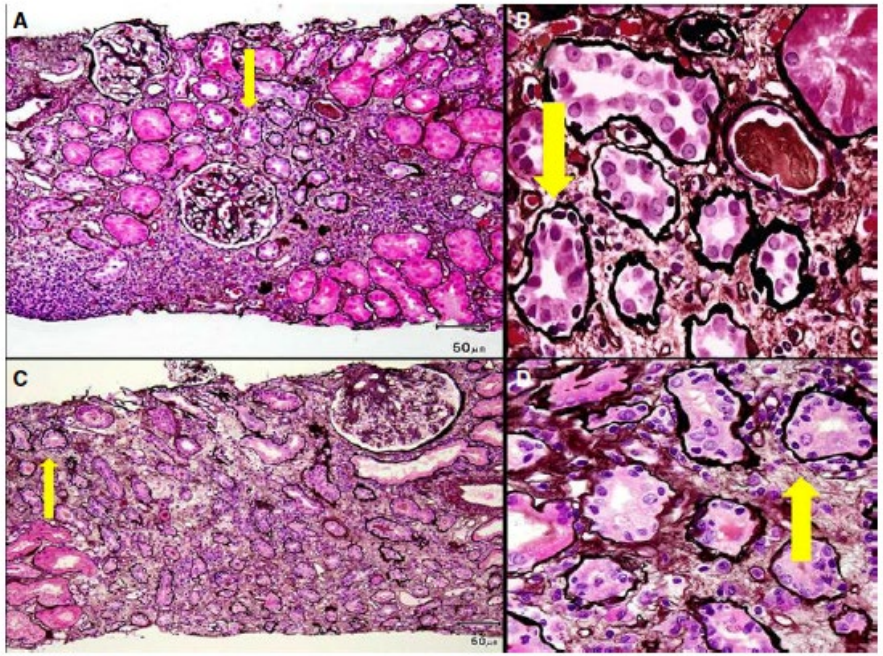
Received: 5 November 2017 | Revised: 6 December 2017 | Accepted: 7 December 2017
DOI: 10.1111/ajt.14625

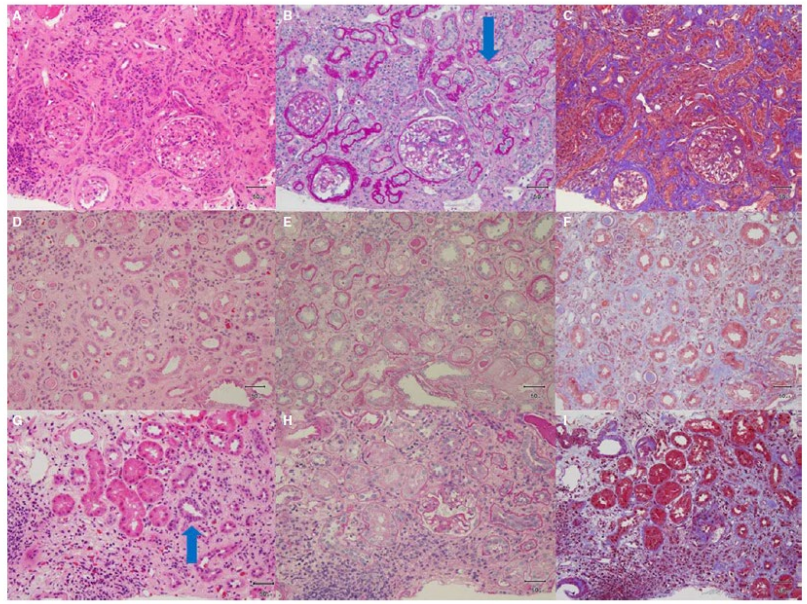
MEETING REPORT

The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell–mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials

TABLE 5 (Continued)

Chronic Active TCMR	
Grade IA	Interstitial inflammation involving >25% of the total cortex (ti score 2 or 3) and >25% of the sclerotic cortical parenchyma (i-IFTA score 2 or 3) with moderate tubulitis (t2) involving 1 or more tubules, not including severely atrophic tubules[5]; other known causes of i-IFTA should be ruled out
Grade IB	Interstitial inflammation involving >25% of the total cortex (ti score 2 or 3) and >25% of the sclerotic cortical parenchyma (i-IFTA score 2 or 3) with severe tubulitis (t3) involving 1 or more tubules, not including severely atrophic tubules[5]; other known causes of i-IFTA should be ruled out
Grade II[1]	Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell inflammation in fibrosis and formation of neointima)





Haas and Loupy et al. Am J Transpl 2018; 18: 293-307

Subclinical inflammation, non-adherence and ABMR

Table 2: Clinical pathologic course before dnDSA detection

	No dnDSA (n = 268)	Total dnDSA (n = 47)	dnDSA adherent subgroup (n = 24)	dnDSA nonadherent subgroup (n = 23)
Non-adherence	8%	49%***	0%	100%
DGF requiring dialysis	12%	11%	8%	13%
Clinical rejection, 0–6 months	13%	28%*	29%*	26%
Subclinical rejection, 0–6 months	15%	26%	30%	22%
6-Month protocol biopsy, n	151	37	18	19
g	0.02 ± 0.2	0.03 ± 0.2	0.05 ± 0.2	0.0 ± 0.0
i	0.37 ± 0.6	0.62 ± 0.8*	0.33 ± 0.6	0.90 ± 0.9**
t	0.41 ± 0.7	0.62 ± 0.9	0.28 ± 0.7	0.95 ± 1.0**
v	0.01 ± 0.1	0.03 ± 0.2	0.06 ± 0.3	0.0 ± 0.0
ptc	0.11 ± 0.4 (n = 46)	0.60 ± 0.9 (n =30)**	0.14 ± 0.5 (n =14)	1.0 ± 1.0 (n =16)**
C4d+	0% (n =16)	10% (n =31)	7% (n =14)	12% (n =17)
cg	0.02 ± 0.2	0.03 ± 0.2	0.05 ± 0.2	0.0 ± 0.0
ci	0.53 ± 0.6	0.57 ± 0.7	0.56 ±0.7	0.58 ± 0.7
ct	0.65 ± 0.6	0.62 ± 0.6	0.61 ± 0.6	0.63 ± 0.6
cv	0.36 ± 0.6	0.36 ± 0.6	0.44 ± 0.7	0.29 ± 0.5
Clinical rejection, 7–12 months	3%	6%	0%	13%*
12-Month serum Cr. (μmol/L)	113 ± 44	116 ± 44	121 ± 44	110 ± 45
dnDSA onset (months)	–	56 ± 36	51 ± 37	60 ± 34
Month proteinuria ≥0.5 g/d	51 ± 40 (n =43)	67 ± 34 (n =25)	70 ± 40 (n =7)	66 ± 33 (n =18)
Month Cr ≥ 25% baseline	34 ± 31 (n =33)	68 ± 31 (n =29)***	79 ± 28 (n =7)***	65 ± 32 (n =22)***

Significance level compared to the No dnDSA group *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

Wiebe et al. AJT Vol. 12, 1157-1167; 2012

Antibody-Mediated Rejection Due to Preexisting versus *De Novo* Donor-Specific Antibodies in Kidney Allograft Recipients

Olivier Aubert,* Alexandre Loupy,*†‡ Luis Hidalgo,§‖ Jean-Paul Duong van Huyen,¶ Sarah Higgins,** Denis Viglietti,*†† Xavier Jouven,* Denis Glotz,*†† Christophe Legendre,*†‡ Carmen Lefaucheur,*†† and Philip F. Halloran‖‡‡

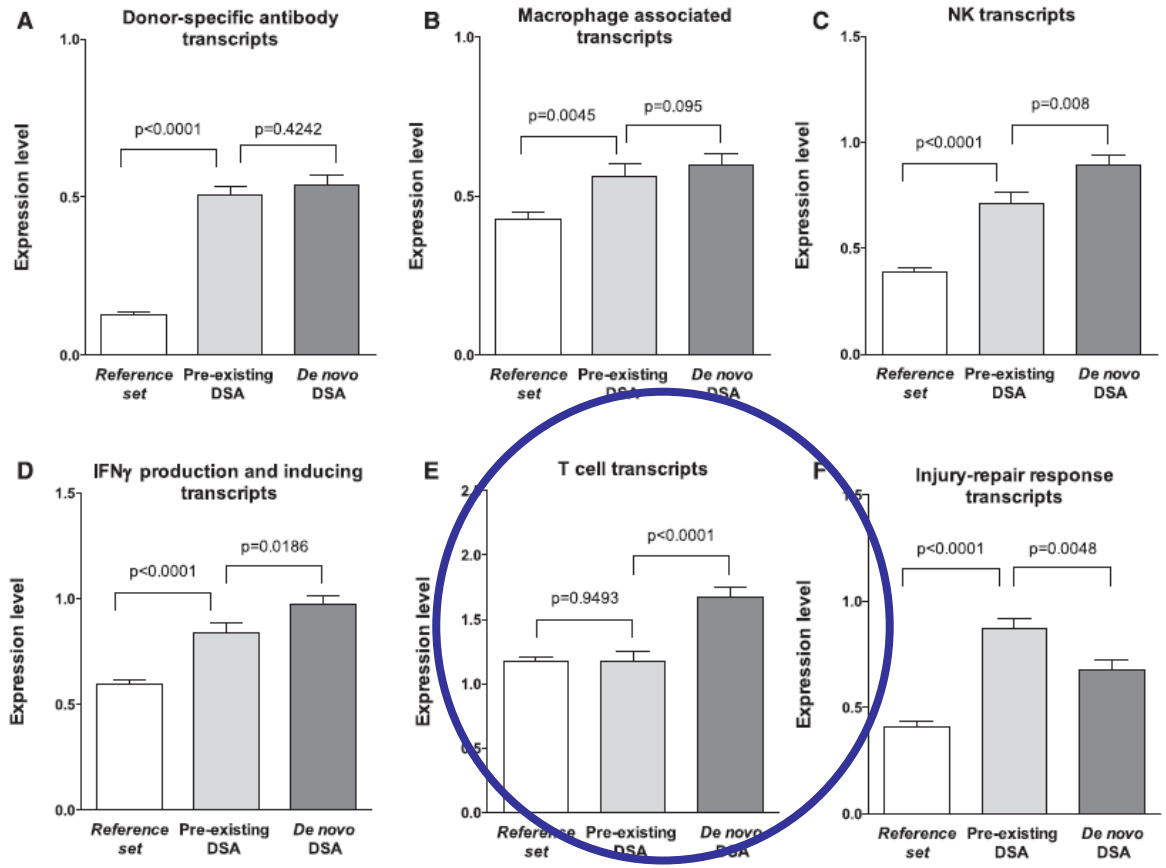
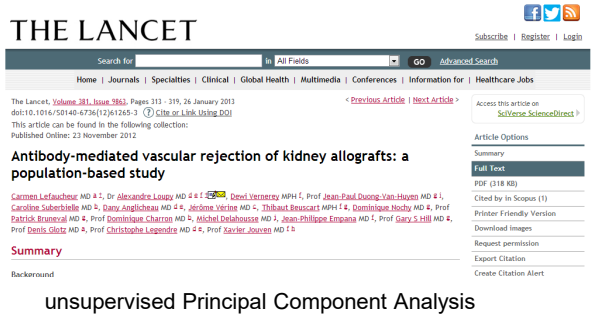


Figure 3. Molecular biopsy scores according to DSA characteristics. Data are on the basis of 666 kidney allograft biopsies assessed for intragraft gene expression of the PBTs ([A] endothelial DSA-selective transcripts, [B] macrophage-inducible transcripts, [C] natural killer cell [NK] transcripts, [D] IFNγ production and inducing transcripts, [E] T cell transcripts, [F] injury–repair response transcripts) according to circulating anti-HLA DSA and ABMR status (reference set without ABMR, preexisting DSA ABMR, and *de novo* DSA ABMR). The T bars indicate SEM and DSA denotes anti-HLA DSA.

Effector T cell transcripts significantly higher in the later *de novo* DSA ABMR cohort, c/w concurrent active TCMR, i.e. true mixed ABMR / TCMR rejection in type 2 ABMR

J Am Soc Nephrol 28: ●●●–●●●, 2017.

Overlap between Antibody-mediated and T cell mediated injury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The Lancet, Volume 381, Issue 9863, Pages 313 - 319, 26 January 2013
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Published Online: 23 November 2012

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Antibody-mediated vascular rejection of kidney allografts: a population-based study

Carmen Lefaucheur MD, Dr Alexandre Loupy MD, Dewi Vernerey MPH, Prof Jean-Paul Duong-Van-Huyen MD, Caroline Suberbielle MD, Dany Anglicheau MD, Jérôme Vérine MD, Thibaut Beuscart MPH, Dominique Nochy MD, Prof Patrick Bruneval MD, Prof Dominique Charron MD, Michel Delahousse MD, Jean-Philippe Empana MD, Prof Gary S Hill MD, Prof Denis Glotz MD, Prof Christophe Legendre MD, Prof Xavier Jouven MD

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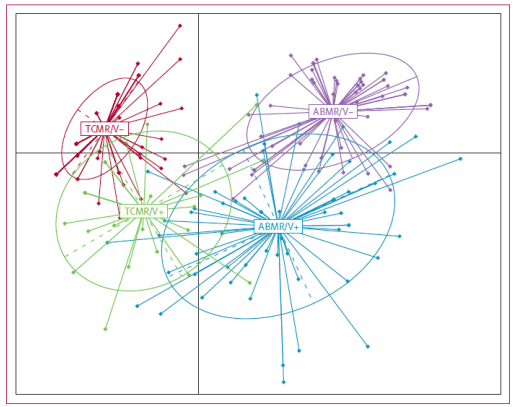
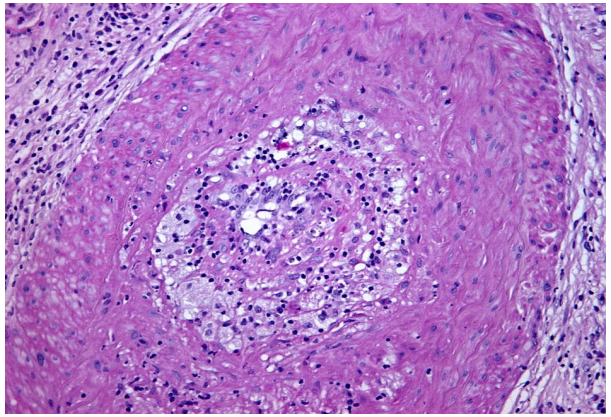
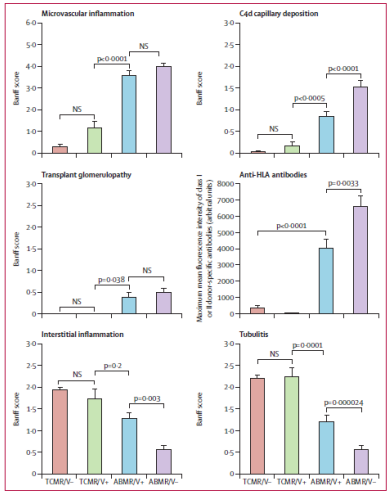
unsupervised Principal Component Analysis

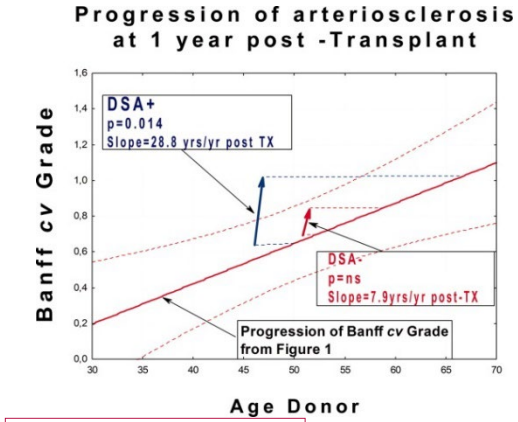


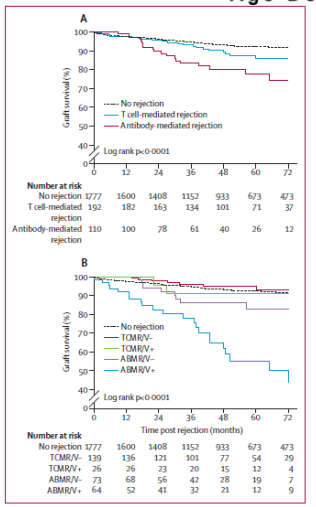
Histology lesions are ambivalent, and show Overlap between T cell and Antibody-mediated rejection.





Banff lesions





Graft Survival

Natural course of antibody-mediated rejection

Wiebe et al. AJT Vol. 12, 1157-1167; 2012 – modified from originally Colvin et al.

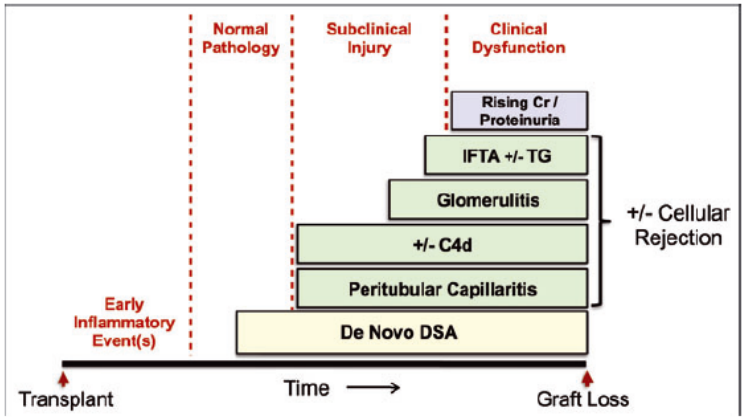


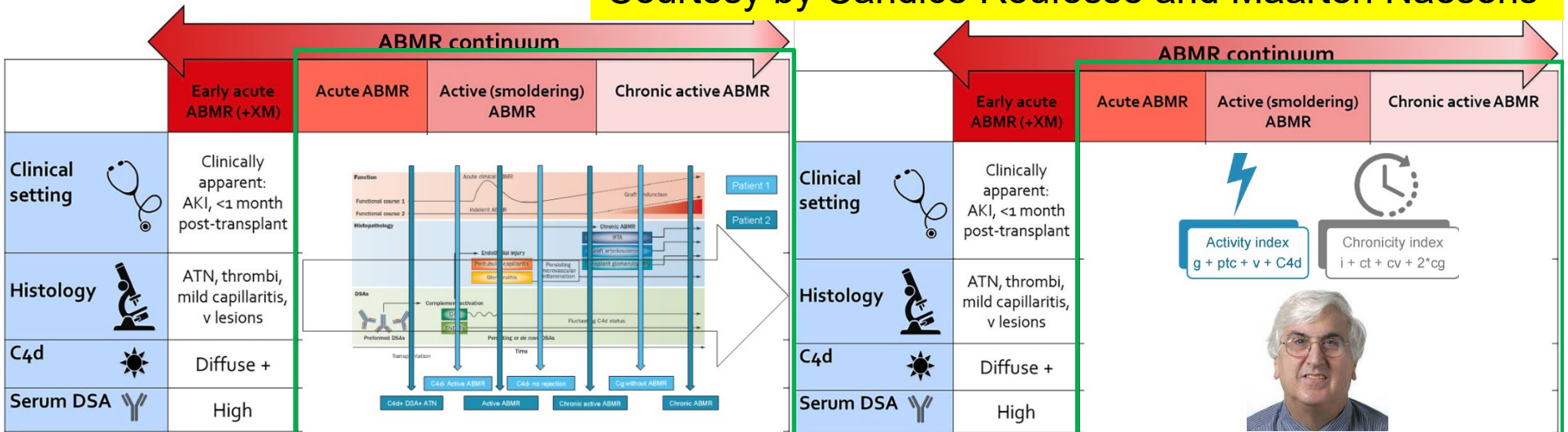
Figure 4: Proposed natural history of dnDSA. This figure shows a proposed model for patients developing *de novo* donor-specific antibodies as they evolve from transplantation to graft failure. IFTA, interstitial fibrosis and tubular atrophy; TG, transplant glomerulopathy. Adapted from Ref.

American Journal of Transplantation 2012; 12: 1157–1167 1165

ABMR continuum

	Early acute ABMR (+XM)	Acute ABMR	Active (smoldering) ABMR	Chronic active ABMR
Clinical setting	Clinically apparent: AKI, <1 month post-transplant	Usually clinically apparent: AKI	Subclinical	Subclinical or clinically apparent: Progressive renal insufficiency, proteinuria, hypertension
Histology	ATN, thrombi, mild capillaritis, v lesions	ATN, thrombi, capillaritis, v lesions	Capillaritis only (g, ptc)	Capillaritis and TG, TA, or PTCBMML
C4d	Diffuse +	+	Negative, focal +, occasionally diffuse +	Negative, focal +, occasionally diffuse +
Serum DSA	High	High	Low, mid	Low, mid

Courtesy by Candice Roufosse and Maarten Naesens



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https://www.molecular-microscope.com

Current MMDx-Kidney Report (page 1) - ABMR

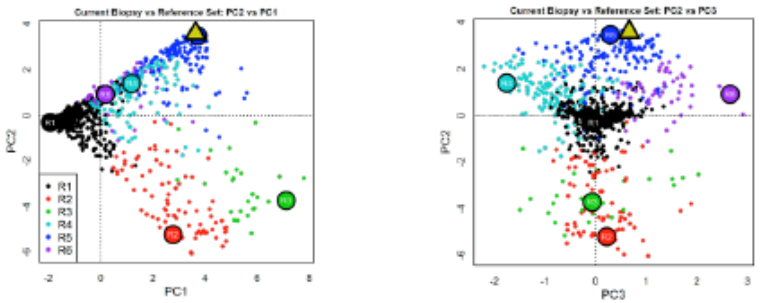
General Information

KCL Report ID		Sample ID	
Date Received (Y-M-D)		Time of Biopsy Post-Tx	8.2 years
Date Reported (Y-M-D)		Transplant Type	DD (Deceased)
Date of Transplant (Y-M-D)		Biopsy Indication	Investigate proteinuria
Date of Biopsy (Y-M-D)		Primary Disease	Hypertension, biopsy proven

Pure molecular interpretation
Severe early-stage ABMR with g and ptc molecular features. No TCMR. Moderate atrophy-fibrosis with mild AKI.

	Classifier/gene sets	Biopsy score	Range of values[1]	Upper limit of normal[2]	Interpretation
Injury Scores	Global Disturbance Score	1.59	-3.8 - 5.8	0.03	Moderate
	Acute Kidney Injury (AKI) Score	0.42	-0.6 - 1.6	0.39	Mild
	Atrophy-Fibrosis Score	0.58	0.0 - 1.0	0.76	Moderate
Rejection Scores	Rejection Score	0.88	0.0 - 1.0	0.30	Severe
	TCMR Score	0.01	0.0 - 1.0	0.10	Normal
	ABMR Score	0.95	0.0 - 1.0	0.20	Severe

Rejection phenotype[3] (six scores, R1-R6, adding up to 1.0)	R1 Non-rejection	0.00	All ABMR (Sum of R4,R5, and R6)	1.00
	R2 TCMR	0.00	R4 Early-Stage ABMR (EABMR)	0.00
	R3 Mixed Rejection	0.00	R5 Fully-Developed ABMR (FABMR)	0.96
			R6 Late-Stage AMBR (LABMR)	0.04



Survival in patients with similar biopsies in the Reference Set		Percent cortex[4]
1-year: 70%	3-years: 50%	90%

Many other classifiers (page 2 of the reports - not shown for simplicity) are also run to establish details of ABMR. For example, these estimate the probability of glomerular double contours (cg) as an estimate of late-stage ABMR. For the first biopsy shown, these estimated the probability of microcirculation inflammation (ptc- and g-changes) and cg as high, indicating that this biopsy has fully-developed ABMR. The net result of all of these measurements is integrated by a novel method called "Archetypal Analysis"[23].

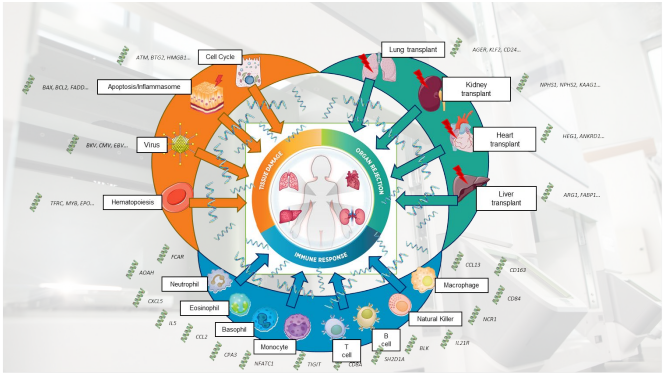
Received: 10 March 2020 | Revised: 19 April 2020 | Accepted: 27 April 2020
DOI: 10.1111/ajt.16059

AJT

MEETING REPORT

Banff 2019 Meeting Report: Molecular diagnostics in solid organ transplantation–Consensus for the Banff Human Organ Transplant (B-HOT) gene panel and open source multicenter validation

nCounter® Human Organ Transplant Panel
Gene Expression Panel
Organ Rejection • Immune Response • Tissue Damage



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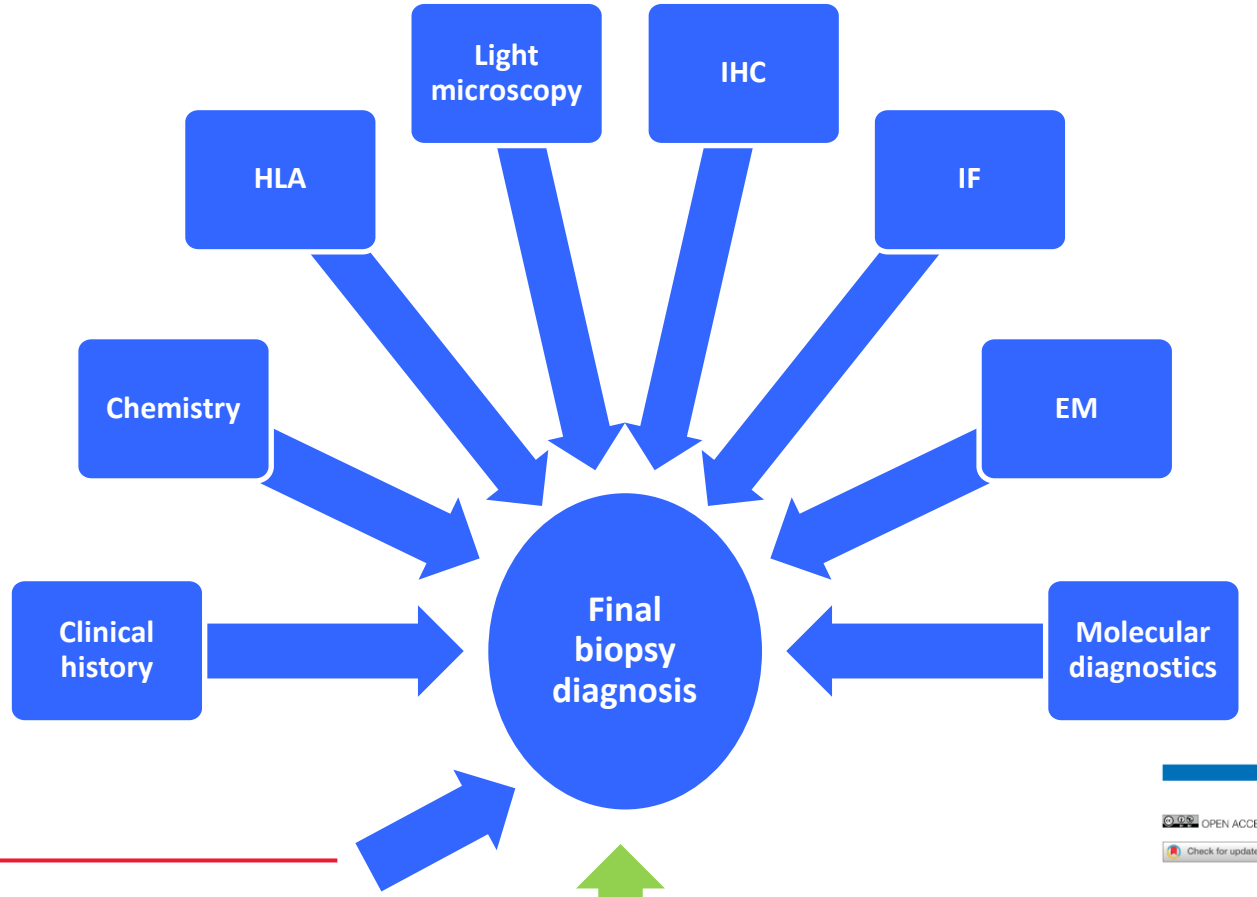
Precision = Integration of Complementary diagnostic tools



The ibox

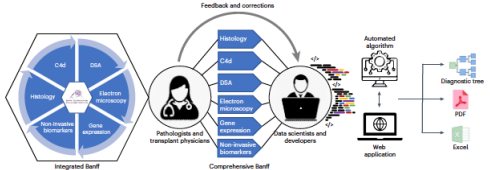
1) eGFR (mL/min/1.73m²)
2) Proteinuria
3) MFI of anti-HLA DSA
4) IFTA Banff score
5) i Banff score
6) t Banff score
7) cg Banff score
8) g Banff score
9) ptc Banff score

nature medicine

Article

https://doi.org/10.1038/s41591-023-02323-6

An automated histological classification system for precision diagnostics of kidney allografts



Machine Decision Support

Accurate Prediction

RESEARCH

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Prediction system for risk of allograft loss in patients receiving kidney transplants: international derivation and validation study

Alexandre Loupy,[1,2] Olivier Aubert,[1,2] Babak J Orandi,[3] Maarten Naesens,[4] Yassine Bouatou,[1] Marc Raynaud,[1] Gillian Divard,[1] Annette M Jackson,[5] Denis Viglietti,[1,6] Magali Giral,[7] Nassim Kamar,[8] Olivier Thaunat,[9] Emmanuel Morelon,[9] Michel Delahousse,[10] Dirk Kuypers,[4] Alexandre Hertig,[11] Eric Rondeau,[11] Elodie Bailly,[11] Farsad Eskandary,[12] Georg Böhmig,[12] Gaurav Gupta,[13] Denis Glotz,[1,6] Christophe Legendre,[1,2] Robert A Montgomery,[14] Mark D Stegall,[15] Jean-Philippe Empana,[1,16] Xavier Jouven,[1] Dorry L Segev,[17] Carmen Lefaucheur[1,6]

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Additional material is published online only. To view please visit the journal online.

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Accepted: 5 July 2019

ABSTRACT

OBJECTIVE
To develop and validate an integrative system to predict long term kidney allograft failure.

DESIGN
International cohort study.

SETTING
Three cohorts including kidney transplant recipients from 10 academic medical centres from Europe and the United States.

PARTICIPANTS
Derivation cohort: 4000 consecutive kidney recipients prospectively recruited in four French centres between 2005 and 2014. Validation cohorts: 2129 kidney recipients from three centres in Europe and 1428 from

median post-transplant follow-up time of 7.12 (interquartile range 3.51-8.77) years. In the derivation cohort, eight functional, histological, and immunological prognostic factors were independently associated with allograft failure and were then combined into a risk prediction score (iBox). This score showed accurate calibration and discrimination (C index 0.81, 95% confidence interval 0.79 to 0.83). The performance of the iBox was also confirmed in the validation cohorts from Europe (C index 0.81, 0.78 to 0.84) and the US (0.80, 0.76 to 0.84). The iBox system showed accuracy when assessed at different times of evaluation post-transplant, was validated in different clinical scenarios including type of immunosuppressive regimen used and response to rejection therapy, and outperformed previous

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Defining BPAR (in the clinical context)

past: uni-dimensional, dichotomy, histology only

present: several-dimensional, overlapping phenotypes

future: multi-dimensional, probabilistic archetypes

Managing BPAR Under Contemporary Immunosuppression:

The Transplant Clinician Perspective

Roy D. Bloom MD
University of Pennsylvania

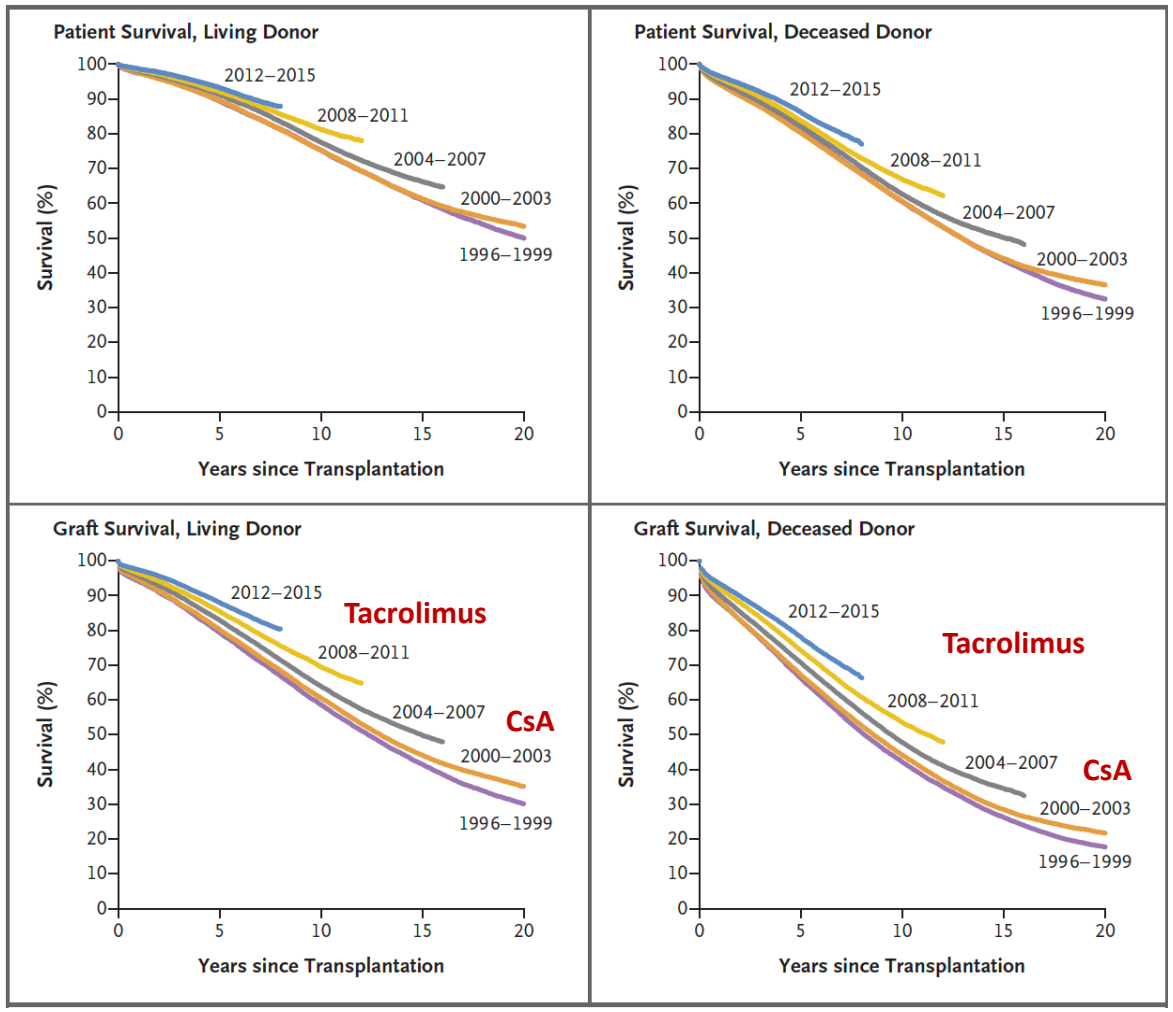
Disclosures

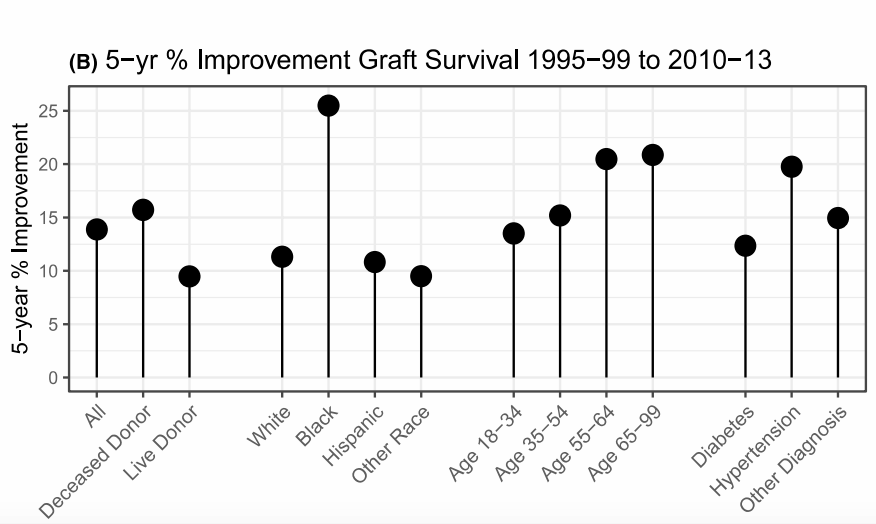
- Research support: Veloxis, CareDx, Natera, CSL Behring, Memo
- Royalties: UpToDate
- Editorial Board, AJKD

Objectives

- Discuss the clinical relevance of BPAR in 2023
- Review existing data regarding treatment of BPAR
- Highlight what the guidelines tell us regarding BPAR therapy
- Describe how transplant clinicians treat BPAR

Transplant outcomes have improved





Prolongation of graft survival beyond the 1st post-transplant year

- Tac more efficacious than CyA
- Increased use of depleting Ab induction
- Improved HLA technology

Hariharan *et al*, NEJM (2021); Poggio *et al,* am J Transplant 2021

Causes of death-censored graft loss

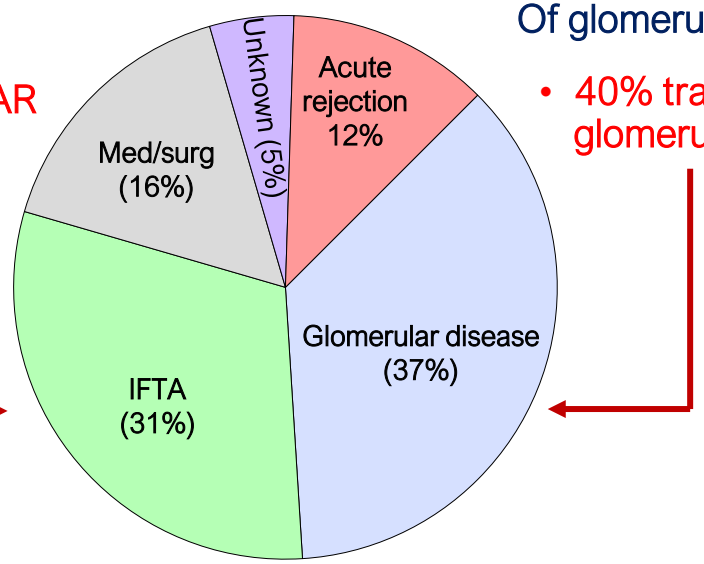
n=153/1317 pts, sequential protocol biopsy

Of IFTA

- 25% hx of BPAR

Of glomerular disease

- 40% transplant glomerulopathy



n=303/1642 pts, for-cause biopsy

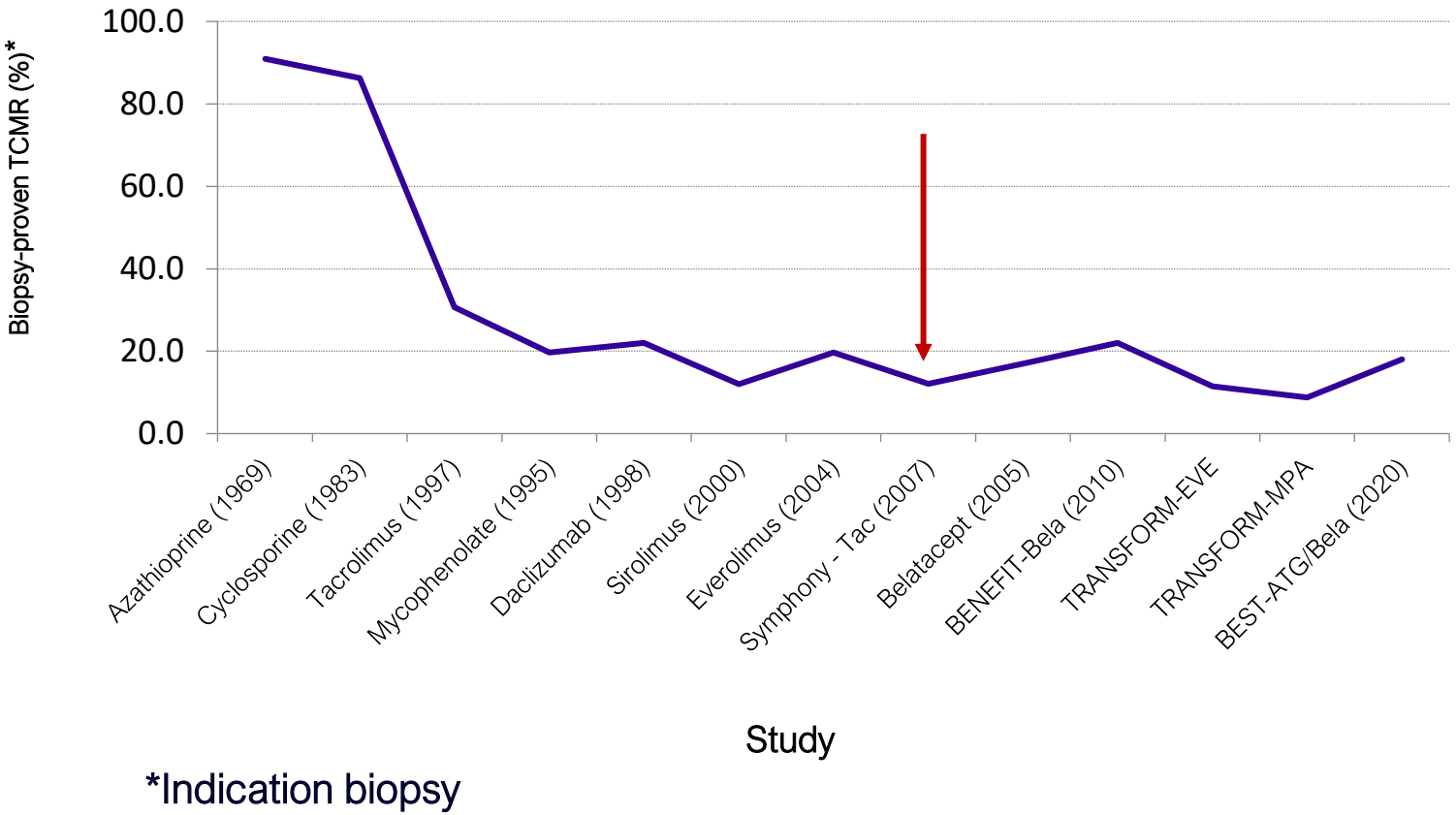
Causes for Graft Failure, *n* (%)	Primary (%)*
TCMR	39 (12.9)
ABMR	65 (21.5)
Medical event	64 (21.1)
CNI toxicity	2 (0.7)
PVN	10 (3.3)
Perioperative event	23 (7.6)
Poor transplant quality	9 (3.0)
Recurrent disease	19 (6.3)
Other cause	5 (1.7)
Total	236 (77.9)

*cause responsible for persistent eGFR decrease>50% of maximal GFR

Rejection (Acute/Chronic) is the commonest cause of death-censored graft loss

El-Zhogby *et al*, Am J Transplant 2009 ; Mayrdorfer *et al*, J Am Soc Nephrol 2021

Incidence of Clinical TCMR:
Data from RCTs



*Indication biopsy

- Most registration trials did not specify:
  - grade of rejection
  - borderline rejection

- Association between borderline rejection and outcome in indication biopsies not well studied

Woodruff et al Lancet 1969; Canadian study NEJM 1983; Grinyo et al Lancet 1995; Tricontinent. study Transplant. 1996; Vincenti et al NEJM 1998; Pirsch et al Transplantation 1997; Kahan et al Lancet 2000; Vitko et al Transplantation 2004; Ekberg et al NEJM 2007; Vincenti et al NEJM 2005; Vincenti *et* al, Am J Transplant 2010; Pascual et al. J Am Soc Nephrol 2018, Woodle Am J Transplant 2020

Subclinical TCMR with protocol biopsies:

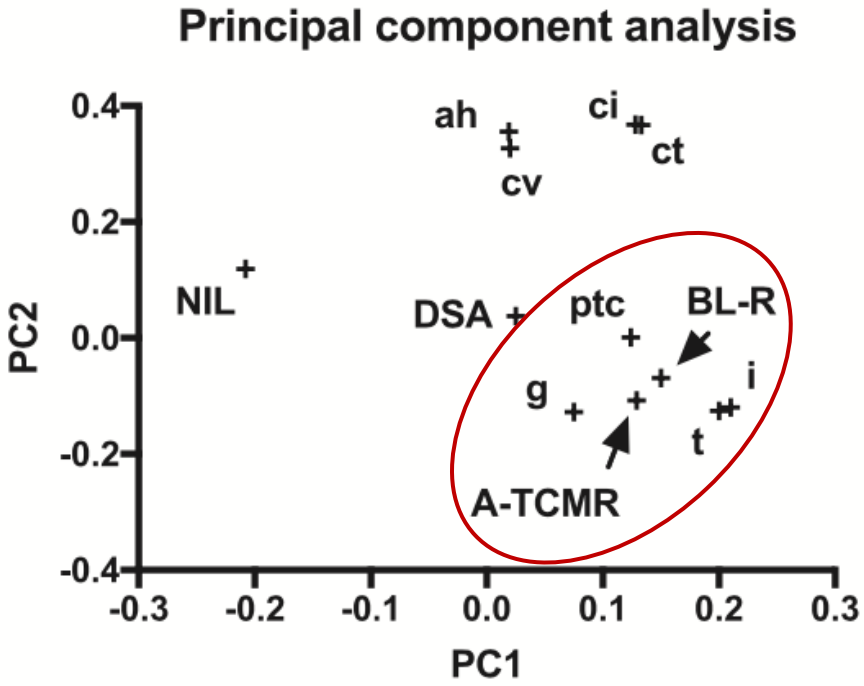
Prevalence in Tacro-MMF era

Study	# pts	Time to bx (mos)	Total TCMR*(%)	Borderline (%)#
Kee, 2006	88	1, 3	47	34
Rush, 2007	111	1, 2, 3, 6	<5	<3
Heilman, 2011	457	1, 4, 12	10	4
Nankivell, 2018	551	Not given	20	14
Friedewald, 2019	382	2-6, 12, 24	24	23
Zhang, 2019	191	3	24	18
Seifert, 2021	441	6	10	7
Chen, 2021	68	24	19	16
Mehta, 2022	586	3, 12	51	31

*all subclinical rejections includes borderline; # percentage of all subclinical rejections

Should borderline rejection be considered TCMR: The Transplant Clinician Perspective

- Clusters with acute TCMR
- Associates with adverse outcomes
- Broad diagnostic phenotype
  - i1/t1 → i3/t1 →i1/t3
  - Potential for overlap with TCMR
  - Sampling error
  - Consistent with under-immunosuppression
- Some correlation with AR biomarkers
- May differ whether clinical or subclinical



Nankivell *et al*, Am J Transplant 2019

Treatment of BPAR: Data from RCTs

Cochrane Library

Cochrane Database of Systematic Reviews

Polyclonal and monoclonal antibodies for treating acute rejection episodes in kidney transplant recipients (Review)

1st TCMR [17 studies, 1005 pts] ← All RCTs, 1973-2000

- Antibody vs steroids alone: 10 (588)
- Antibody + steroids vs steroids alone: 2 (50)
- Antibody vs other antibody: 3 (234)
- Antibody vs other treatment: 2 (133)

ntation

HE DOUBLE-BLIND, RANDOMIZED,
, PHASE III CLINICAL TRIAL OF
ILIN VERSUS ATGAM IN THE
F ACUTE GRAFT REJECTION EPISODES
AFTER RENAL TRANSPLANTATION

Gaber *et al*, Transplant 1998 ← Last Multicenter TCMR RCT

Outcome	Ab v CS RR (95% CI)	Certainty
Failure of AR reversal	0.50 (0.30-0.82)	Moderate
Recurrent ACR	0.70 (0.50-0.99)	Moderate
DCGL	0.80 (0.57-1.12)	Low
Adverse effects	23.88 (5.10-111.86)	Moderate

Ab probably better

Ab probably better

Ab may be better

Probably reduced by steroids

- No difference in death at 12 mos

- Most RCTs in CyA-Aza era
  - Likely included ABMR
- Limited data with contemporary IS
- Knowledge gaps
  - Rejection grade
  - Optimal Rx
  - Response to Rx
  - Subclinical rejection

Webster *et al*, Cochrane Review 2017

Treatment of BPAR: Real-World Data
Tac-MMF-based regimen

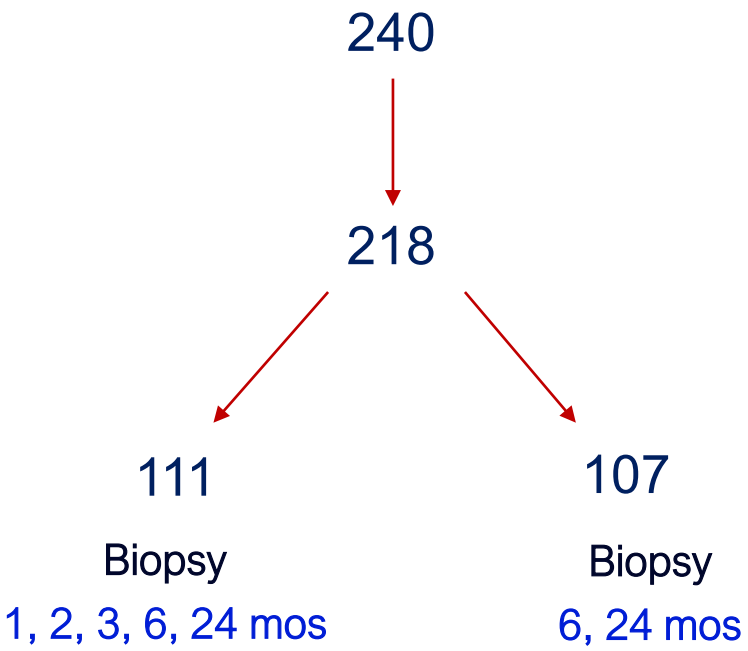
- 12 studies (1255 patients), 2015-2021, 1 single center RCT, 7 prospective observational, 4 retrospective
- Rejection diagnosis mainly in 1st post-transplant year:
  - 5 protocol bx
  - 6 protocol + indication bx
  - 1 indication bx

TCMR	TCMR therapy
Subclinical borderline	5/11 no treatment; 6/11 studies: no therapy, ↑maintenance immunosuppression, oral/IV pulse steroids, tocilizumab (variable practices)
Clinical borderline	↑maintenance immunosuppression , oral/IV pulse steroids (variable practices)
Subclinical ≥Banff 1A	Methylprednisolone 250-500mg IV x 3 days, variable taper
Clinical ≥Banff 1A	Methylprednisolone 250-500mg IV x 3 days, variable taper
Steroid resistant	Thymoglobulin IV, variable doses
Clinical ≥ Banff 2A	Thymoglobulin IV (3-4 studies)

Adapted from Ho *et al*, Am J Transplant 2022

Does treating subclinical make a difference:
Surveillance biopsy RCT

n=240, open-label multicenter RCT, low-risk, **basiliximab-tac-MMF-pred**; all rejection treated as clinically indicated;

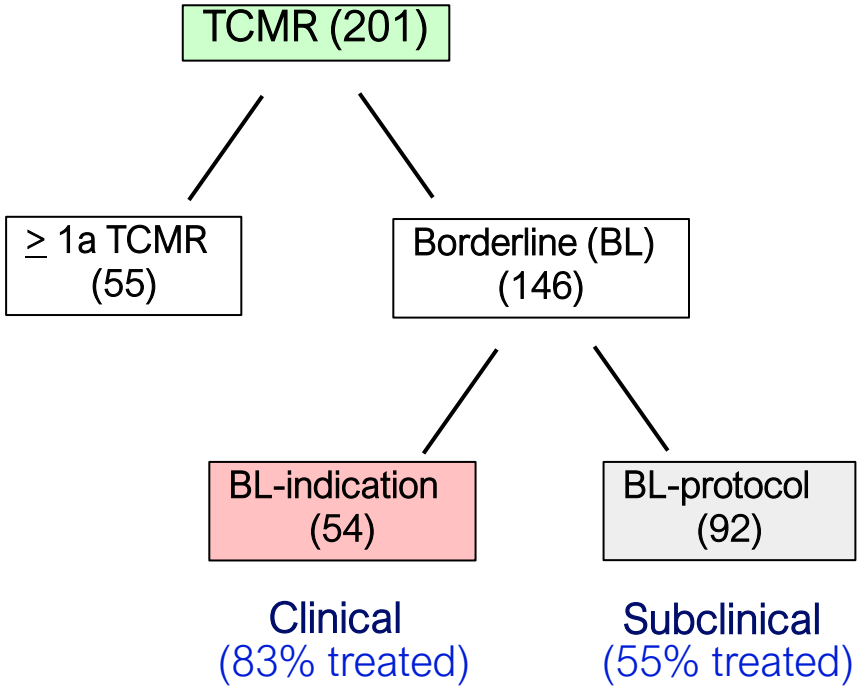


- At 6 mos: subclinical TCMR prevalence: 4.6%
- At 6 and 24 mos:
  - No difference in kidney function, pt or graft survival
  - More fibrosis in biopsy group
- Treating subclinical rejection did not prevent chronic injury

Rush *et al*, Am J Transplant, 2007; Rush *et al*, Transplant 2019

Should borderline TCMR be treated?

- n=551, 1,027 bx (86% protocol), Bas-94% Tac, 90% MMF, index bx ~12 mos post-transplant
- 201 pts TCMR:
- Treatment of borderline TCMR varied (none, methylpred, RATG, ↑IS)



Histological and immunological outcomes of borderline TCMR by bx indication*

	Resolved (%)	Persistent (%)	Worse (%)	Late AR (%)
All borderline	72.6	16.8	10.6	39.4
BL indication bx	75.6	13.6	13.6	50
BL protocol bx (n=75)	72.0	18.7	9.3	32.6

*108 repeat biopsies, BL=borderline TCMR

Nankivell *et al*, Am J Transplant 2019

Chapter 6: Treatment of Acute Rejection

6.1: We recommend biopsy before treating acute rejection, unless the biopsy will substantially delay treatment. *(1C)*

6.2: We suggest treating subclinical and borderline acute rejection. *(2D)*

6.3: We recommend corticosteroids for the initial treatment of acute cellular rejection. *(1D)*

6.3.1: We suggest adding or restoring maintenance prednisone in patients not on steroids who have a rejection episode. *(2D)*

6.3.2: We suggest using lymphocyte-depleting antibodies or OKT3 for acute cellular rejections that do not respond to corticosteroids, and for recurrent acute cellular rejections. *(2C)*

6.4: We suggest treating antibody-mediated acute rejection with one or more of the following alternatives, with or without corticosteroids *(2C)*:

- plasma exchange;
- intravenous immunoglobulin;
- anti-CD20 antibody;
- lymphocyte-depleting antibody.

6.5: For patients who have a rejection episode, we suggest adding mycophenolate if the patient is not receiving mycophenolate or azathioprine, or switching azathioprine to mycophenolate. *(2D)*

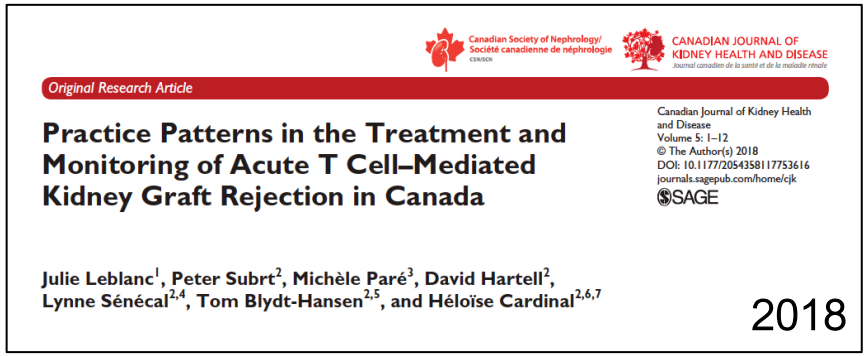
Grade*	Wording
Level 1	'We recommend'
Level 2	'We suggest'

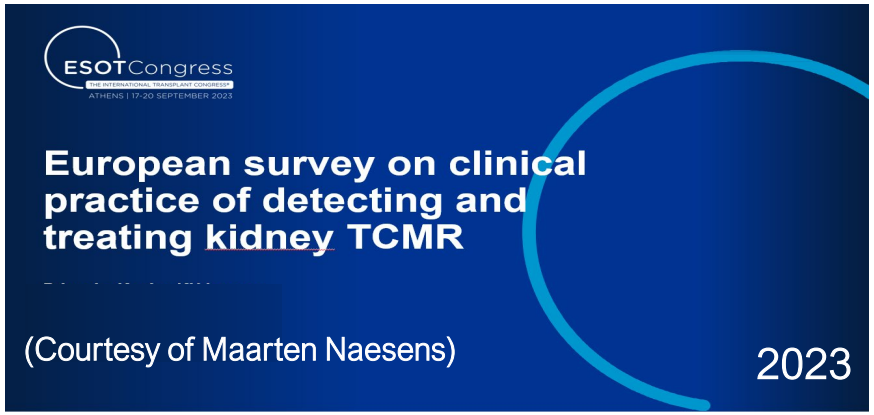
Grade for quality of evidence	Quality of evidence
A	High
B	Moderate
C	Low
D	Very low

- Low/very low quality of evidence
- Unresponsive = function not back to baseline after last dose of Rx (time frame not defined)
- No distinction between persistent vs recurrent AR
  - Use of repeat bx to assess response
- Does not provide guidance for AR treatment:
  - Specific drug dosing
  - Based on rejection grade
  - If subclinical borderline TCMR
  - Diagnosed by indication vs protocol bx

KDIGO AJT (2009) 9 (Suppl 3):S21-22

What do transplant physicians say they do?





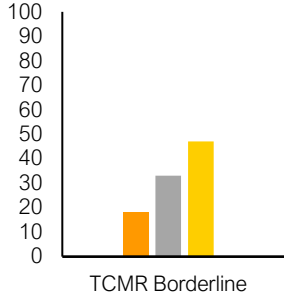
- 47 respondents (of 196)
  - 28% protocol biopsies
- 18/25 transplant centers

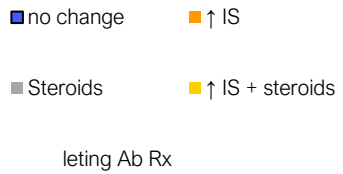
- 104 respondents (of 470)
- 88/235 transplant centers
  - 40% protocol biopsies
  - Induction: primarily RATG

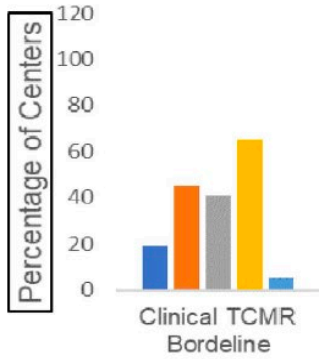
- 129 respondents
- 129 transplant centers
  - 36% protocol biopsies as SOC (+21% in specific subgroups)
  - Induction: basiliximab or RATG

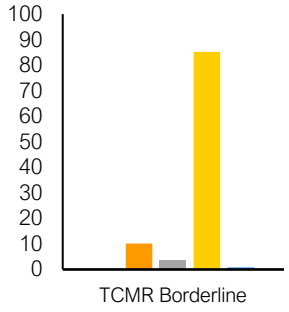
- 235 transplant centers in North America and Europe

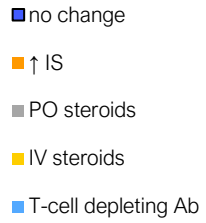
Treatment of clinical TCMR











Grades of clinical TCMR

6.2: We suggest treating subclinical and borderline acute rejection. *(2D)*

6.3.1: We suggest adding or restoring maintenance prednisone in patients not on steroids who have a rejection episode. *(2D)*

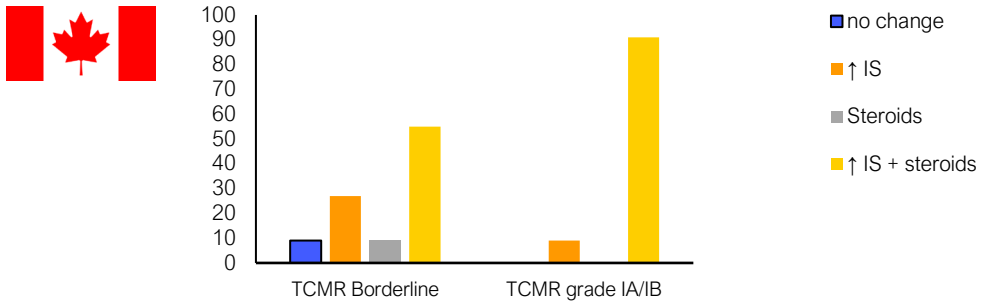
6.3.2: We suggest using lymphocyte-depleting antibodies or OKT3 for acute cellular rejections that do not respond to corticosteroids, and for recurrent acute cellular rejections. *(2C)*

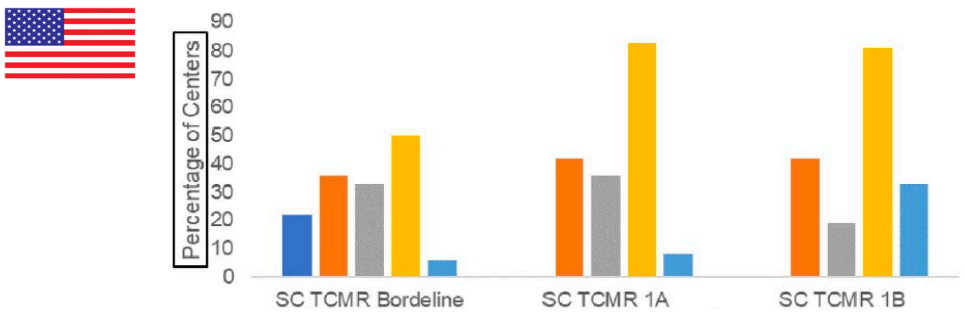
6.5: For patients who have a rejection episode, we suggest adding mycophenolate if the patient is not receiving mycophenolate or azathioprine, or switching azathioprine to mycophenolate. *(2D)*

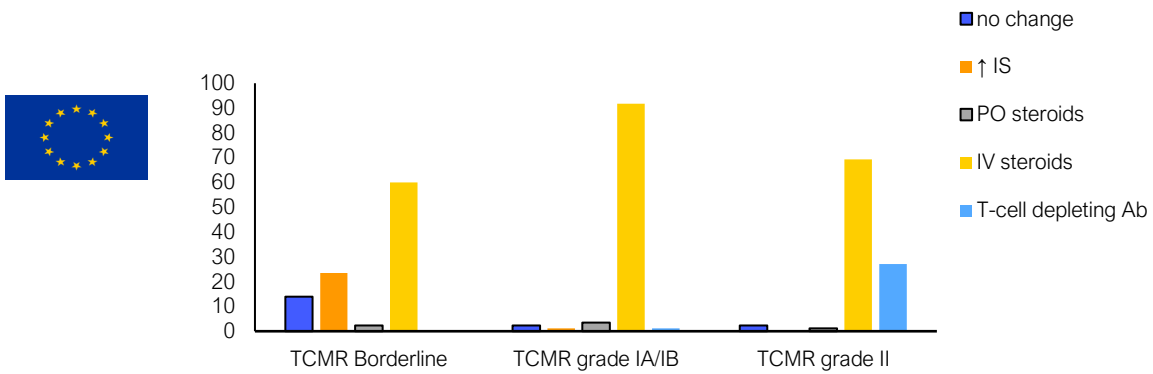
Clinical TCMR	Harmonization yes	no	Comment
Borderline			

Modified from Leblanc *et al*, Can J Kidney Health & Dis 2018; Sood *et al*, Clin Transplant 2021; Naesens (by courtesy)

Treatment of subclinical TCMR







Grades of subclinical TCMR

6.2: We suggest treating subclinical and borderline acute rejection. *(2D)*

6.3: We recommend corticosteroids for the initial treatment of acute cellular rejection. *(1D)*

6.3.1: We suggest adding or restoring maintenance prednisone in patients not on steroids who have a rejection episode. *(2D)*

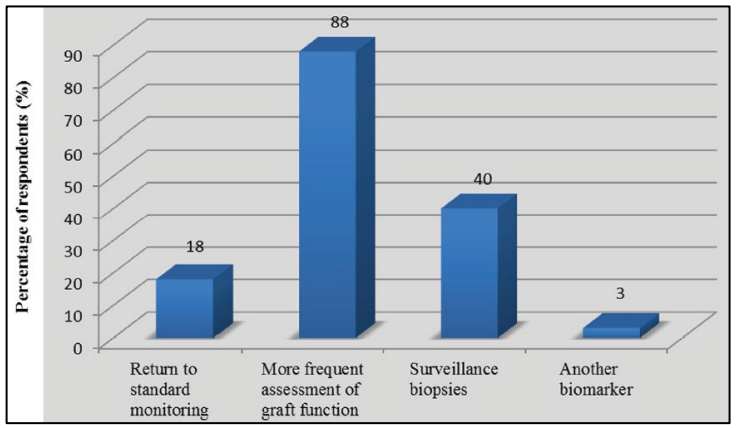
6.3.2: We suggest using lymphocyte-depleting antibodies or OKT3 for acute cellular rejections that do not respond to corticosteroids, and for recurrent acute cellular rejections. *(2C)*

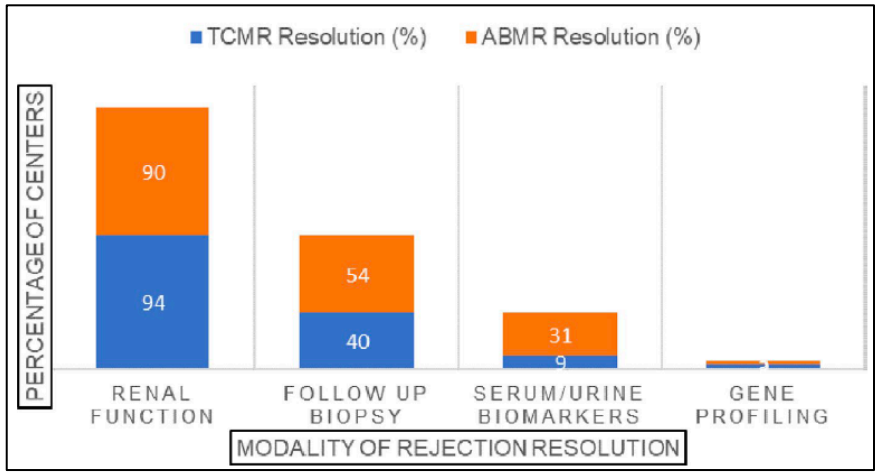
6.5: For patients who have a rejection episode, we suggest adding mycophenolate if the patient is not receiving mycophenolate or azathioprine, or switching azathioprine to mycophenolate. *(2D)*

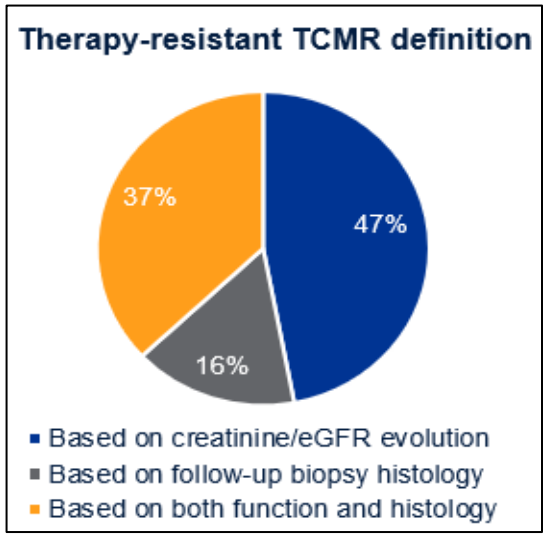
Subclinical TCMR	Harmonization yes	Harmonization no	Comment
Borderline	✓	✓	5-20% no Rx (all); most ↑IS
Grade IA	✓		Most Rx with steroids; most ↑IS
Grade IB	✓	✓	Steroids (EU, CAN, US); rATG (US)
Grade II	✓	✓	Steroids/rATG (EU, US)

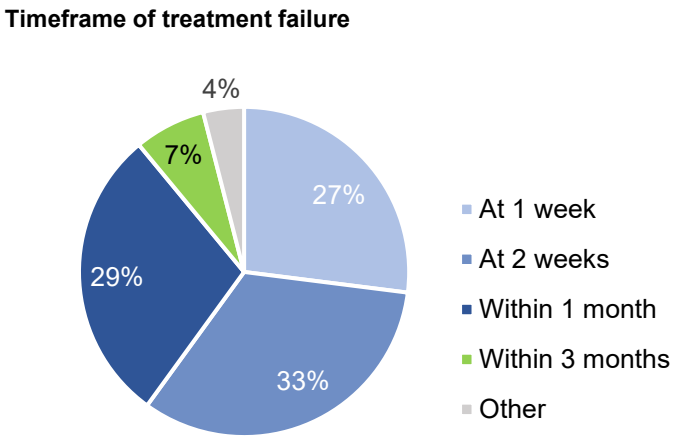
Modified from Leblanc *et al*, Can J Kidney Health & Dis 2018; Sood *et al*, Clin Transplant 2021; Naesens (by courtesy)

Assessing response to Therapy









- No standardization of post-rejection treatment follow up:
  - Kidney function
  - Whether to biopsy
  - When to biopsy

Leblanc *et al*, Can J Kidney Health & Dis 2018; Sood *et al*, Clin Transplant 2021; Naesens (by courtesy)

Conclusions

- Rejection remains the commonest cause of death censored graft loss
- No large RCTs have evaluated BPAR treatment under contemporary immunosuppression; the arsenal is limited
- Heterogeneity in treating BPAR
  - When or whether to treat (especially borderline)
  - How to treat
  - How and when to assess response to Rx
  - Protocol biopsies
- Optimal management of BPAR remains to be established

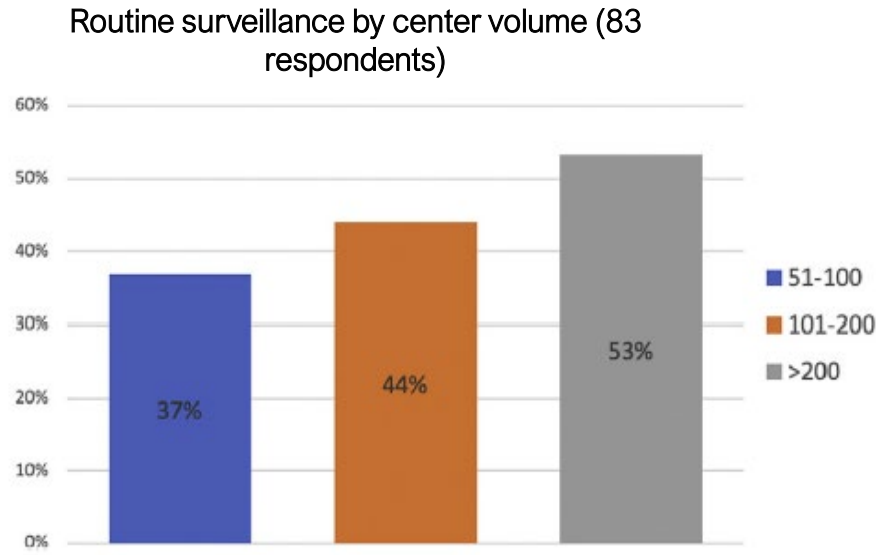
Heterogenous clinical practice in performing protocol biopsies

Count	Always n (%)	Never n (%)	Sometimes n (%)	Unanswered n (%)	Total n
Africa	1 (8)	2 (15)	10 (77)	0 (0)	13
Asia	1 (5)	11 (55)	8 (40)	0 (0)	20
Australia/Oceana	7 (64)	0 (0)	4 (36)	0 (0)	11
Central/South America	7 (18)	24 (60)	9 (22)	0 (0)	40
Europe	20 (35)	21 (37)	15 (26)	1 (2)	57
North America	30 (33)	37 (41)	22 (24)	1 (1)	90
Unanswered	1	0	0	0	1
Total	67 (29%)	95 (41%)	68 (29%)	2 (1)	232

Schinstock C, et al. Transplant Int 2021

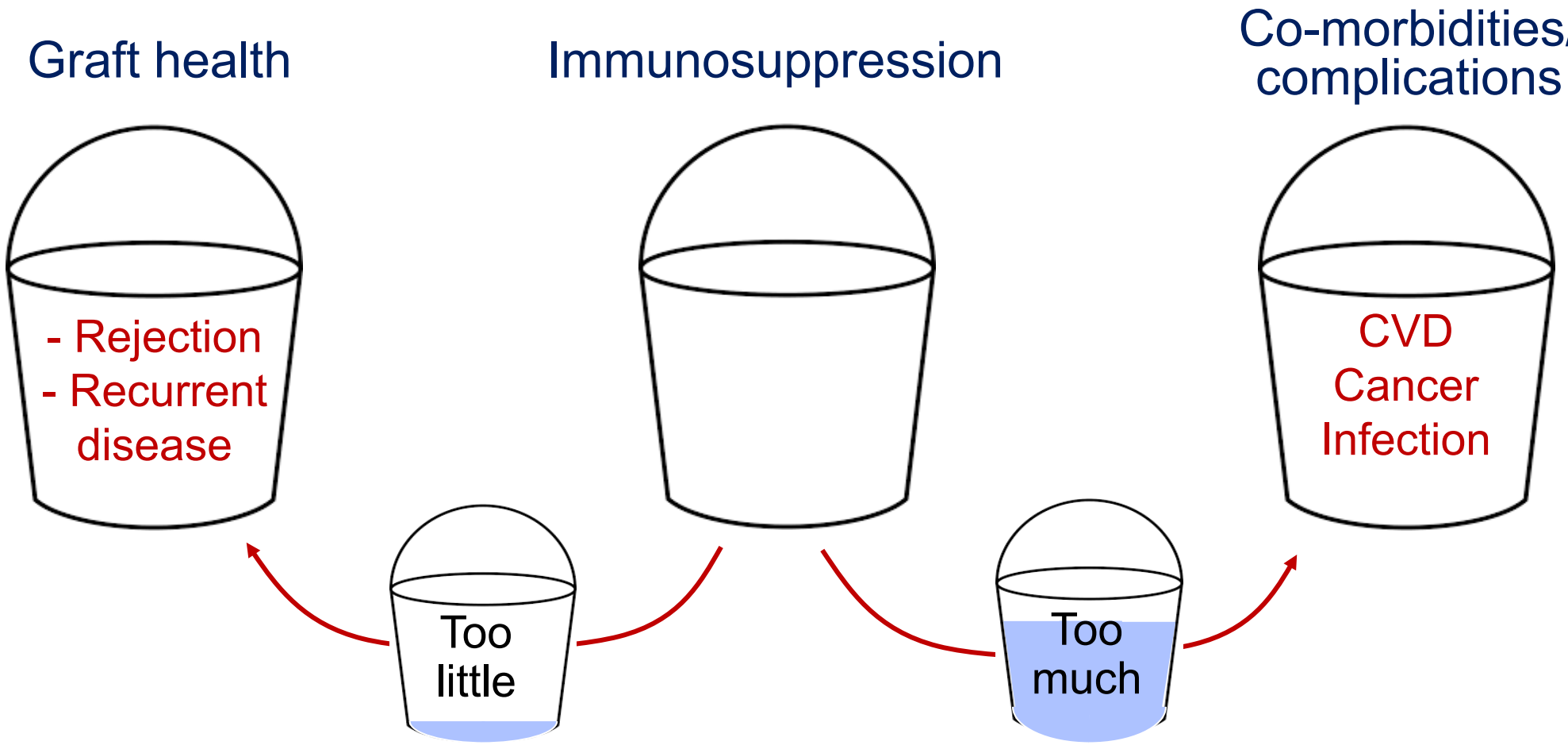
Surveillance Biopsy

- Rationale:
  - Determine subclinical rejection
  - Opportunity to intervene
- Low risk of major complications
- Limitations
  - Timing and frequency?
  - Cost/inconvenience
  - Sampling error
  - Intra-observer reproducibility
  - Some risk
- Not performed by most centers



Lee *et al*. Transplant Proc, 2020

Recipient Management Fundamentals



Biomarkers in blood, urine, tissue

SOC according to GUIDELINES

KDIGO 2009 guideline (Chapter 6):

6.3.2: We suggest using lymphocyte-depleting antibodies or OKT3 for acute cellular rejections that do not respond to corticosteroids, and for recurrent TCMR. (2C)

When a steroid-resistant rejection or a recurrent rejection does not respond to a lymphocyte-depleting antibody or OKT3, a new biopsy should be considered to rule out alternative causes of graft dysfunction

BTS Clinical Practice Guidelines 2017

Guideline 4.10 – KTR: Treatment of acute rejection

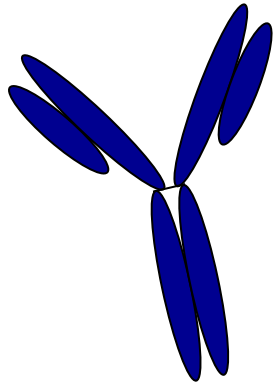
We suggest that lymphocyte depleting agents may be considered for refractory acute cellular rejection or aggressive vascular cellular rejection (i.e. Banff category 4 Type II and III) (2C)

Egyptian clinical practice guideline for KT *(Shokeir et al. Arab J Urology 2021)*

We recommend adding lymphocyte-depleting Abs for acute TCMR that do not respond to corticosteroids, *those above Banff Grade I, and for recurrent TCMRs* (2C).

The Negative Impact of BPAR

In the Modern Era of Immunosuppression



9th Nov 2023

FDA Workshop

Peter Nickerson, MD, FRCPC, FCAHS

Flynn Family Chair in Kidney Transplantation

Distinguished Professor of Medicine and Immunology

Relevant Financial Relationship Disclosure Statement

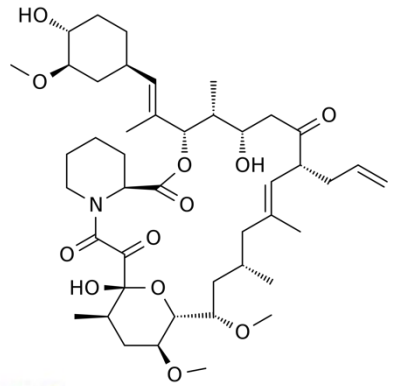
Peter Nickerson, University of Manitoba, Winnipeg, Canada

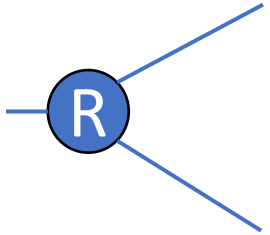
- Consultancies: CSL Behring LLC

The presentation does not include discussion of off-label or investigational use of drugs

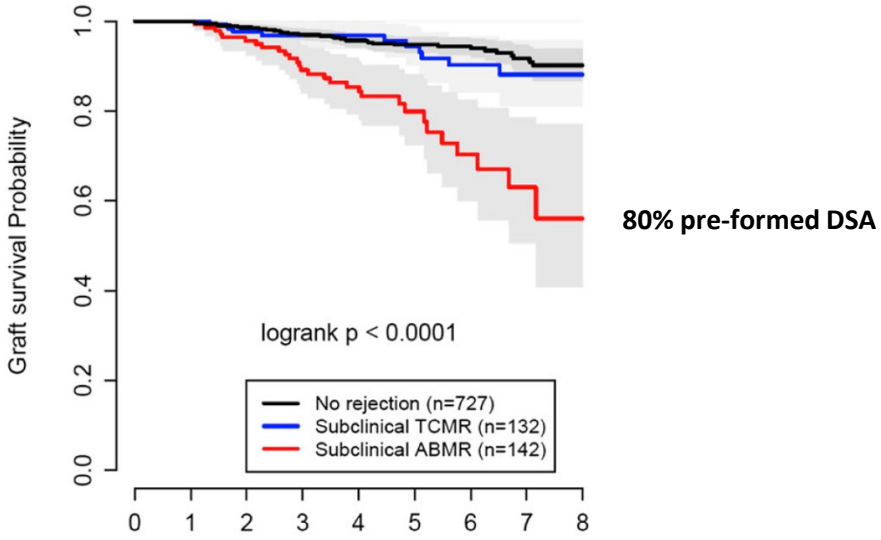
Objectives

- Review the **efficacy of modern immunosuppression** on **BPAR**
- Discuss relative impact of **DGF, TCMR and ABMR** on graft outcomes
- Discuss **future directions** to improve graft outcomes



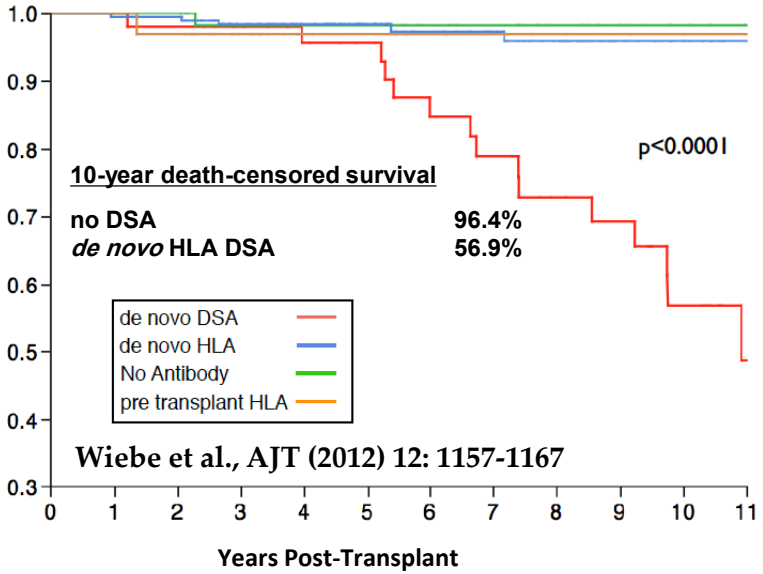


Post-Transplant there has been intense focus on DSA/ABMR

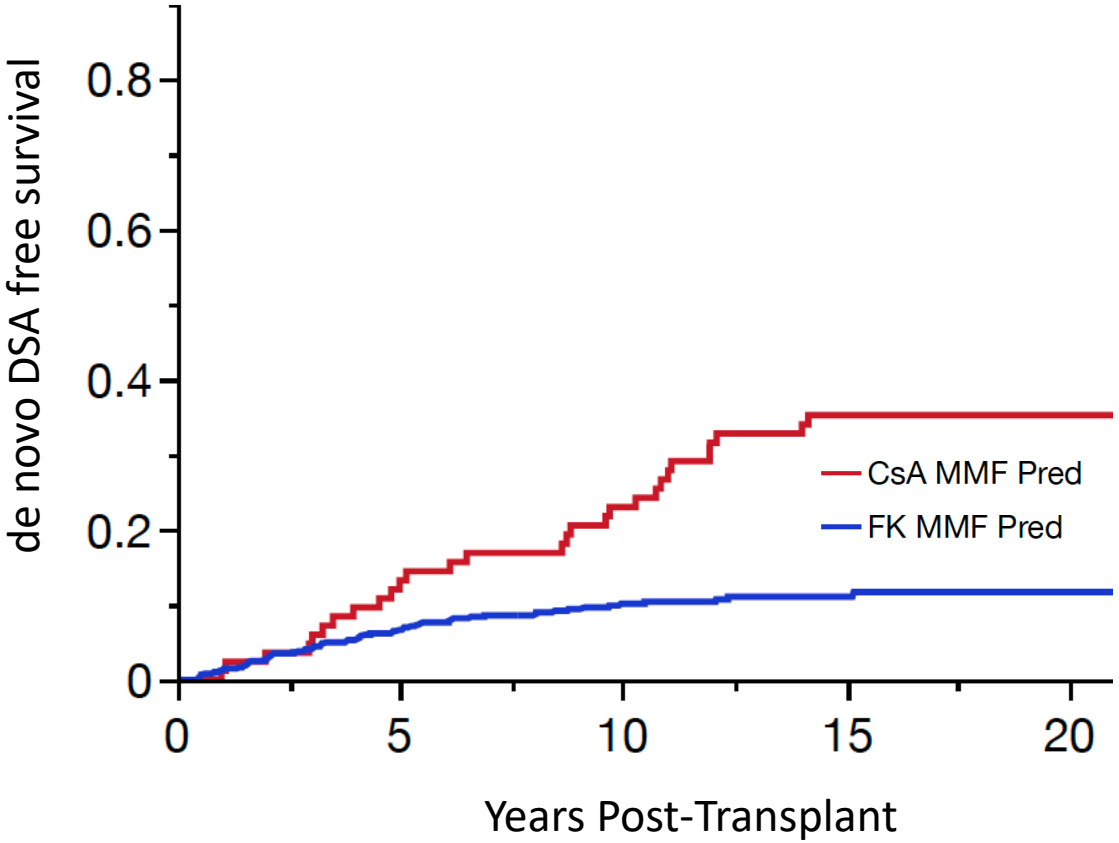


80% pre-formed DSA

Loupy et al, JASN (2015) 26: 1721-1731



Wiebe et al., AJT (2012) 12: 1157-1167



Lower Tacrolimus Exposure and Time in Therapeutic Range Increase Risk of *de novo* DSA

1st Year Post-Transplant (Colorado Cohort)

Davis et al., AJT (2018) 18:907-915

Target $Tac_{mo\ 0\text{-}3}$ C_0 6-9 ng/ml
Target $Tac_{mo\ 4\text{-}12}$ C_0 5-8 ng/ml

mean $Tac_{mo\ 0\text{-}12}$ C_0	≥ 8.0 ng/ml	24.0%
mean $Tac_{mo\ 0\text{-}12}$ C_0	6.0-7.9 ng/ml	57.2%
mean $Tac_{mo\ 0\text{-}12}$ C_0	< 6.0 ng/ml	18.8%

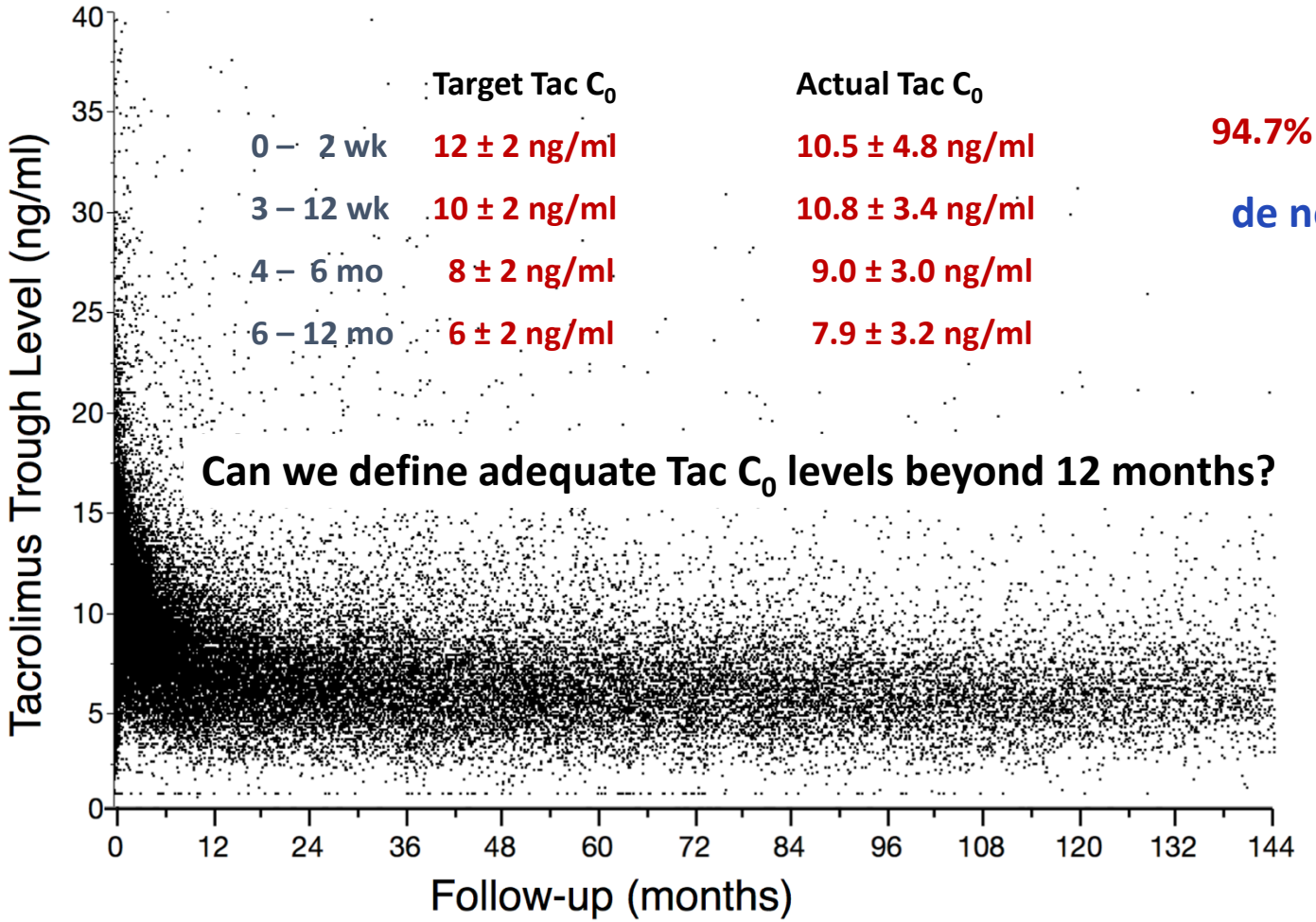
dnDSA 1mo	7.4%	(n= 40)
dnDSA 6mo	14.3%	(n= 77)
dnDSA 12mo	21.7%	(n=117)

		dnDSA		Acute rejection		DCGL	
Mean TAC C0 range (ng/mL)		OR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
57.2% 6–7.9 vs. ≥8	Univariate	1.49 (0.85-2.61)	.164	1.03 (0.47-2.24)	.951	1.76 (0.59-5.24)	.308
	Multivariable	1.86 (1.02-3.39)	.044	1.12 (0.51-2.46)	.784	1.67 (0.55-5.10)	.368
18.8% 4–5.9 vs. ≥8	Univariate	2.89 (1.50-5.57)	.001	2.55 (1.11-5.90)	.028	3.65 (1.14-11.63)	.029
	Multivariable	4.44 (2.14-9.20)	<.001	3.20 (1.35-7.59)	.008	3.86 (1.14-13.02)	.030
0–3.9 vs. ≥8	Univariate	4.82 (1.34-17.40)	.016	19.08 (7.54-48.27)	<.001	12.13 (2.71-54.20)	.001
	Multivariable	5.87 (1.42-24.30)	.015	23.07 (8.44-63.08)	<.001	18.79 (3.56-99.08)	<.001

Assessment of Tacrolimus C_0 levels to prevent *de novo* DSA

(Manitoba Cohort)

(n=492 Tac C_0 levels = 50,011)



	Target Tac C_0	Actual Tac C_0
0 – 2 wk	12 ± 2 ng/ml	10.5 ± 4.8 ng/ml
3 – 12 wk	10 ± 2 ng/ml	10.8 ± 3.4 ng/ml
4 – 6 mo	8 ± 2 ng/ml	9.0 ± 3.0 ng/ml
6 – 12 mo	6 ± 2 ng/ml	7.9 ± 3.2 ng/ml

Can we define adequate Tac C_0 levels beyond 12 months?

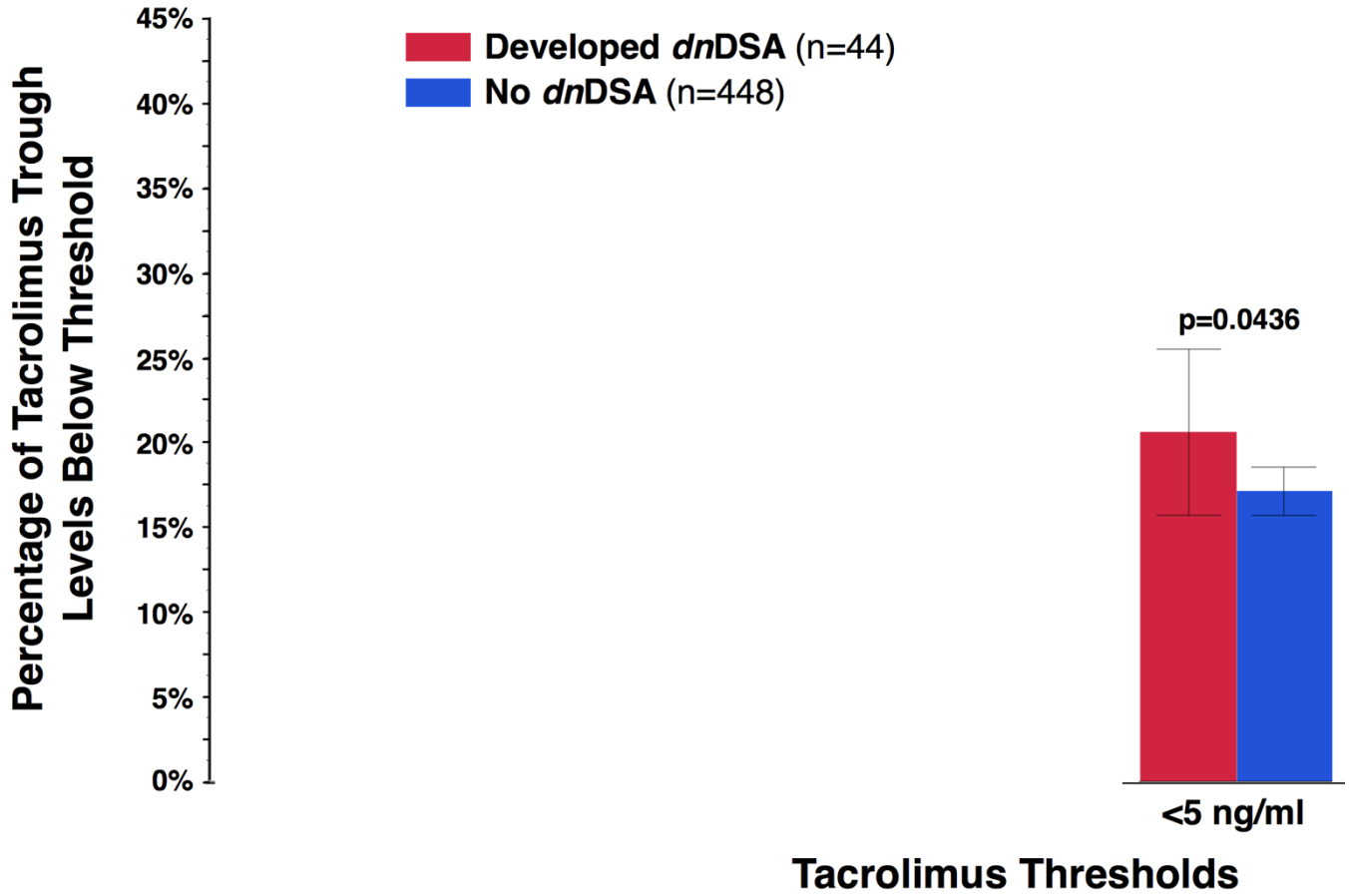
94.7% mean $Tac_{mo\ 0\text{-}12}$ C_0 ≥ 8.0 ng/ml

de novo DSA at 12 months **1%**

Wiebe et al., JASN (2017) 28:3353-3362

Defining Adequate Long-Term Tacrolimus Immunosuppression Levels

⇑ % Tacrolimus C_0 < 5.0 ng/ml increases the risk for *de novo* DSA



Wiebe et al., JASN (2017) 28:3353-3362

French Multi-Centre Randomized Control Trial

Impact of low dose extended-release Tacrolimus in "low-risk" steroid free kidney transplants

Gatault et al., AJT (2017) 17:1370-1379

Adults 18-70
LD/NDD
Non-HLA Identical
No pre-transplant DSA
No $BPAR_{0-3\ months}$

$T_{0-3\ months}$: 300 Pts Enrolled — IL2R mAb Induction, Tacrolimus/MMF/Steroid Taper

$T_{4\ months}$: 188 Pts Randomized — ER Tacrolimus (**Tac C_0 = 8-12 ng/ml**), MMF ≥ 500 mg bid, Steroid Free

$T_{4-12\ months}$

ITT

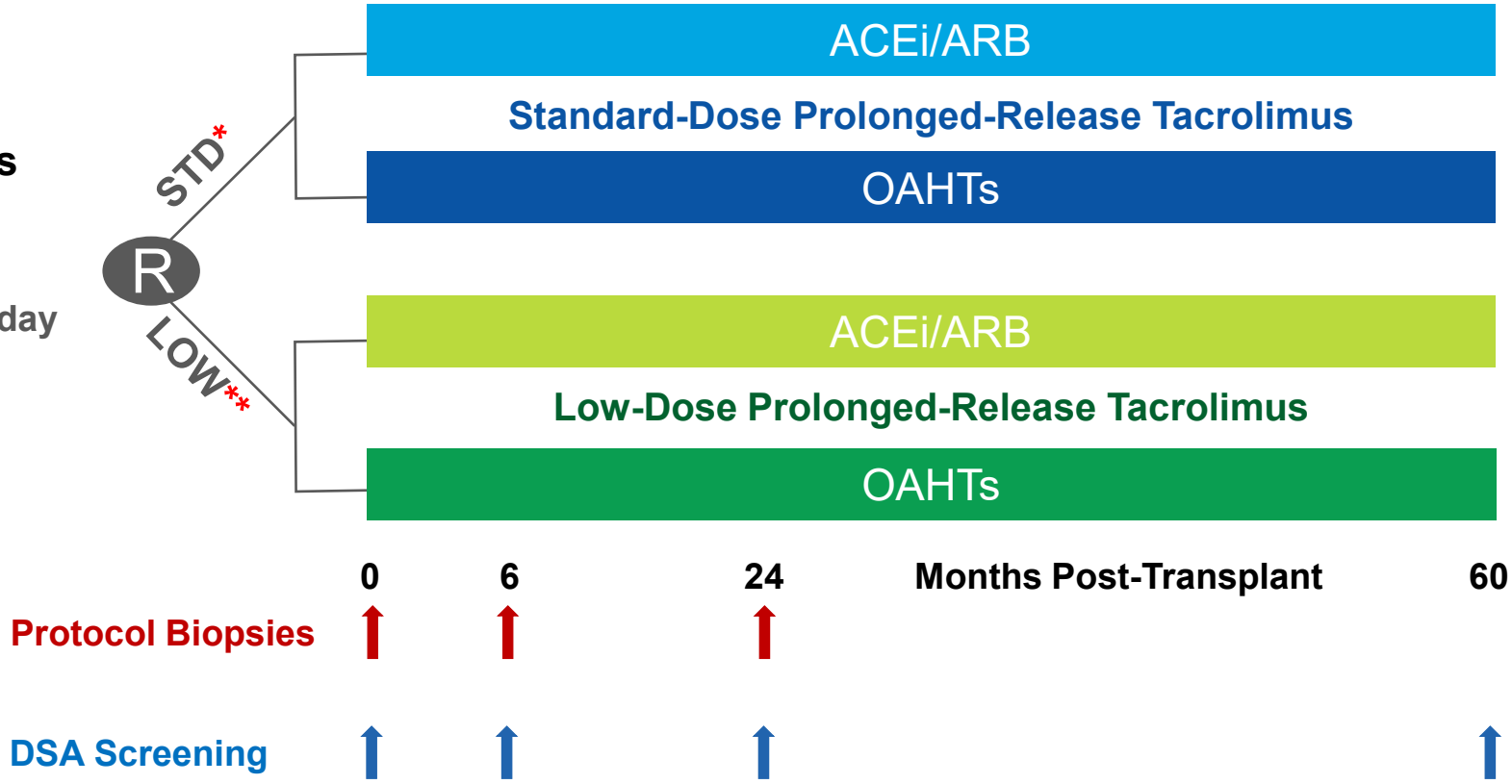
	87 Pts 50% Tac Dose (**Tac C_0 > 3 ng/ml**)	99 Pts Stable Tac Dose (**Tac C_0 = 7-12 ng/ml**)	
Tac C_0 6 mo	**5.3 ± 1.7 ng/ml**	**8.4 ± 2.1 ng/ml**	p<0.0001
Tac C_0 12 mo	**5.6 ± 2.0 ng/ml**	**7.4 ± 2.0 ng/ml**	p<0.0001
1° eGFR @ 12 mo	**56.0 ± 17.5 ml/min**	**56.0 ± 22.1 ml/min**	p = NS
2° BPAR	**11%**	**3%**	**p=0.016**
DSA	**6** (5 Class II, 1 Class I)	0	**p=0.008**
BK Viremia	1	**6**	p=0.123
Protocol $Bx_{12\ mo}$ i>0	**21.4%**	8.8%	**p=0.047**
IFTA (CI)$_{12mo}$	**50.0%**	**44.1%**	p=0.514

Canadian Multi-Centre Randomized Study (FKC-014)

Comparison of the effects of STANDARD vs. LOW-DOSE Tacrolimus with or without ACEi/ARB on Histology and Renal Function

~280 First Kidney Transplant Recipients

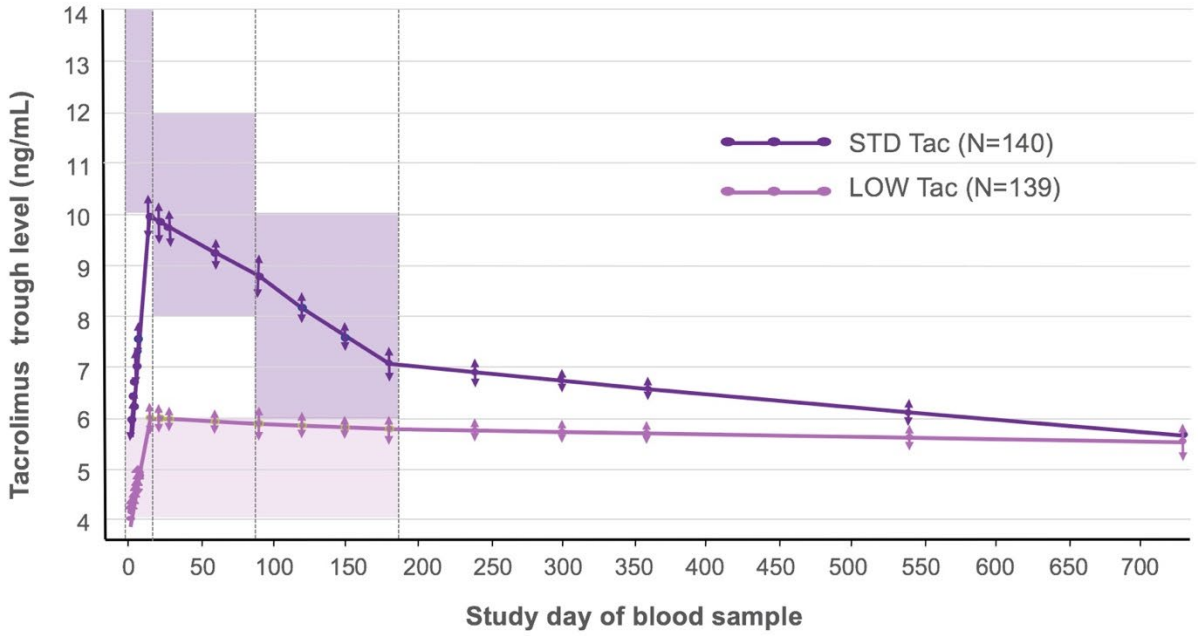
- α-IL2R mAb induction
- MMF/MPA
- Steroid taper to 5 mg/day

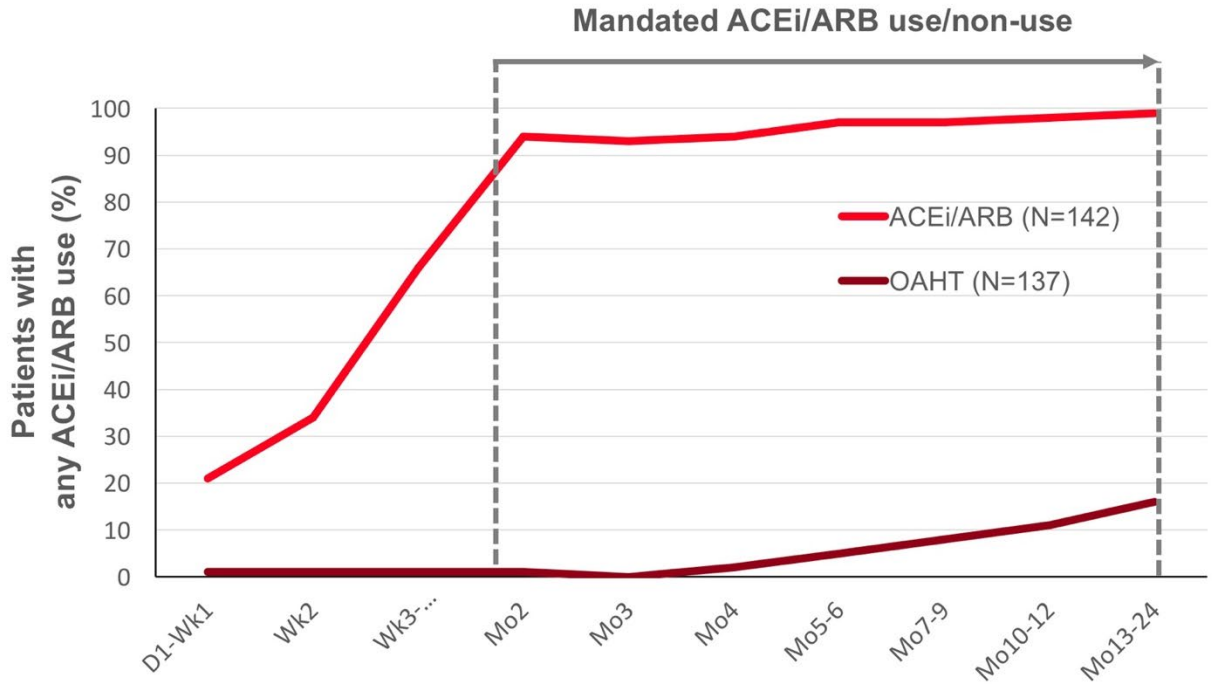


Cockfield et al., AJT (2019) 19:1730-1744

Canadian Multi-Centre Randomized Study (FKC-014)

Comparison of the effects of STANDARD vs. LOW-DOSE Tacrolimus with or without ACEi/ARB on Histology and Renal Function





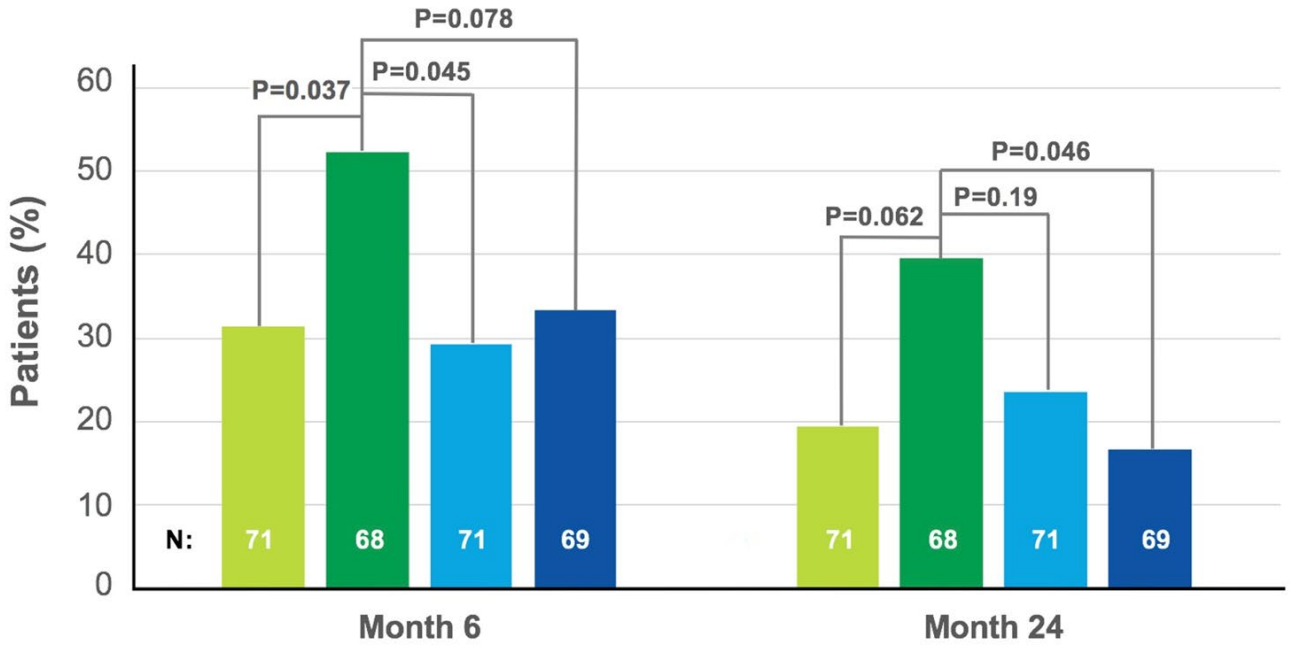
	LOW Tac		STD Tac	
BK Viremia $_{6mo}$	6.4%	vs.	16.3%	p=0.028

Cockfield et al., AJT (2019) 19:1730-1744

Canadian Multi-Centre Randomized Study (FKC-014)

Comparison of the effects of STANDARD vs. LOW-DOSE Tacrolimus with or without ACEi/ARB on Histology and Renal Function

Incidence of T-cell Mediated Rejection Including Banff Borderline Changes



Tac	LOW	LOW	STD	STD	LOW	LOW	STD	STD	
AHT	ACEi/ARB	OAHT	ACEi/ARB	OAHT	ACEi/ARB	OAHT	ACEi/ARB	OAHT	
0-6 Banff Grade IA+	7.0%	16.2%	4.2%	7.2%	11.3%	19.1%	11.3%	10.1%	0-24 Banff Grade IA+

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor 1 blocker; mFAS, modified Full Analysis Set; (O)AHT, (other) antihypertensive therapy; STD, standard; Tac, tacrolimus.

Cockfield et al., AJT (2019) 19:1730-1744

Canadian Multi-Centre Randomized Study (FKC-014)

Comparison of the effects of STANDARD vs. LOW-DOSE Advagraft with or without ACEi/ARB on Histology and Renal Function

De Novo Donor-Specific Antibody (DSA) Development

	LOW Tac ACEi/ARB	LOW Tac OAHT	STD Tac ACEi/ARB	STD Tac OAHT
N=	71	68	71	69
DSA developed by Month 6 (%)	2 (3.0%)	1 (1.5%)	1 (1.5%)	1 (1.6%)
DSA developed by Month 24 (%)	4 (5.9%)	6 (8.8%)	3 (4.5%)	2 (3.1%)
DSA developed by Month 60 (%)*	7 (9.9%)	12 (17.6%)	4 (5.6%)	5 (7.2%)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor 1 blocker; FAS, Full Analysis Set; OAHT, other antihypertensive therapy; STD, standard; Tac, tacrolimus.

Cockfield et al., AJT (2019) 19:1730-1744
***Rush et al, AJT (2019) 19 (Suppl 3, C207)**

Dr. Chris Wiebe

Dr. Julie Ho

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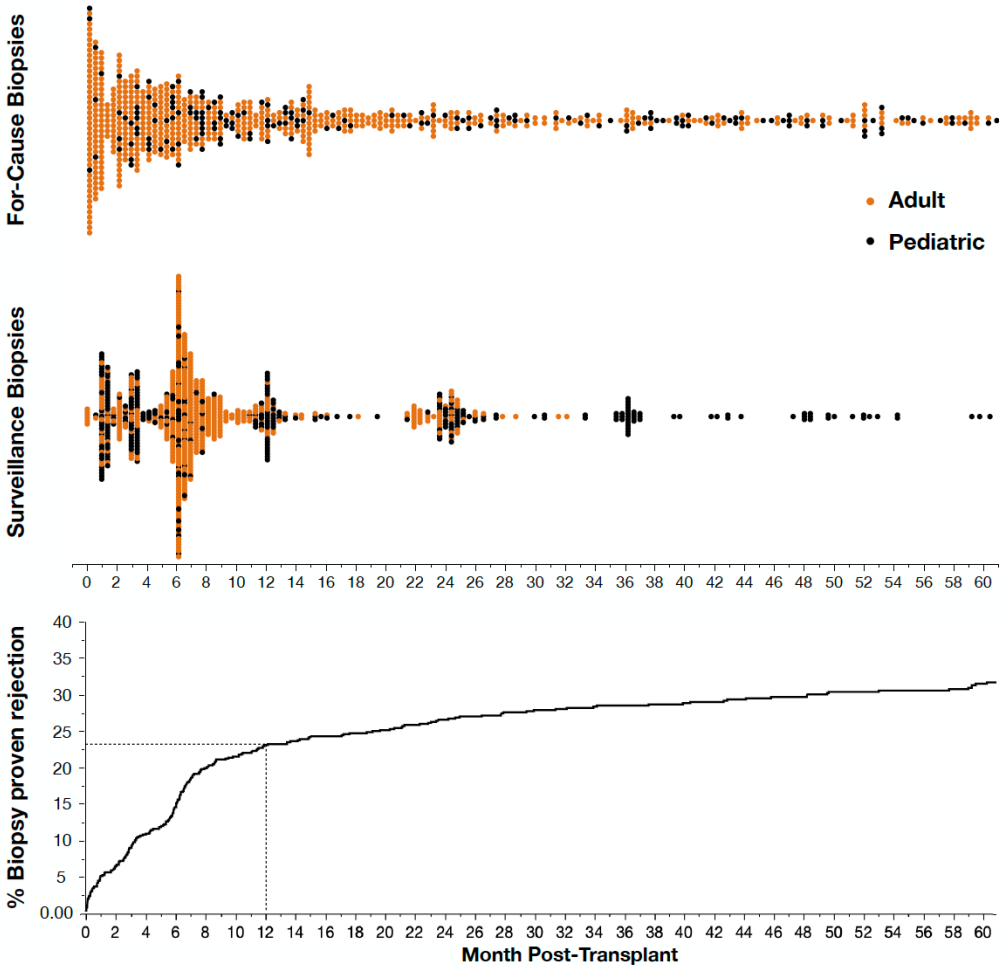
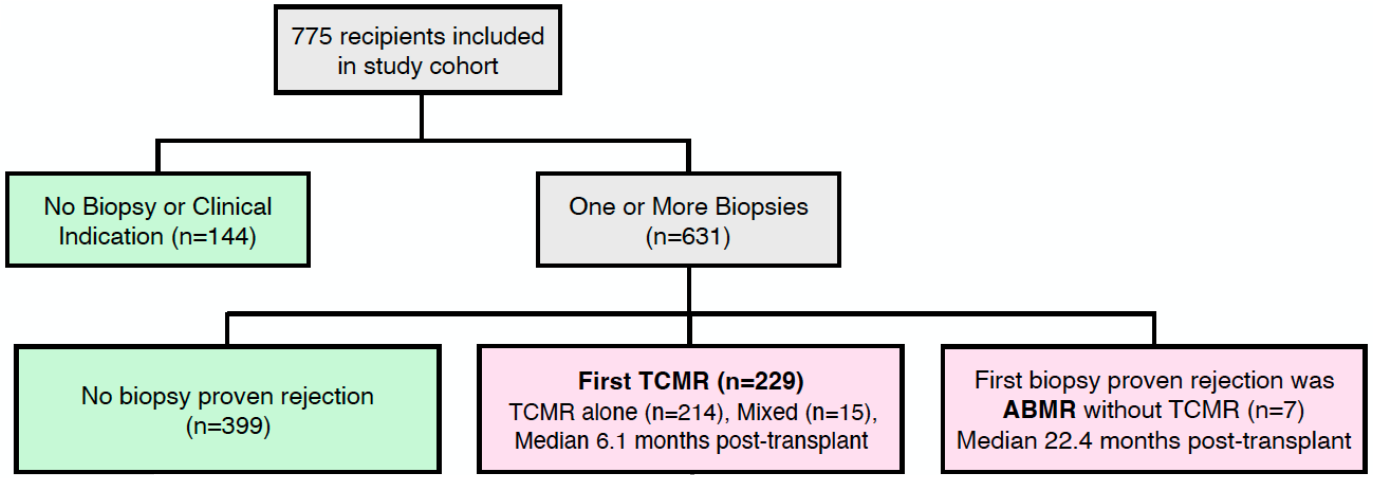
TCMR is still common in Kidney Recipients on Tac/MPA-based therapy

(Despite no pre-existing memory as defined by absence of DSA by Single Antigen Bead Testing)

Consecutive Naïve Cohort on Tac/MPA/Pred (n=775)

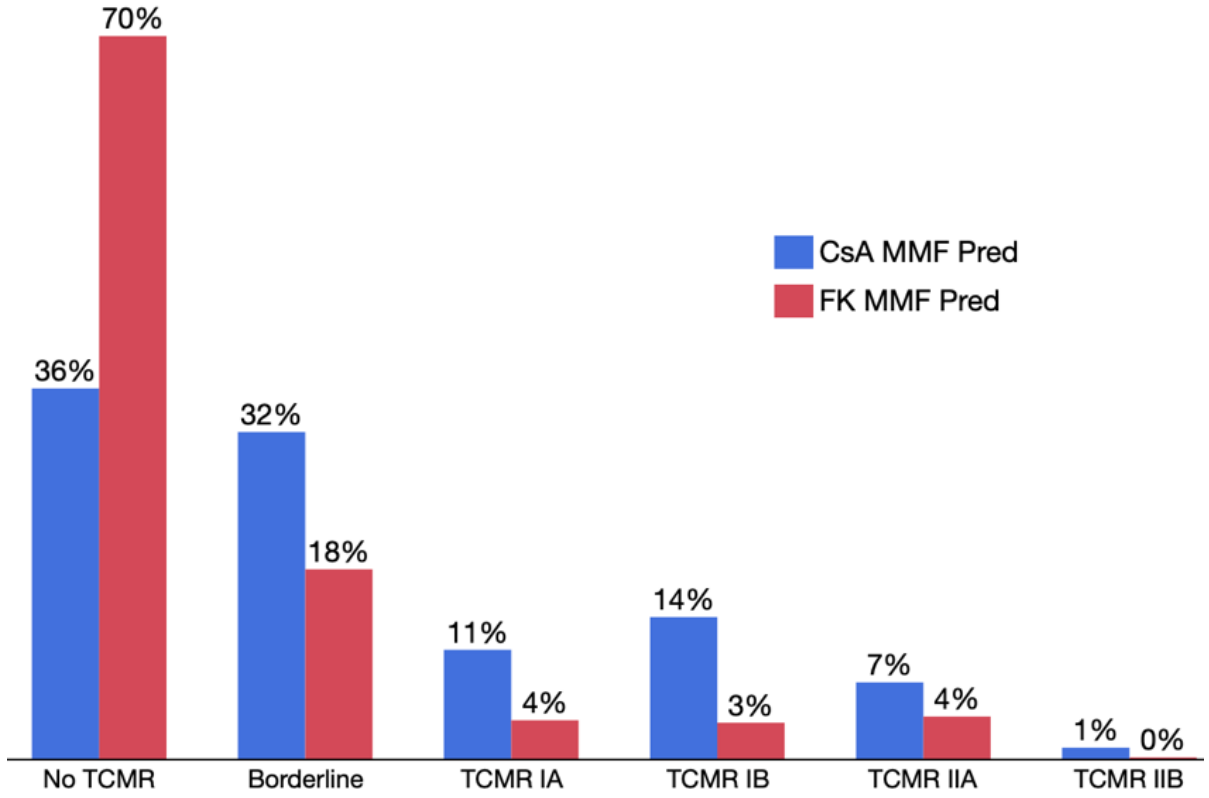


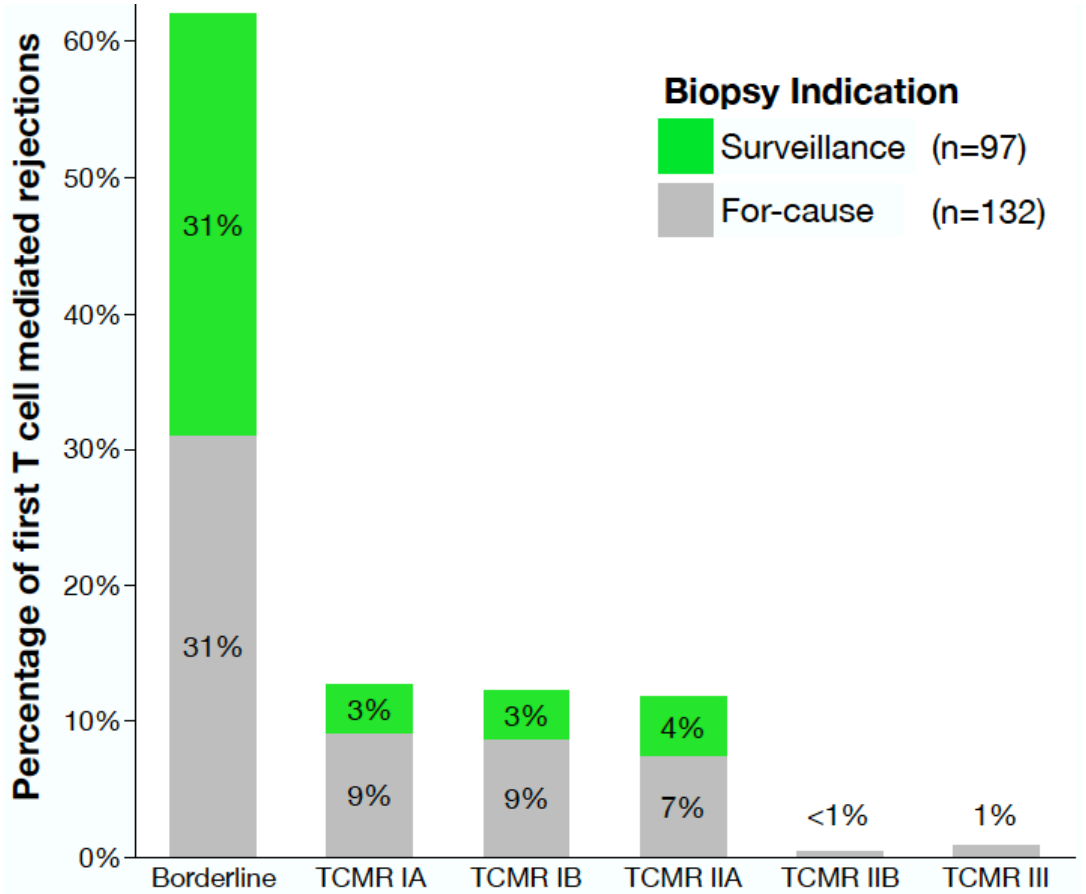


30%

Rampersad et al, AJT (2022) 22:761-771

Borderline (i>0 & t>0)$_{1997/2019}$ most common Banff Grade of 1st TCMR





1993 Banff Classification: Threshold set between Banff Borderline and Grade IA to define acute rejection.

Solez K. *Kidney Int*. 1993;44(2):411-422

Rampersad et al, AJT (2022) 22:761-771

DGF, TCMR and ABMR are Independent Predictors of Graft Loss

(time dependent covariate analysis)

Death-Censored Graft Loss n=74 events	HR	95% CI	p value
Model 2			
DGF	1.99	(1.08, 3.69)	0.028
First TCMR	**3.08**	**(1.77, 5.36)**	**<0.001**
ABMR	**5.47**	**(2.88, 10.38)**	**<0.001**

All-Cause Graft Loss n=187 events	HR	95% CI	p value
Model 2			
DGF	1.89	(1.30, 2.75)	<0.001
First TCMR	**1.62**	**(1.14, 2.3)**	**0.007**
ABMR	**3.06**	**(1.83, 5.12)**	**<0.001**

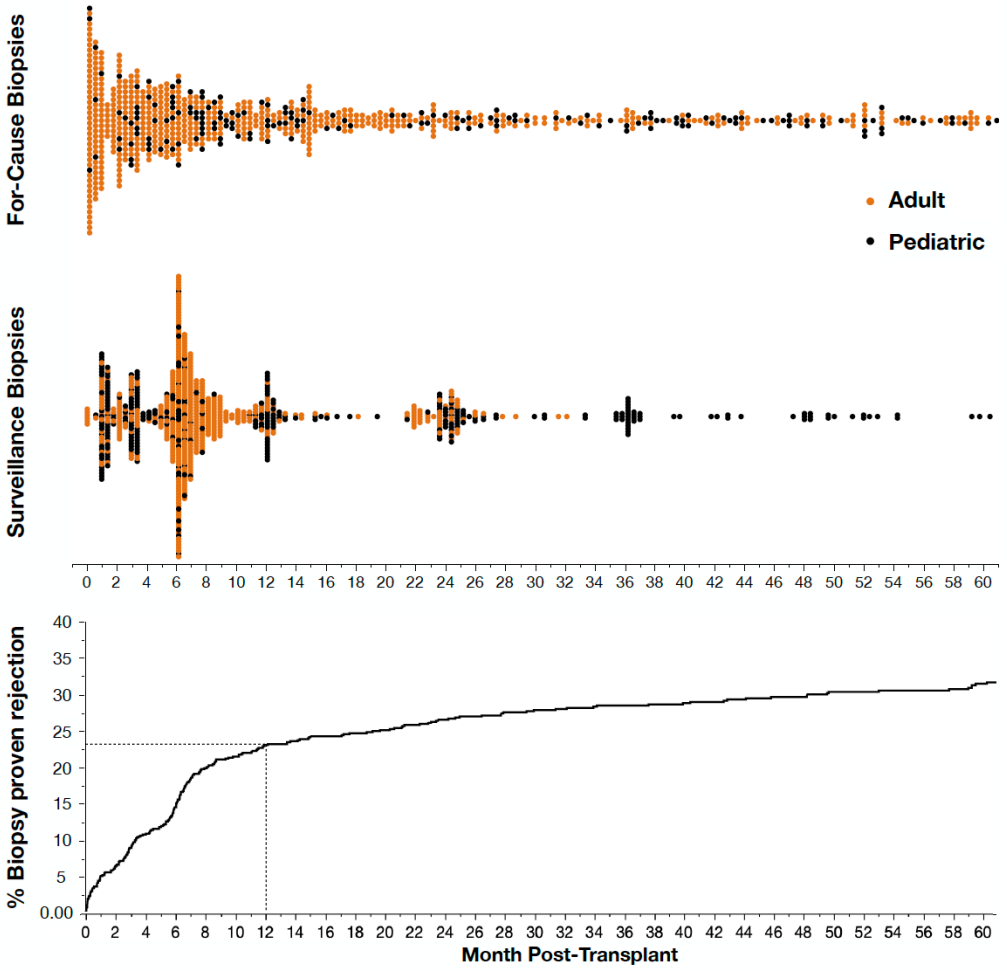
*** Models adjusted for baseline covariates**

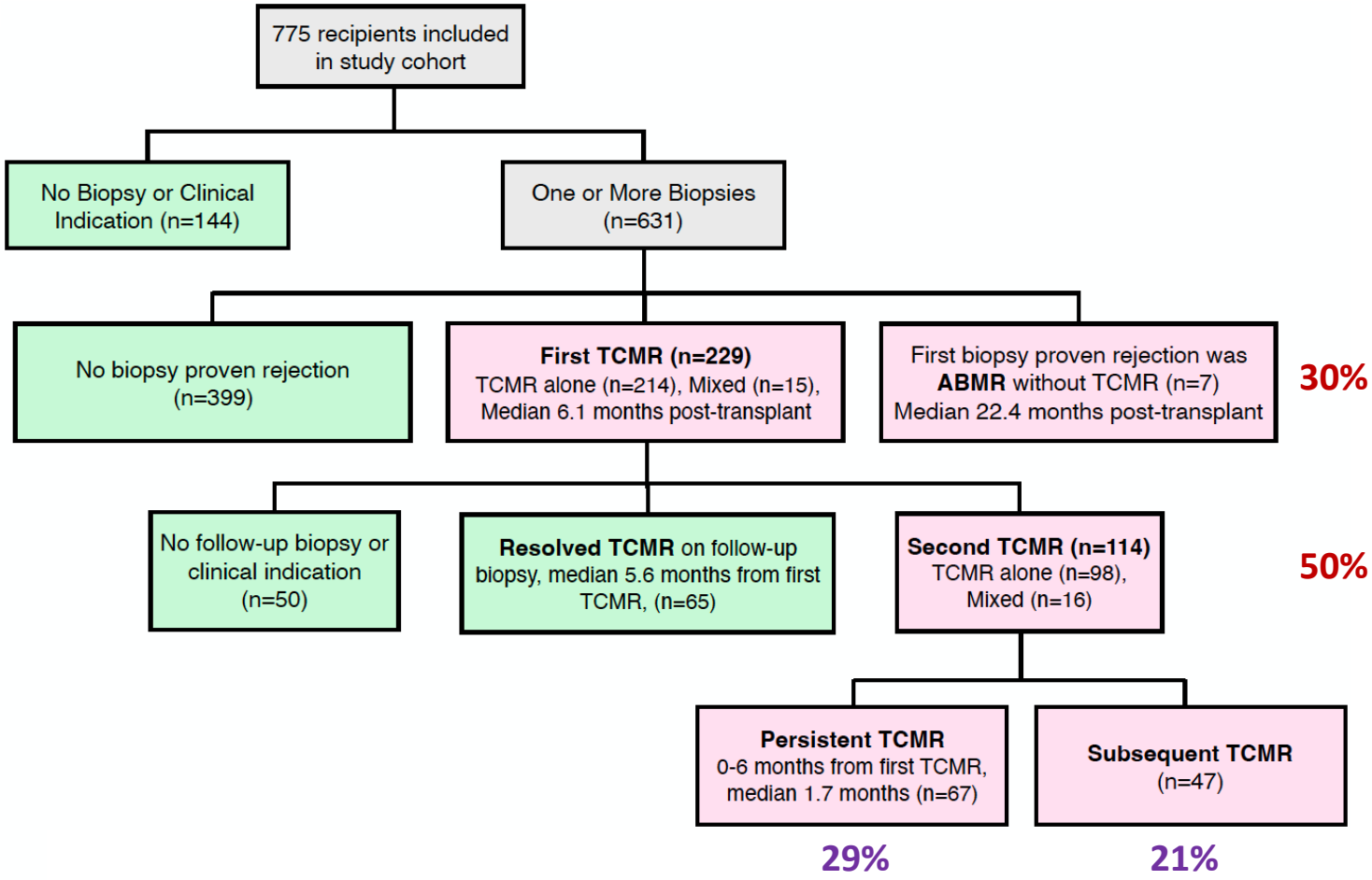
Rampersad et al, AJT (2022) 22:761-771

TCMR is still common in Kidney Recipients on Tac/MPA-based therapy

(Despite no pre-existing memory as defined by absence of DSA by Single Antigen Bead Testing)

Consecutive Naïve Cohort on Tac/MPA/Pred (n=775)





Rampersad et al, AJT (2022) 22:761-771

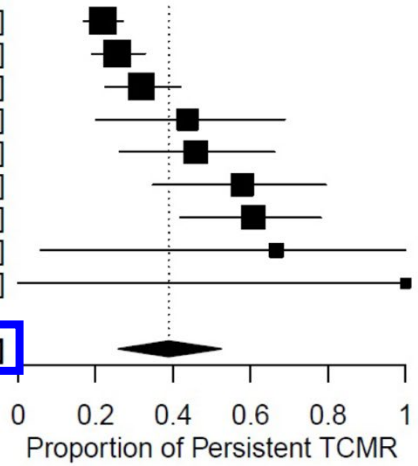
Persistent TCMR is Common in the Context of Tac/MPA-based Therapy

(Systematic Review and Meta-Analysis)

Initial TCMR ≥ Banff Borderline

Study	Cases	Total	Weight	Proportion	95% C.I.
Bouatou 2019	56	256	16.8%	0.22	[0.17; 0.27]
Nankivell 2019	40	156	16.4%	0.26	[0.19; 0.33]
Hoffman 2019	28	88	15.5%	0.32	[0.22; 0.42]
Chandran 2021	7	16	10.2%	0.44	[0.20; 0.69]
Seifert 2018	11	24	11.8%	0.46	[0.26; 0.66]
Friedewald 2019	11	19	10.9%	0.58	[0.35; 0.79]
Hoffmann 2021	17	28	12.4%	0.61	[0.42; 0.78]
Naumnik 2017	2	3	4.0%	0.67	[0.06; 1.00]
Zhu 2018	1	1	2.0%	1.00	[0.00; 1.00]
Total (95% CI)		**591**	**100.0%**	**0.39**	**[0.26; 0.53]**

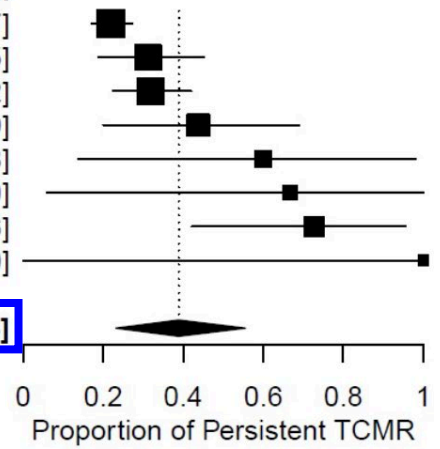
Heterogeneity: $Tau^2 = 0.0208$; $Chi^2 = 34.88$, df = 8 ($P < 0.01$); $I^2 = 77\%$



Initial TCMR ≥ Banff 1A

Study	Cases	Total	Weight	Proportion	95% C.I.
Bouatou 2019	56	256	21.4%	0.22	[0.17; 0.27]
Nankivell 2019	15	48	18.2%	0.31	[0.19; 0.45]
Hoffman 2019	28	88	19.9%	0.32	[0.22; 0.42]
Seifert 2018	7	16	13.4%	0.44	[0.20; 0.69]
Friedewald 2019	3	5	7.5%	0.60	[0.14; 0.98]
Naumnik 2017	2	3	5.4%	0.67	[0.06; 1.00]
Hoffmann 2021	8	11	11.5%	0.73	[0.42; 0.96]
Zhu 2018	1	1	2.7%	1.00	[0.00; 1.00]
Total (95% CI)		**428**	**100.0%**	**0.39**	**[0.23; 0.56]**

Heterogeneity: $Tau^2 = 0.0229$; $Chi^2 = 23.15$, df = 7 ($P < 0.01$); $I^2 = 70\%$



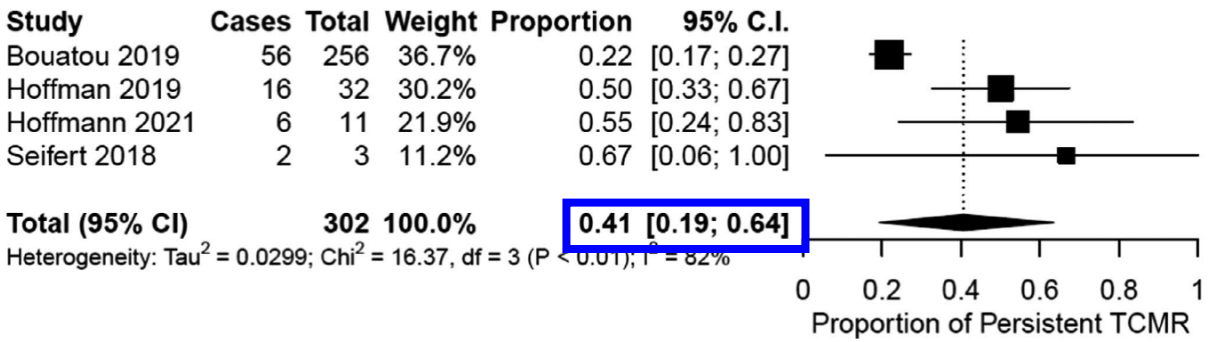
39% Persistence of TCMR ≥ Banff Borderline in the next 2-9 months following anti-rejection therapy

Ho et al, AJT (2022) 22:772-785

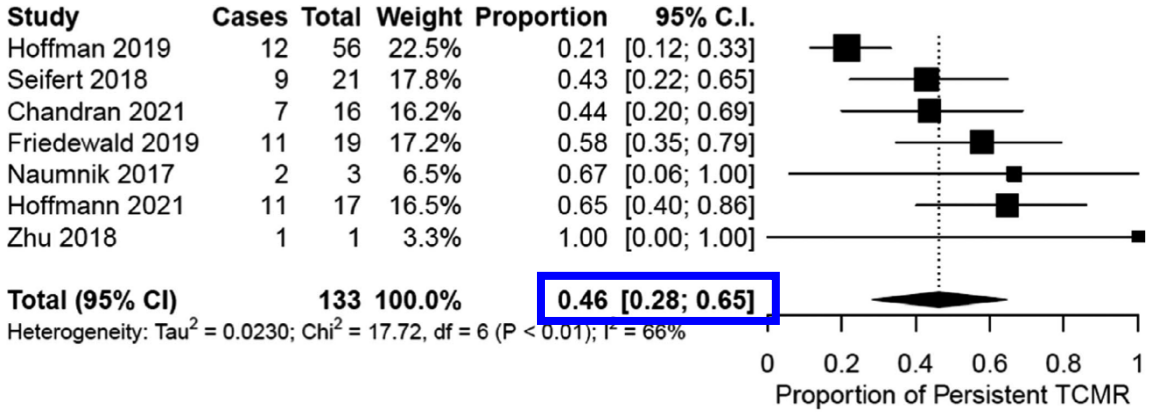
Persistent TCMR is Common in the Context of Tac/MPA-based Therapy

(Systematic Review and Meta-Analysis)

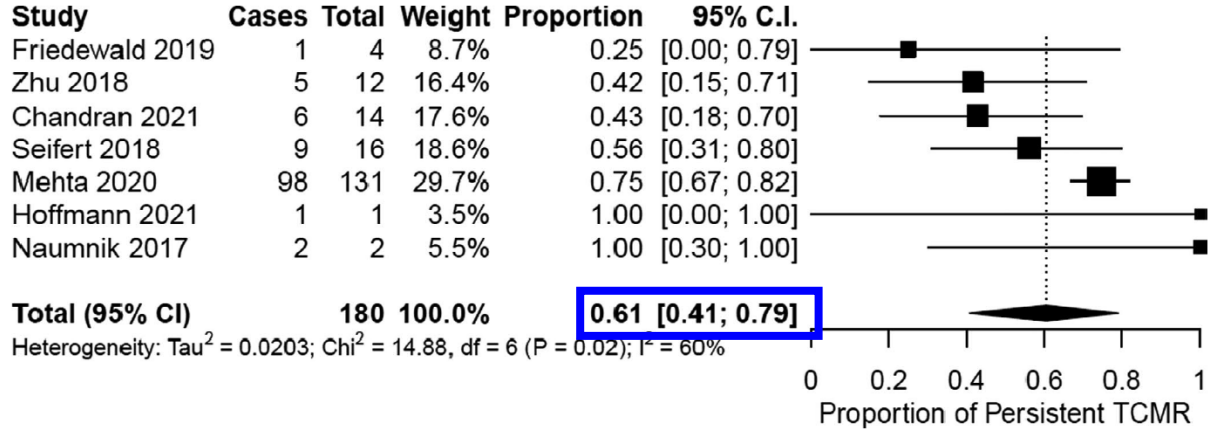
Persistent ≥ Banff Borderline after Treatment of Clinical ≥ Banff Borderline



Persistent ≥ Banff Borderline after Treatment of Subclinical ≥ Banff Borderline



Persistent ≥ Banff Borderline after Untreated ≥ Banff Borderline



Ho et al, AJT (2022) 22:772-785

2nd TCMR (adjusted for DGF, 1st TCMR and ABMR) predicts Graft Loss

(time dependent covariate analysis)

Death-Censored Graft Loss n=74 events	HR	95% CI	p value
Model 3			
DGF	2.19	(1.17, 4.07)	0.014
First TCMR	1.81	(0.91, 3.60)	0.090
Second TCMR	**2.98**	**(1.55, 5.75)**	**0.001**
ABMR	5.18	(2.73, 9.85)	<0.001

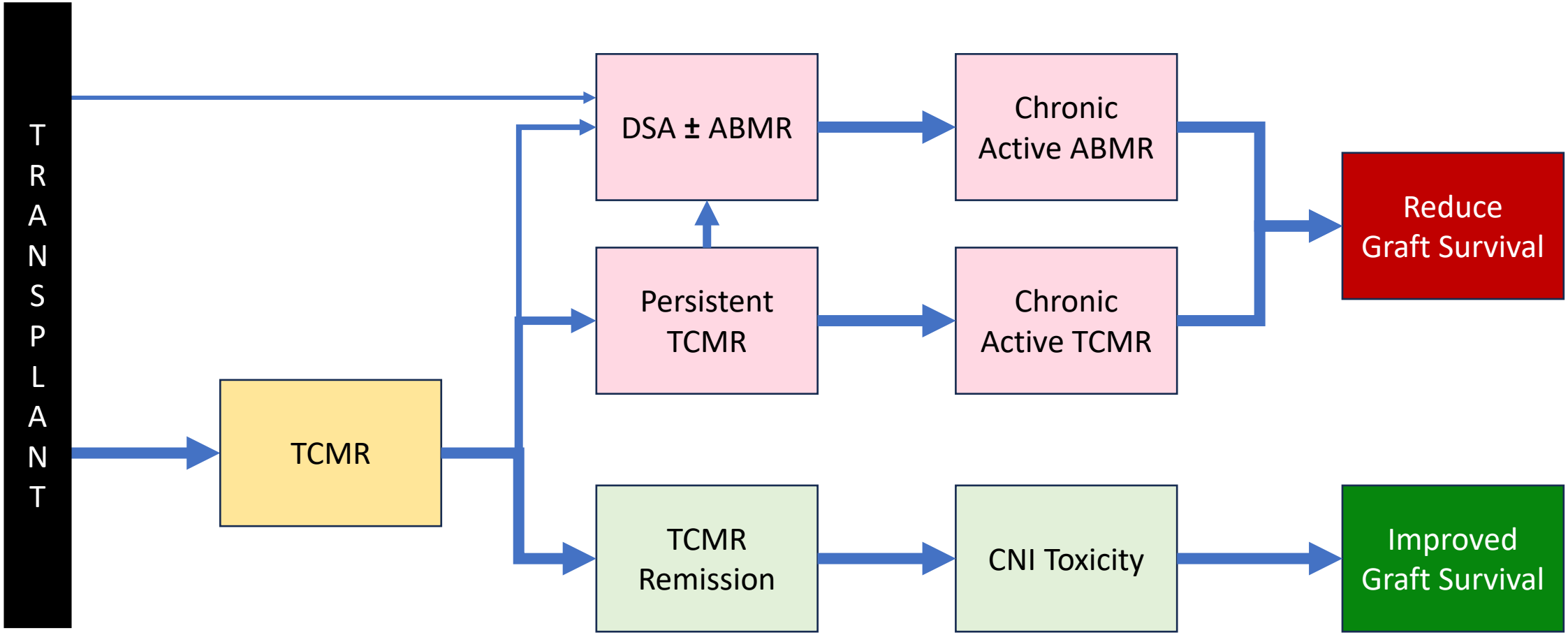
All-Cause Graft Loss n=187 events	HR	95% CI	p value
Model 3			
DGF	2.00	(1.38, 2.92)	<0.001
First TCMR	1.18	(0.77, 1.80)	0.449
Second TCMR	**2.30**	**(1.39, 3.79)**	**0.001**
ABMR	2.69	(1.59, 4.54)	<0.001

*** Models adjusted for baseline covariates**

Rampersad et al, AJT (2022) 22:761-771

Unmet Need

Novel Therapies to Prevent and Treat TCMR & ABMR



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Ian Gibson

Center for Healthcare Innovation

Robert Balshaw

FDA | University of Manitoba

NIH National Institute of Allergy and Infectious Diseases

CIHR IRSC

AST American Society of Transplantation | ASHI American Society for Histocompatibility & Immunogenetics

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PANEL DISCUSSION/AUDIENCE Q&A

SESSION 3: NON-INFERIORITY TRIALS WHAT HAVE WE LEARNED?

Considerations in determining a non-inferiority margin

Karen Higgins, ScD

Division of Biometrics III, Office of Biostatistics

Disclaimer

This presentation is not intended to convey official US FDA policy or views.

Disclosure

I do not have any financial interest to disclose.

Outline

- Superiority trials
- Non-inferiority trials
- Setting the NI margin
- Conclusions

Superiority trials

- Objective: show a new treatment effective by showing it is better than a control
- Control: placebo, active drug, lower dose of test drug

Superiority study design examples

- Placebo controlled *superiority* trials (Add-on trials)
  - Randomize subjects to new drug or placebo
    - all receive standard background regimen
  - Example:

    MMF + CsA + steroids superior to **Placebo** + CsA + steroids

- Active controlled *superiority* trials
  - Randomize subjects to new drug or active drug
    - all receive standard background regimen
  - Example:

    Cyclosporine + steroids superior to **Azathioprine** + steroids

CsA (cyclosporine); MMF (Mycophenolate mofetil; Cellcept)

Important considerations with superiority trials

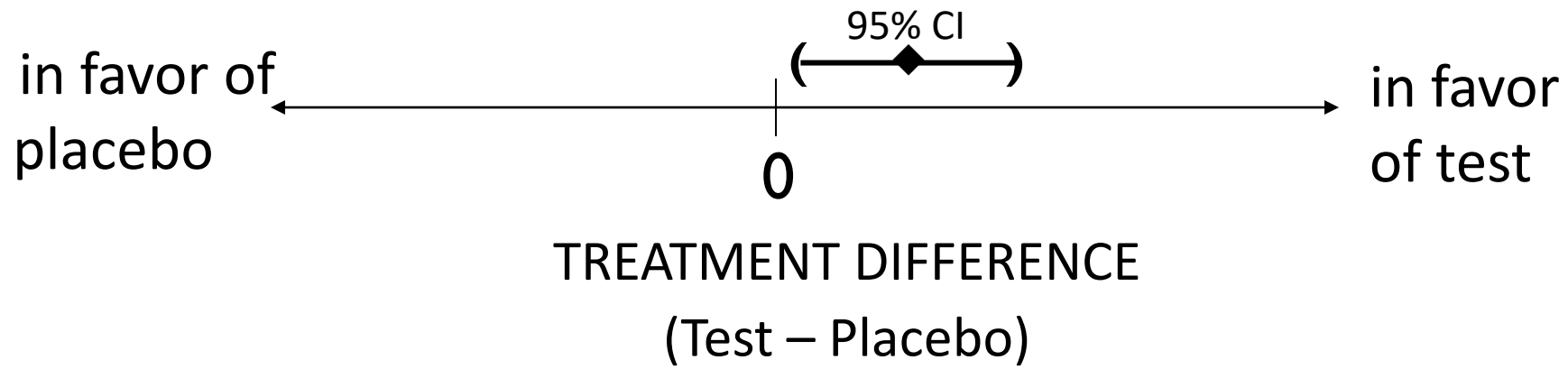
- Make sure statistically significant results point to efficacy of new product rather than merely lack of safety concern
  - For example: Superiority of rate of new onset diabetes after transplant (NODAT) of a new drug compared to tacrolimus would not be evidence of efficacy
- Superiority trials may not be ethical/feasible

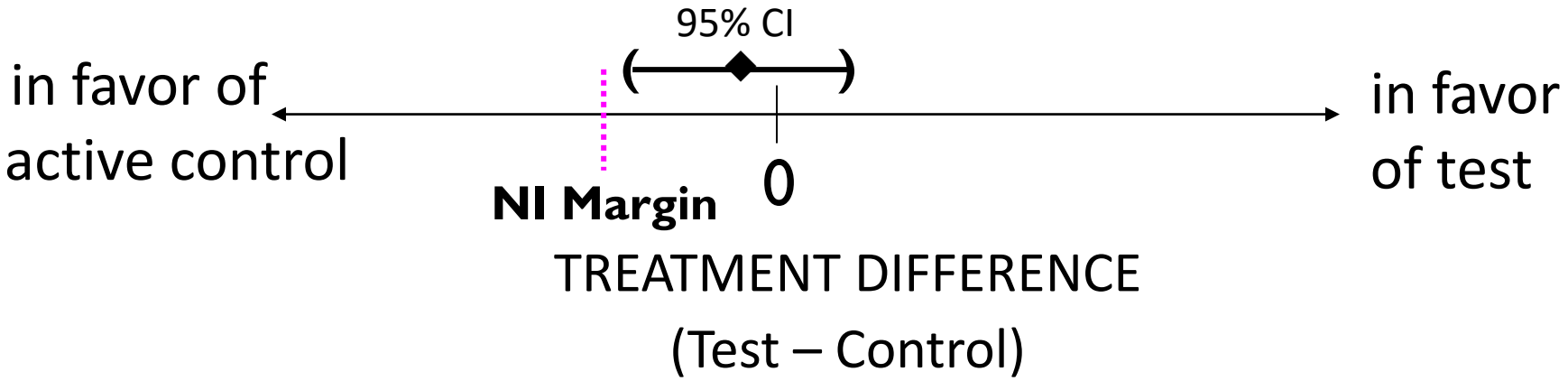
  If new drug is meant to replace an existing effective product:
  - use of placebo might not be ethical
  - might not expect the new drug to be superior to the existing effective product
  - even if expect superior to existing effective product, small treatment effect might lead to very large sample size

Non-inferiority (NI) trials

- Objective: show a new treatment effective by showing it is close enough to an active control
- Ok to be better than active control
- Not OK to be too much worse than active control

Superiority vs. non-inferiority





Non-inferiority trial example

- Nulojix (belatacept)
  - Subjects randomized to Nulojix or CsA
  - Background regimen: Basiliximab induction, MMF, CS
  - Biopsy-proven Acute Rejection at 1 year

	Nulojix (n=226)	CsA (n=221)	95% CI (C-N)
BPAR 1 year	21.7%	16.7%	(**-13.2%,** 3.3%)

  - With a NI margin of 15% this trial would conclude non-inferiority of Nulojix to CsA

CsA (cyclosporine); MMF (Mycophenolate mofetil; Cellcept); CS (corticosteroids)

Archdeacon P, Dixon C, Belen O, Albrecht R, Meyer J. Summary of the US FDA Approval of Belatacept. American Journal of Transplantation 2012;12:554–562.

NI margin terminology

- **M1** is the estimate of how much better the active control is than placebo
  - Based on historical relevant data (i.e., similar trials as NI trial)
  - Should be a conservative estimate
- **M2** is the maximum amount of the treatment effect we would be willing to lose,
  - Based on clinical judgment
  - Includes considering severity of disease and benefits of new therapy
- **M** is the margin used in a trial (the minimum of M1 and M2)

M1: Historical data

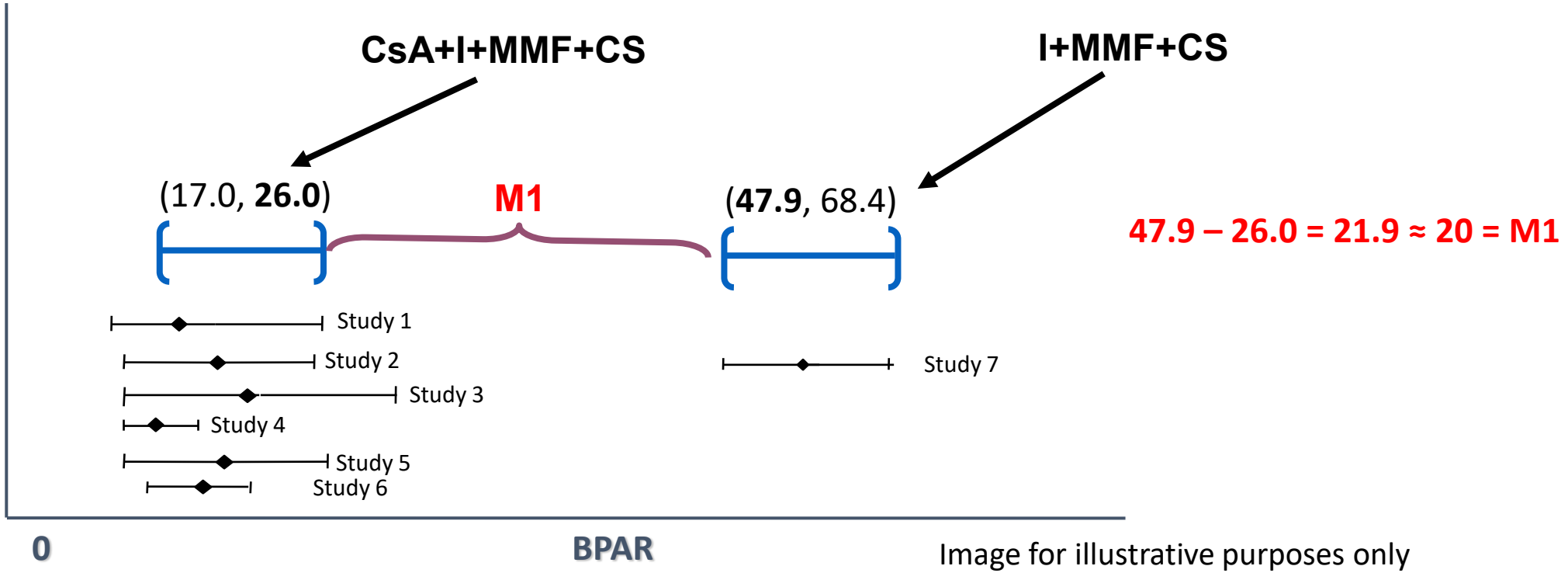
- Determine M1 from multiple studies comparing the effect of the active control to placebo
- Alternative method, determine M1 by comparing two comparable sources of data, one of the active control and one of placebo
- Important! In both cases, need similarity in
  - design, endpoints, timepoint, patient population, background therapy as current NI trial
- "The validity of any conclusion from the NI study depends on the choice of M1 and its relevance to the current NI study." [FDA NI guidance]

M1 determination example

- For Belatacept NI trial:
  - Subjects randomized to Nulojix or CsA with a background regimen of Basiliximab (B) induction (I), MMF (M), CS
- Ideally, NI margin justification would come from similarly designed studies of CsA vs. placebo with same background regimen
  - **CsA** + B + M + CS vs. **Placebo** + B + M + CS
  - None available
- NI margin from 6 studies of CsA + I + M + CS and compared to one study of I+M+CS

CsA (cyclosporine); MMF (Mycophenolate mofetil; Cellcept); CS (corticosteroids)

Example: Belatacept – M1



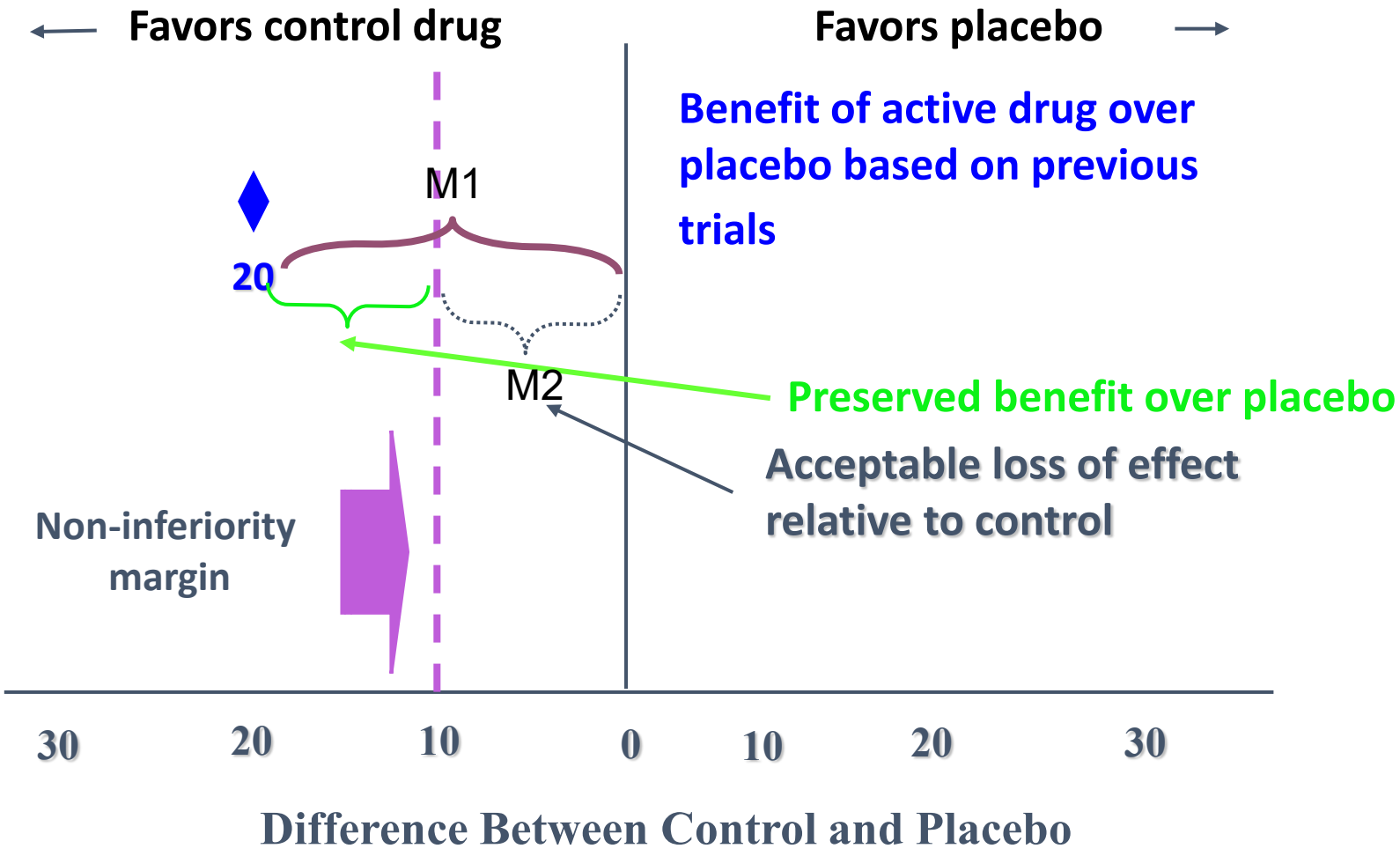
47.9 – 26.0 = 21.9 ≈ 20 = M1

Image for illustrative purposes only

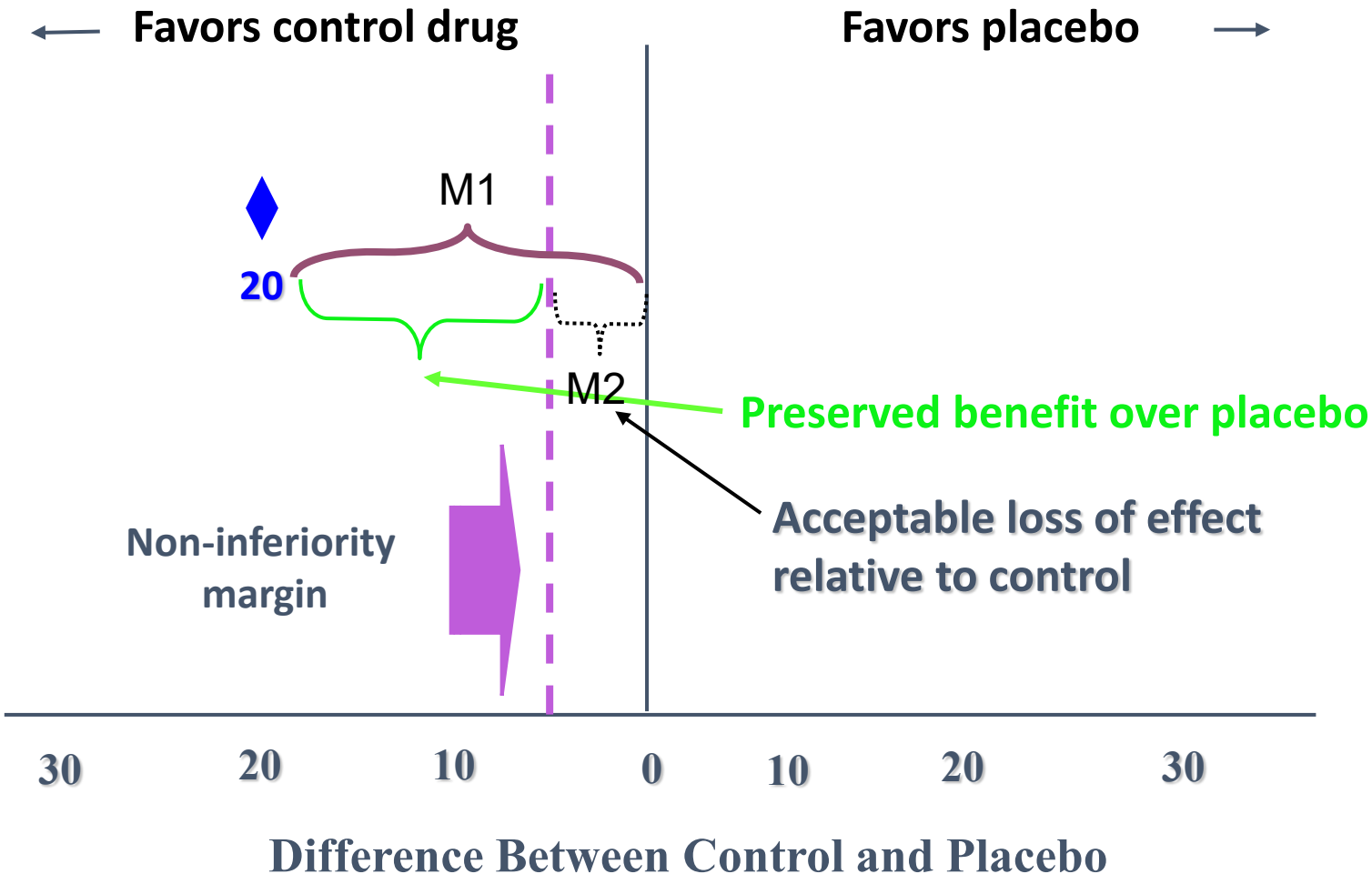
CsA (cyclosporine); MMF (Mycophenolate mofetil; Cellcept); I (Induction), CS (corticosteroids)

Cardiovascular and Renal Drugs Advisory Committee Meeting, March 1, 2010, Briefing materials

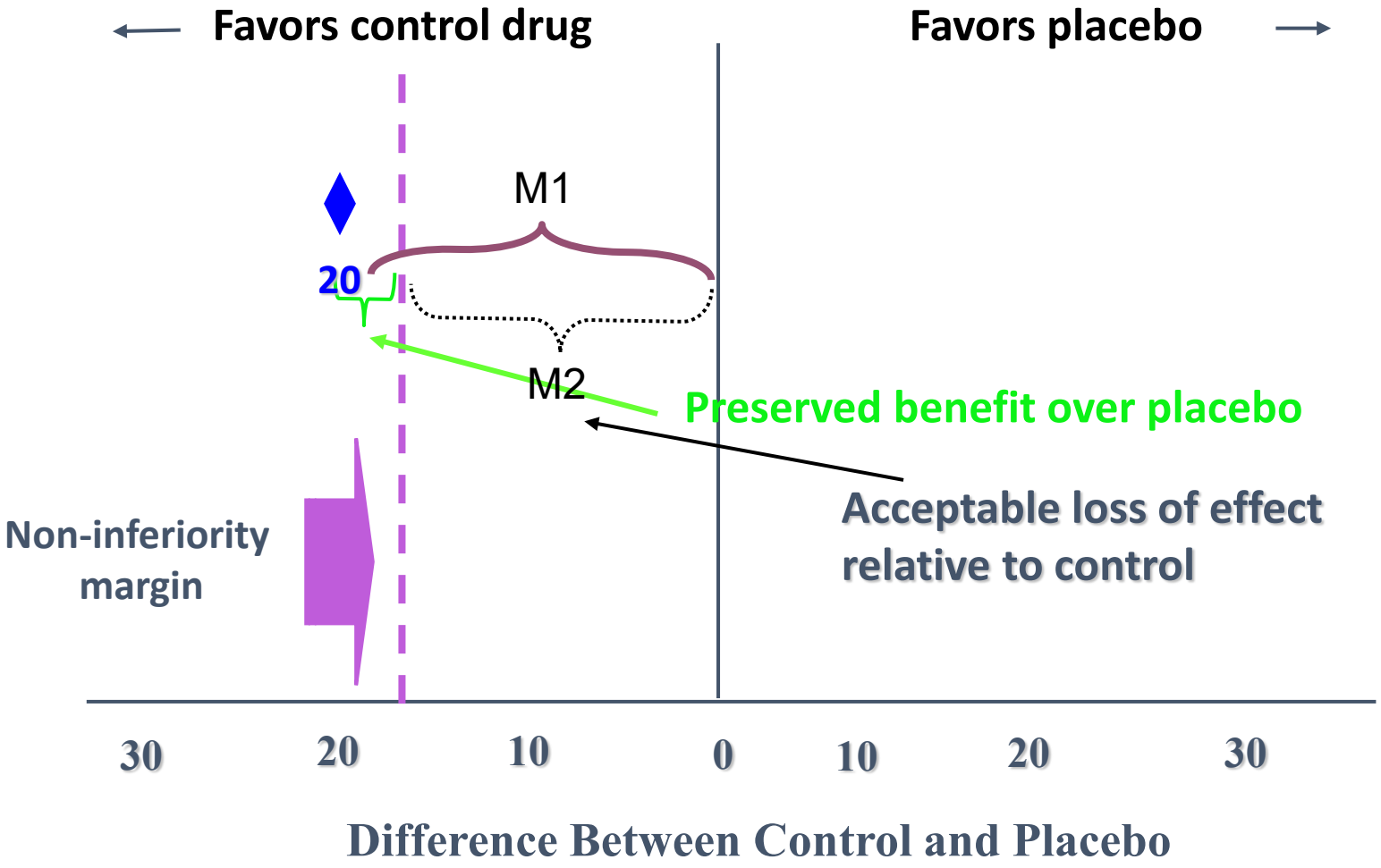
M2: Clinically acceptable limit



M2: Clinically acceptable limit

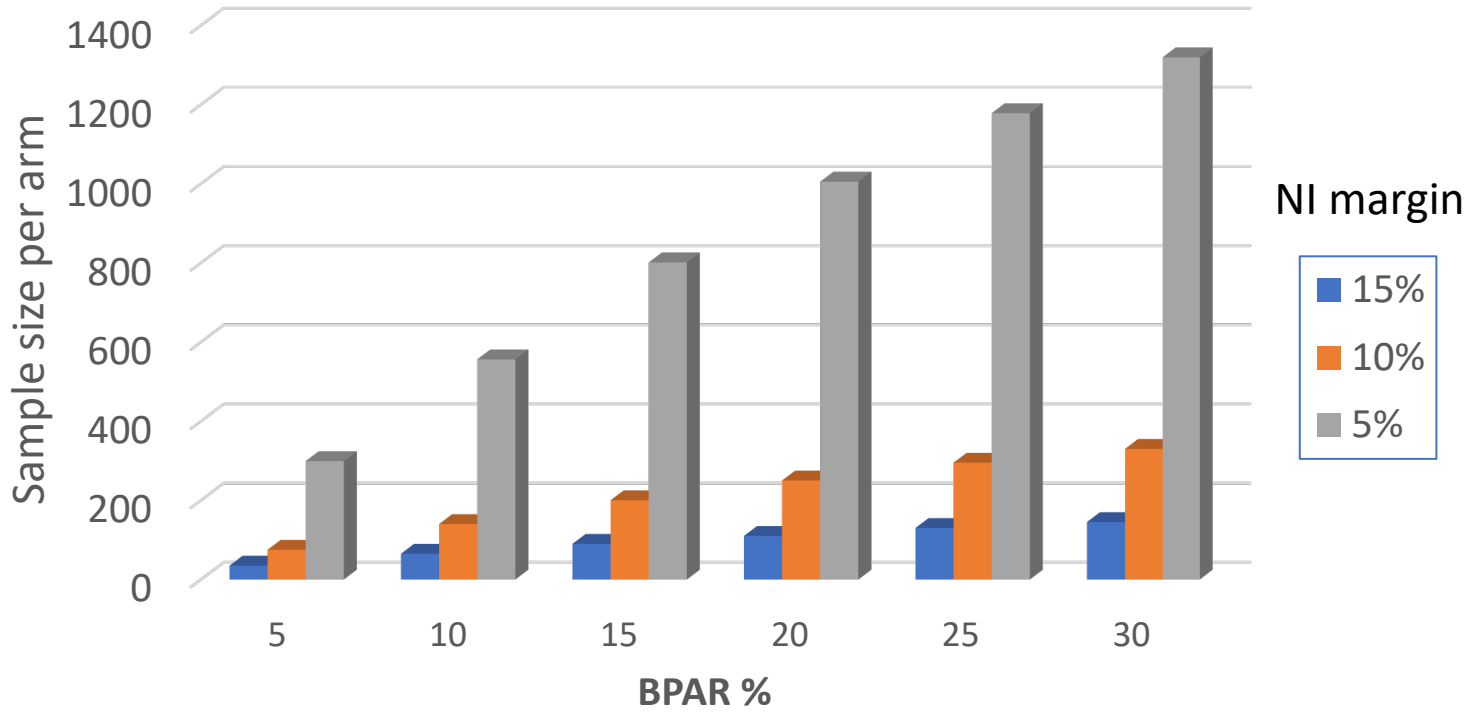


M2: Clinically acceptable limit



M2 impact on sample size

- Note that the smaller the M2 the larger the sample size
- 80% power, 5% 2-sided type I error, test=control



Example: Belatacept – M2

- M2 = M1 of 20% demonstrates an effect over placebo
- Should the margin be smaller than 20%?
  - Considerations: severity of outcome and benefits of new treatment.
  - An M2 of 15% would preserve at least 1/4 of the CsA estimated treatment effect (of 20%)

	Nulojix (n=226)	CsA (n=221)	95% CI (C-N)
BPAR 1 year	21.7%	16.7%	(**-13.2**%, 3.3%)

Conclusions

- NI trials play an important role in assessing efficacy when superiority trials are not feasible/ethical
- NI trials require a valid NI margin justification
  - Requires estimate of treatment effect of active control, M1, based on comparable data
    - Not always possible to conduct NI trial, if data is not available
  - Requires discussion of limit of loss of effect, M2
- Conclusion of NI doesn't mean the new drug is worse than the control
  - The NI margin is the limit of negative effect that we exclude
    - Like we exclude zero in superiority trials

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FDA
U.S. FOOD & DRUG
ADMINISTRATION

Secondary Endpoints in Noninferiority Trials

Primary Endpoints

- Combinatorial endpoint
  - Patient survival
  - Graft survival
  - Lost to followup
  - Biopsy proven rejection
  - Renal function
    - eGFR, eGFR slope
- Co Primary endpoints have been used

Secondary Endpoints in Noninferiority Trials: Considerations

- Importance in post approval marketing
- Potential for future endpoints

- Examples
  - DSA
  - Renal function (eGFR, eGFR slope)
  - Longer term outcome prediction tools (ibox)
  - Cardiovascular risk/cardiovascular events

  - Biopsy proven rejection
  - Histologic endpoints
    - Banff
    - Molecular
      - Basic/simple approaches (molecular microscope)
      - Advanced
        - Single cell genomics (scRNAseq/TCRseq)
          - Expanded CD8 clones
        - Multiomics approaches

DSA as an Endpoint

- Significance is its effect on graft survival

- Problem: varying intensity of effects on graft survival
  - DSA that develops in absence of clinical rejection (eg, found on yearly screen(
  - DSA as component of AMR or late mixed acute rejection
  - DSA at low levels with normal biopsy
  - DSA that are treated effectively may have reduced effects on graft survival

- In late mixed rejections, DSA effect has not been separated from effect of acute cellular rejection
- Controversy exists over DSA quantitation using SAB assays

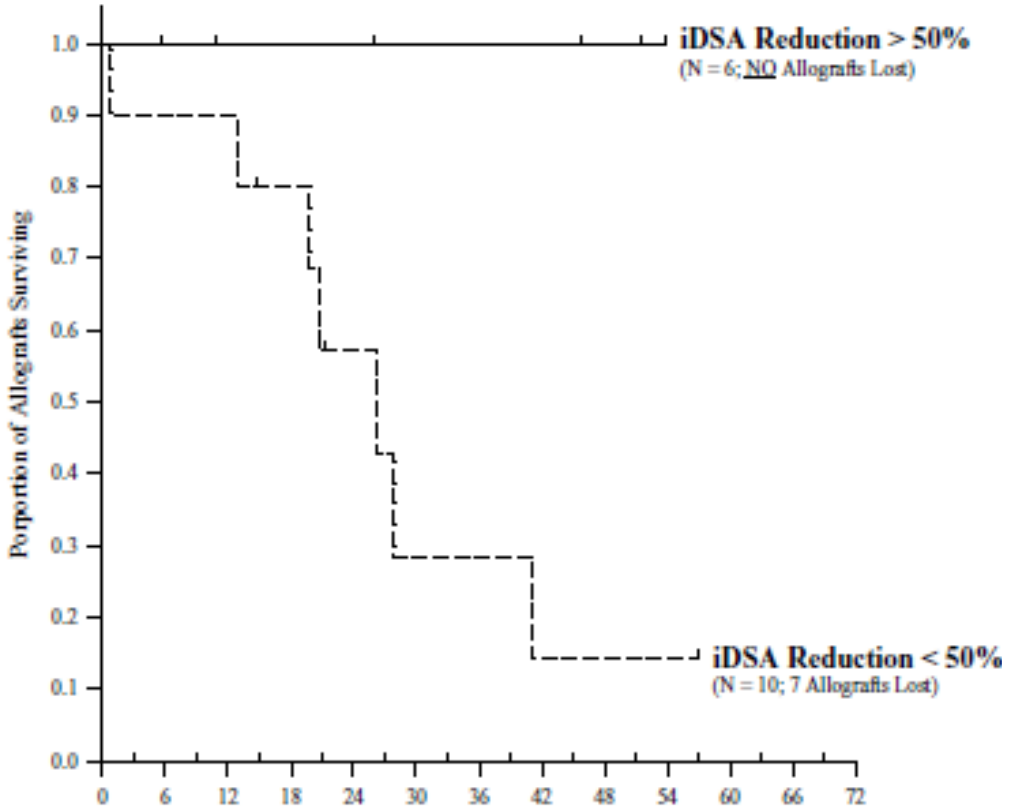
American Journal of Transplantation 2009; 9: 1063–1071
Wiley Periodicals Inc.

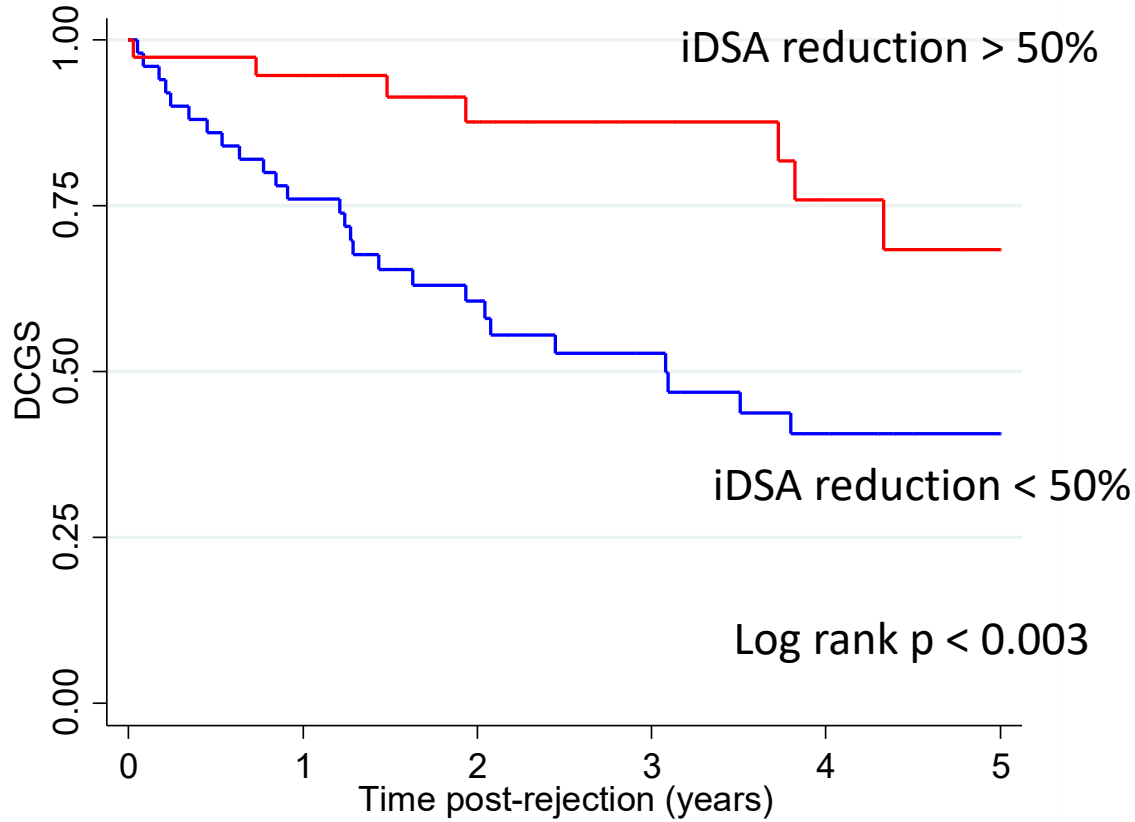
doi: 10.1111/j.1600-6143.2009.02577.x

Reducing De Novo Donor-Specific Antibody Levels during Acute Rejection Diminishes Renal Allograft Loss

M. J. Everly[a,*], J. J. Everly[a], L. J. Arend[c], P. Brailey[b], B. Susskind[b], A. Govil[d], A. Rike[a], P. Roy-Chaudhury[d], G. Mogilishetty[d], R. R. Alloway[d], A. Tevar[a] and E. S. Woodle[a,*]

Am J Transplant 2009; 9: 1063–1071.





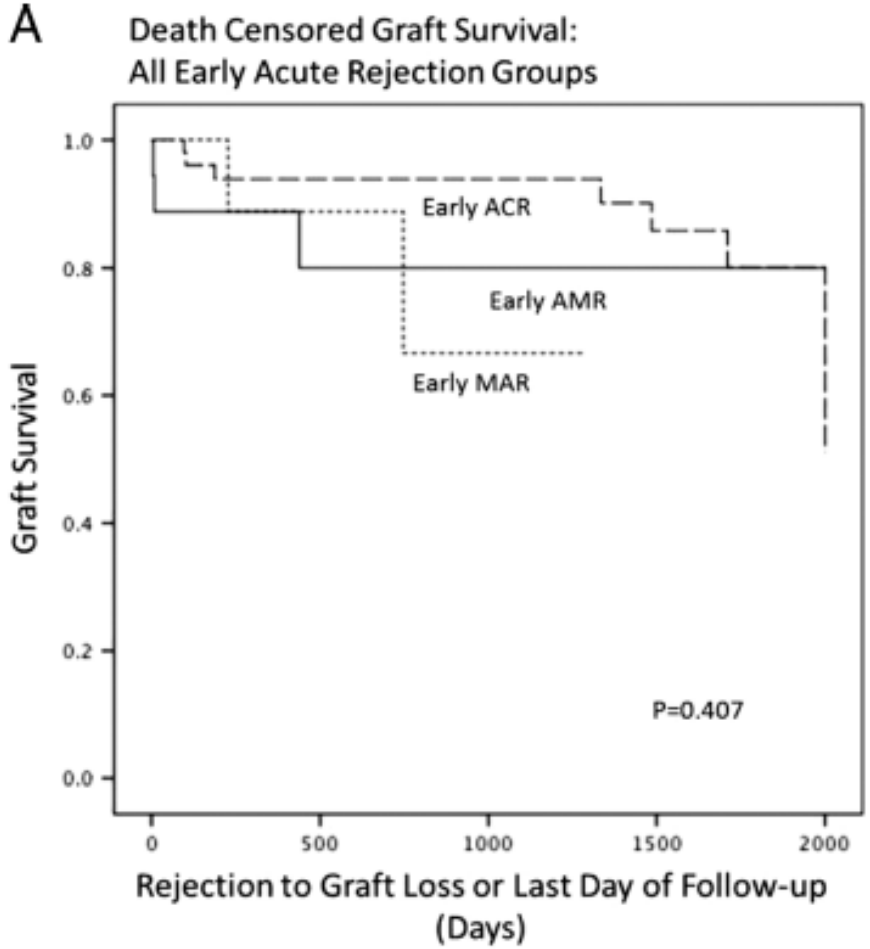
Number at risk						
iDSA reduction < 50%	50	38	25	18	12	8
iDSA reduction > 50%	39	34	21	16	10	8

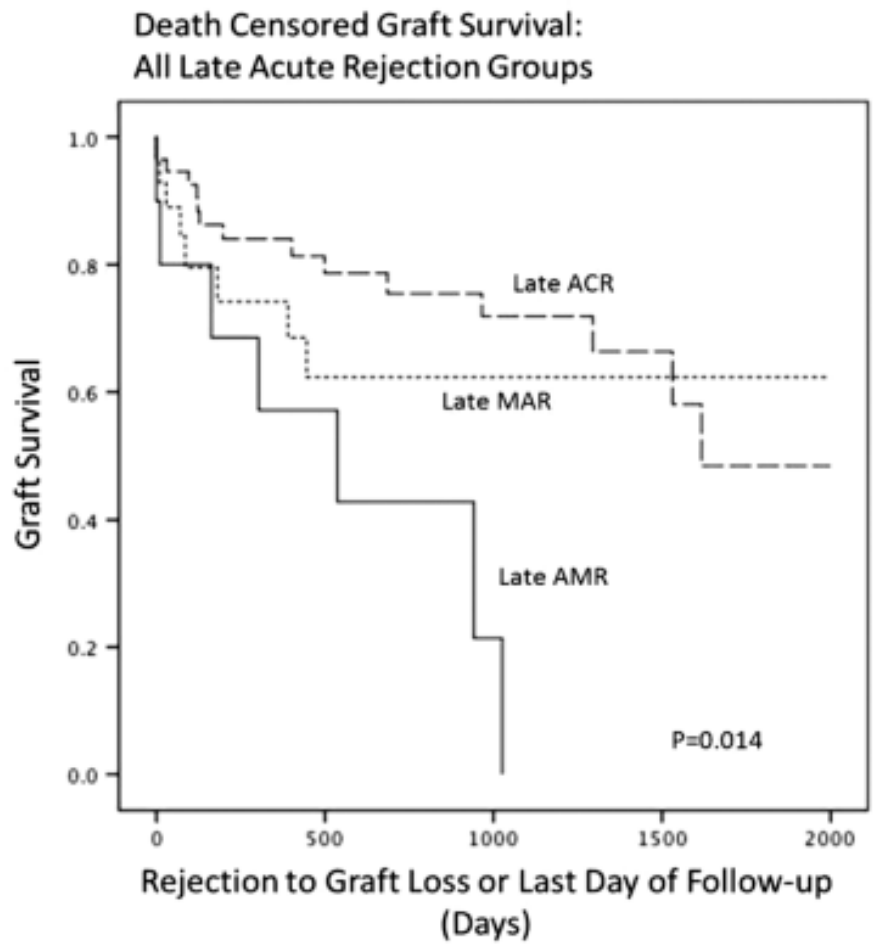
Rejection As an Endpoint: Problems

- Rejections under differing immunosuppression have different implications for endpoints
- Rejection under belatacept is more frequent and more severe by Banff criteria than under CNI blockade, but overall graft survival is better
- Graft function after rejection under tacrolimus is worse than rejection occurring under belatacept

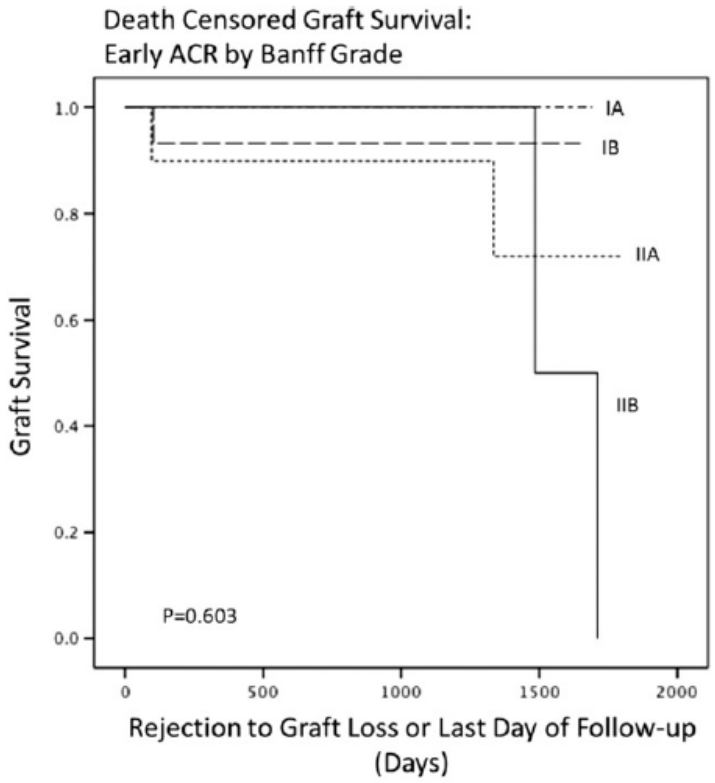
- Rejection treatments (steroids/ATG) are 70 years old and are associated with very poor graft survival for all except Banff 1a rejections
- Requiring rejection to be treated the same under tacrolimus and costimulation blockade (belatacept, anti-CD40/CD40L blockade) is not supported by currently available data

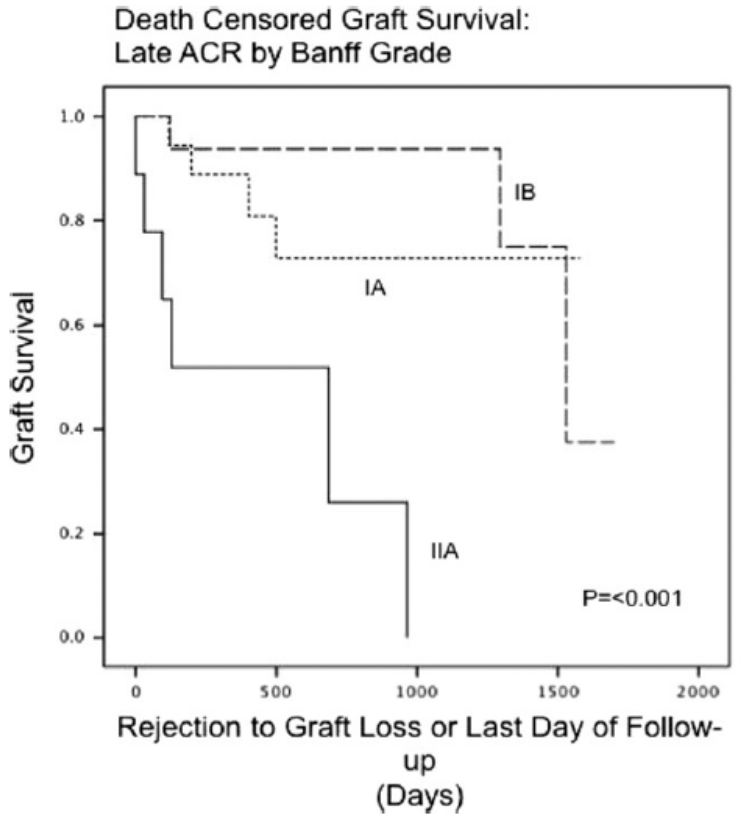
A


Death Censored Graft Survival:
All Early Acute Rejection Groups
Graft Survival
1.0
0.8
0.6
0.4
0.2
0.0
Early ACR
Early AMR
Early MAR
P=0.407
0
500
1000
1500
2000
Rejection to Graft Loss or Last Day of Follow-up
(Days)


Death Censored Graft Survival:
All Late Acute Rejection Groups
Graft Survival
1.0
0.8
0.6
0.4
0.2
0.0
Late ACR
Late MAR
Late AMR
P=0.014
0
500
1000
1500
2000
Rejection to Graft Loss or Last Day of Follow-up
(Days)

Lets Not Forget About ACR





- Initial rejection events can pre-dispose to subsequent rejection and graft loss.
  - >75% of patients with a severe ACR (≥Banff 2A) under CNI lose their grafts within 3 years

JCI The Journal of Clinical Investigation

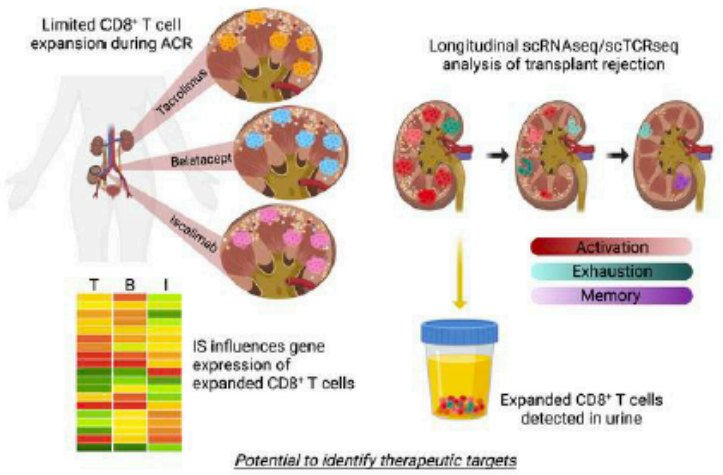
Single cell transcriptomic analysis of renal allograft rejection reveals insights into intragraft TCR clonality

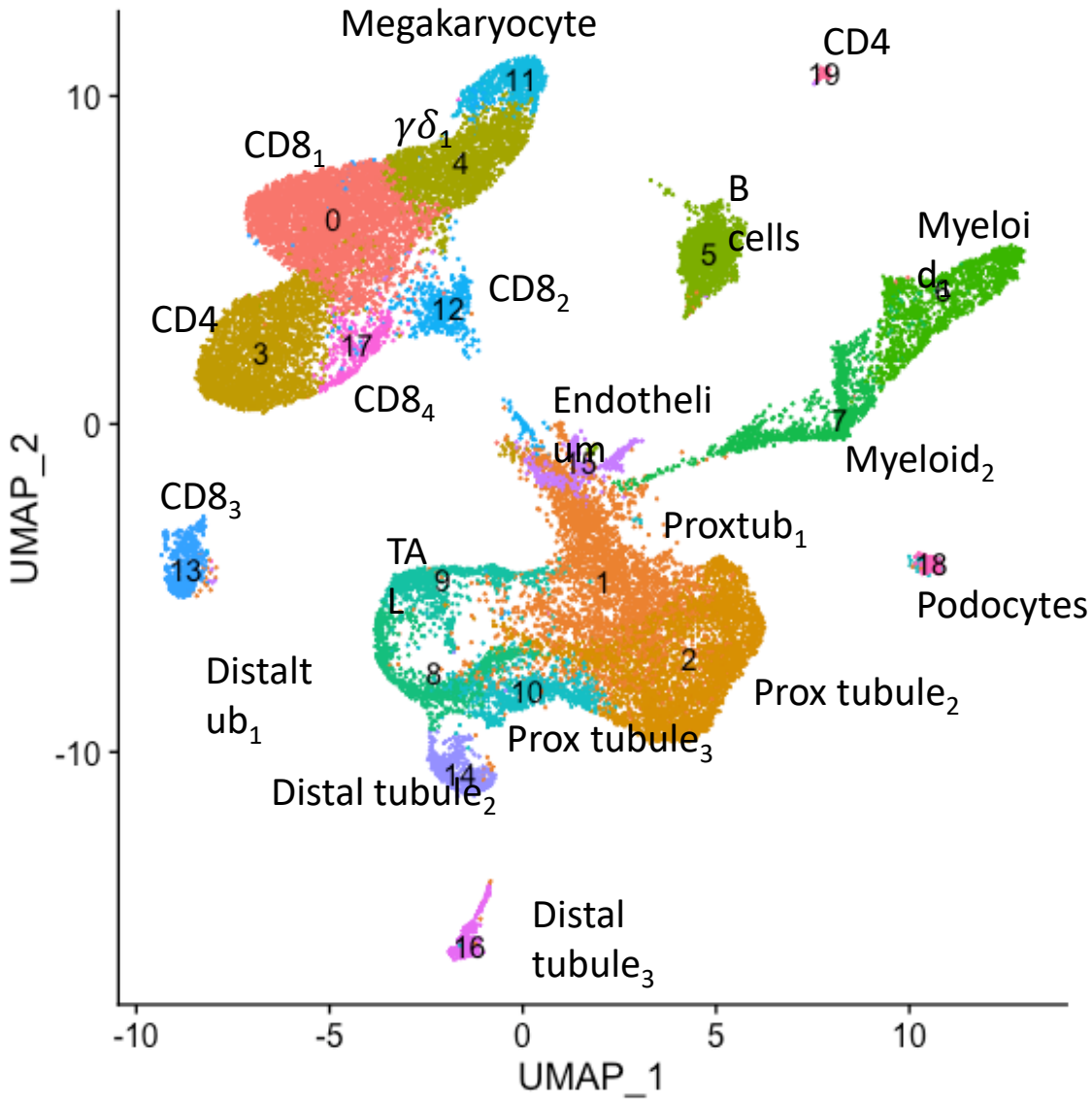
Tiffany Shi, … , E. Steve Woodle, David A. Hildeman

J Clin Invest. 2023. https://doi.org/10.1172/JCI170191.

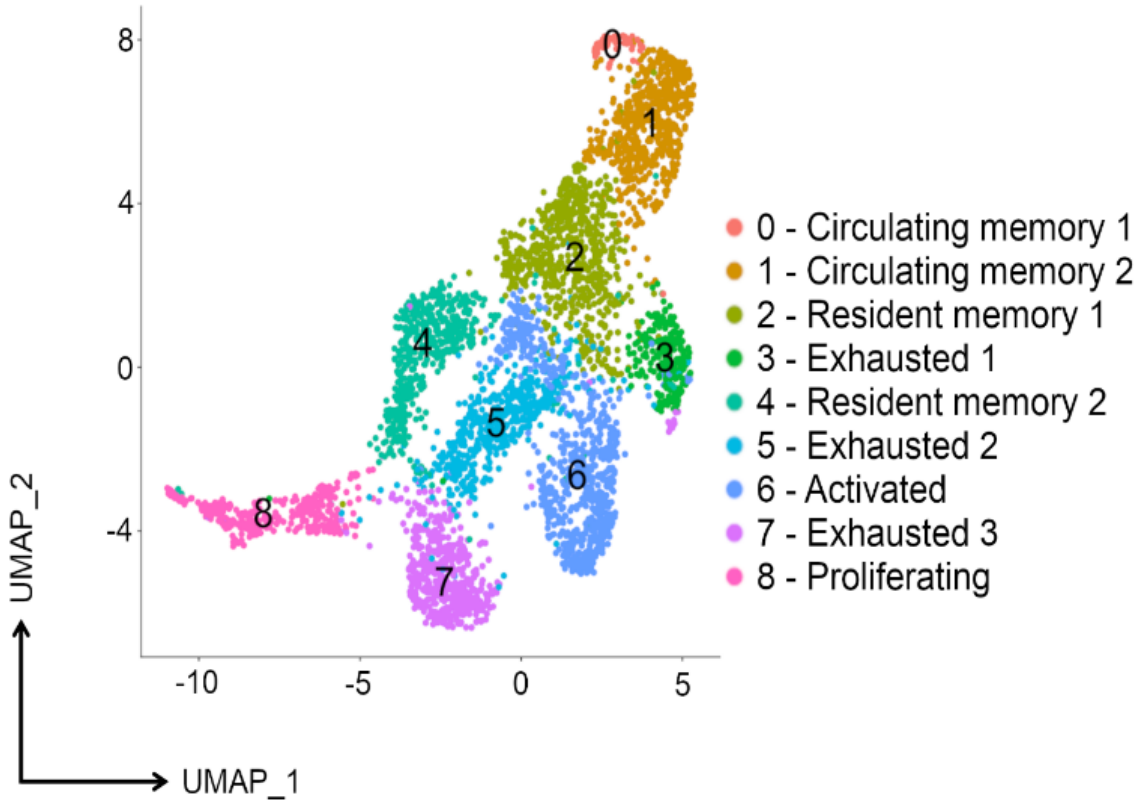
Research In-Press Preview Immunology Transplantation

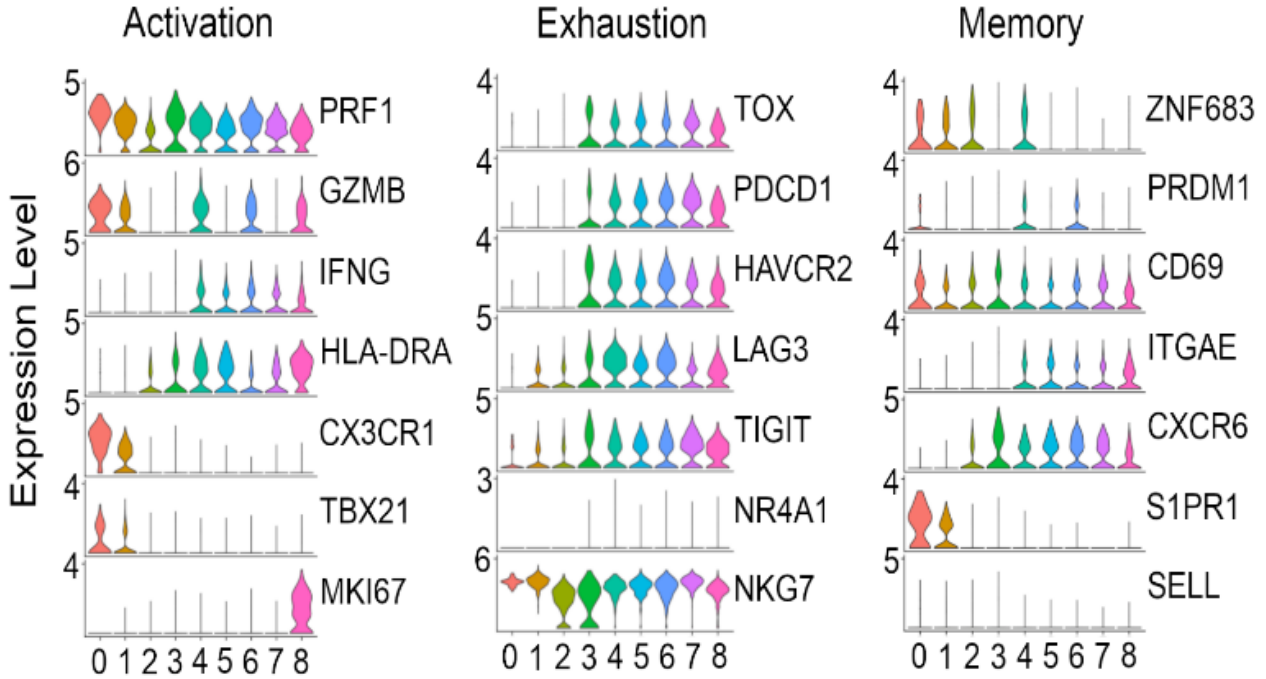
Graphical abstract





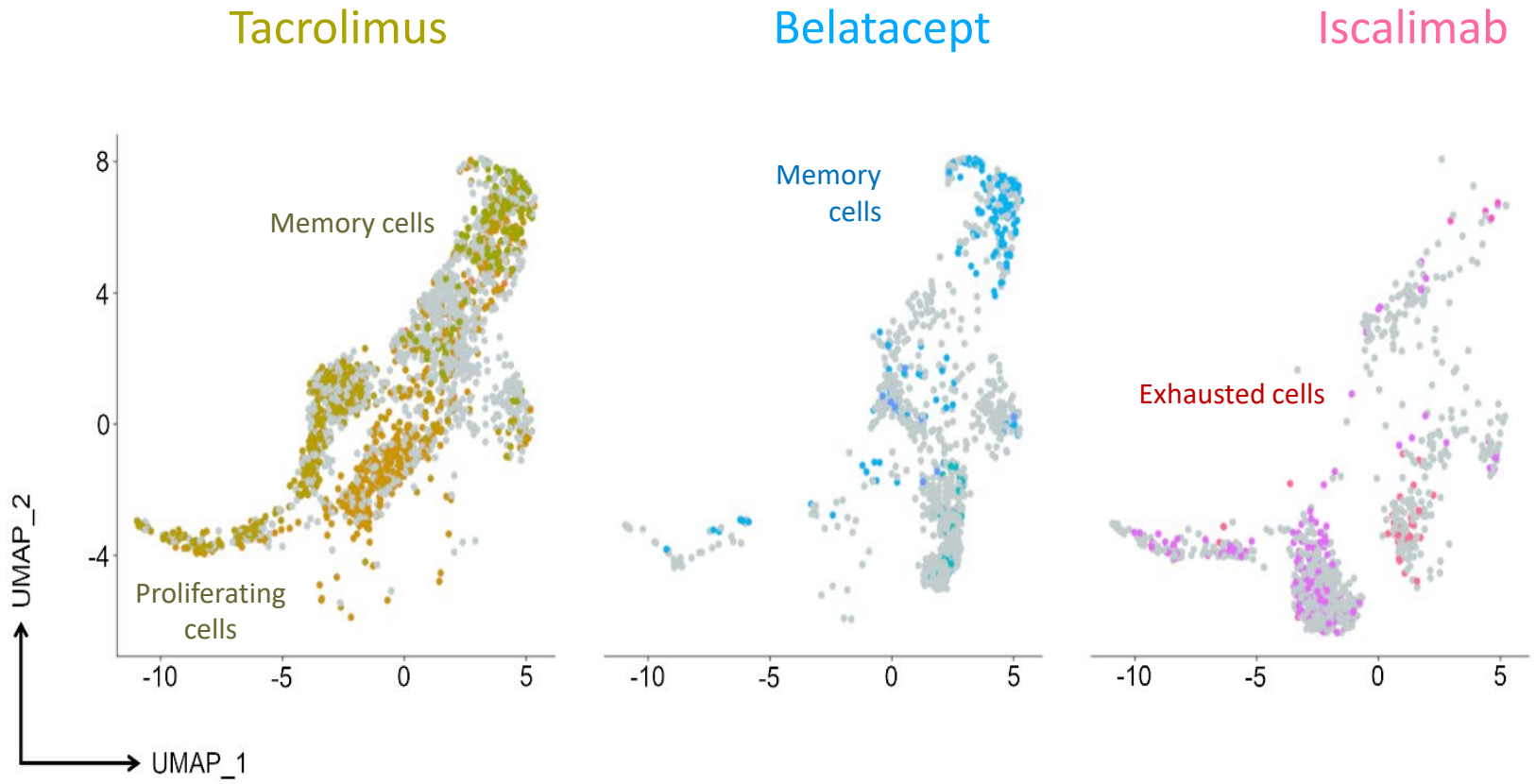
Heterogeneity of graft-resident CD8⁺ T cells





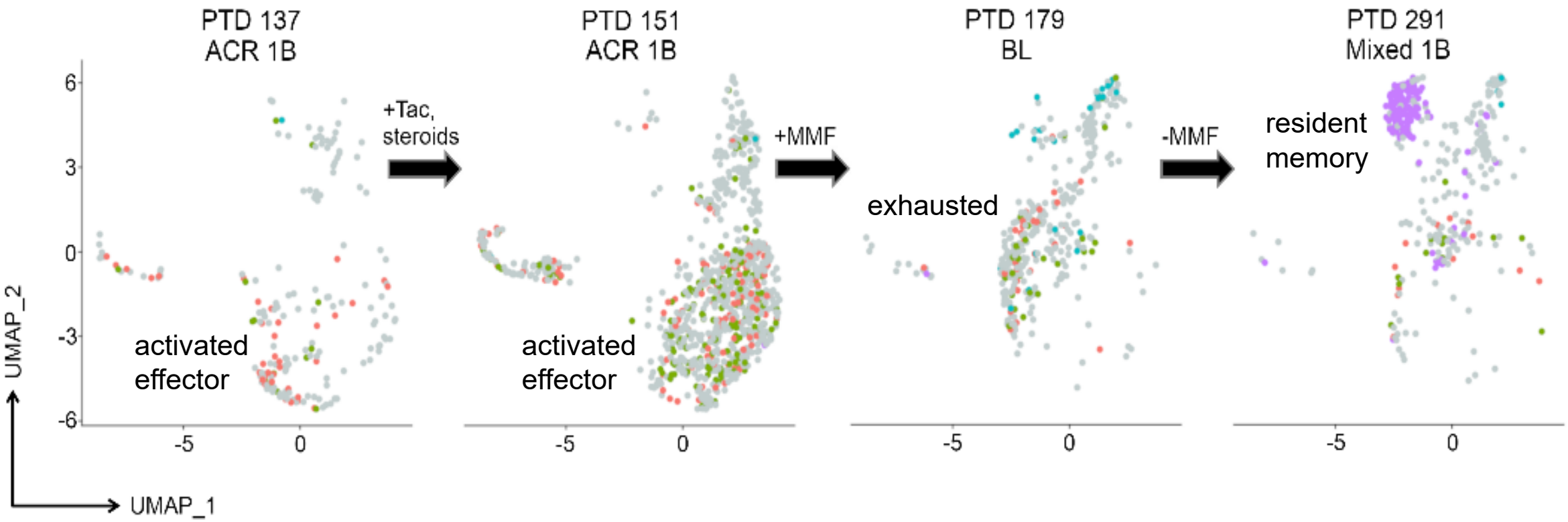
Shi *et al.*, J Clin Invest 2023

$CD8_{EXP}$ adopt distinct phenotypes based on IS



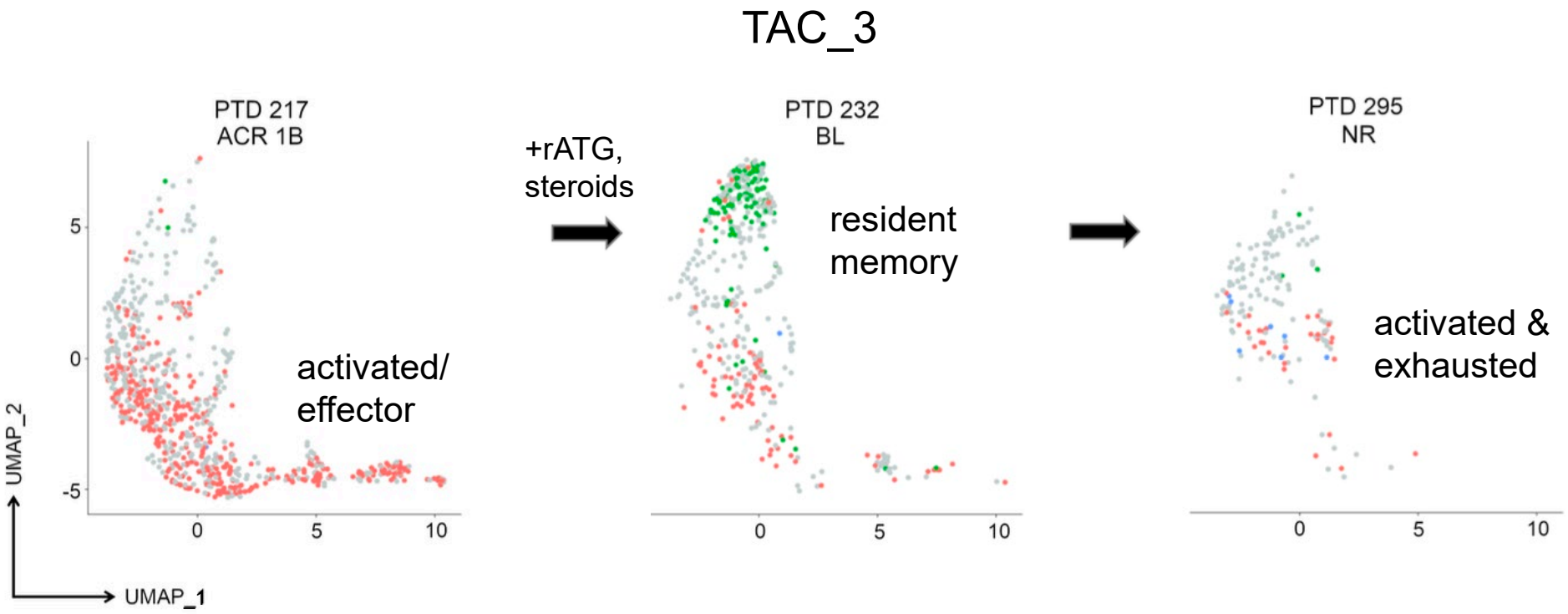
Shi *et al.*, J Clin Invest 2023,

$CD8_{EXP}$ display phenotypic plasticity



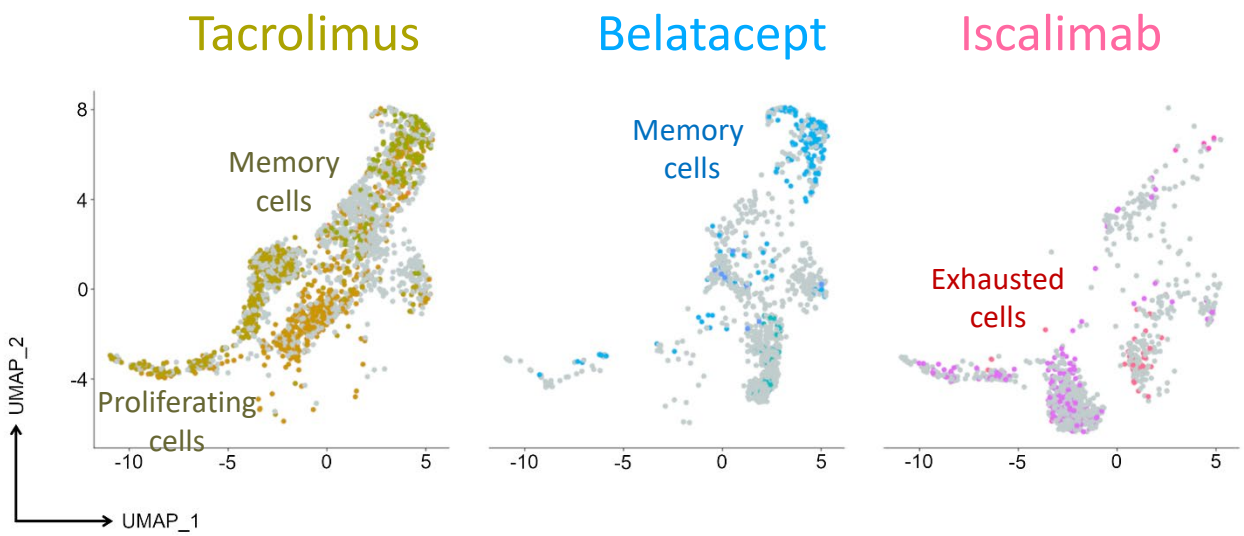
Shi *et al.*, J Clin Invest 2023

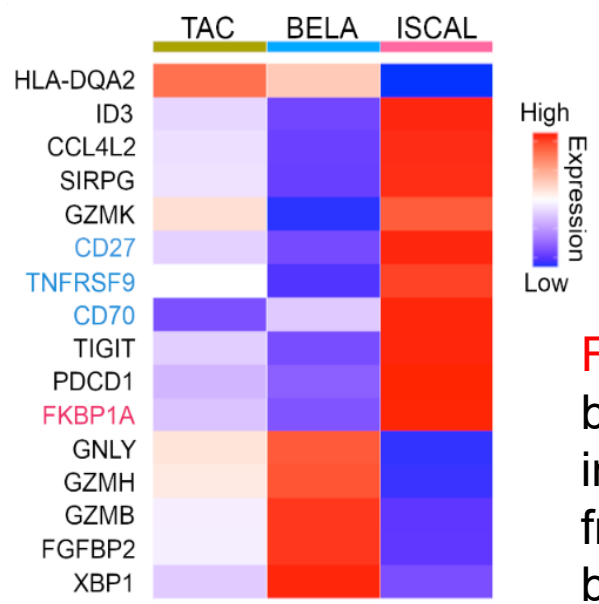
$CD8_{EXP}$ persist despite histologic resolution



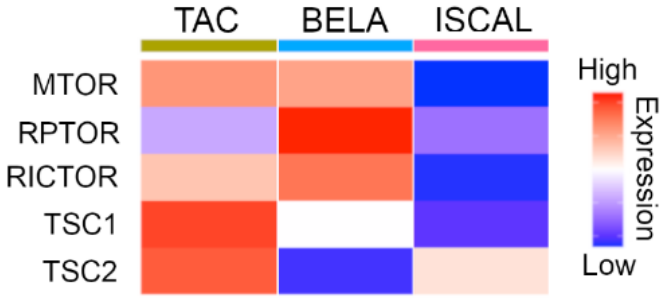
Shi *et al.*, J Clin Invest 2023

$CD8_{EXP}$ adopt distinct phenotypes based on IS





FKBP1A (tacrolimus binding protein) is increased in $CD8_{EXP}$ from iscal, but not bela or tac

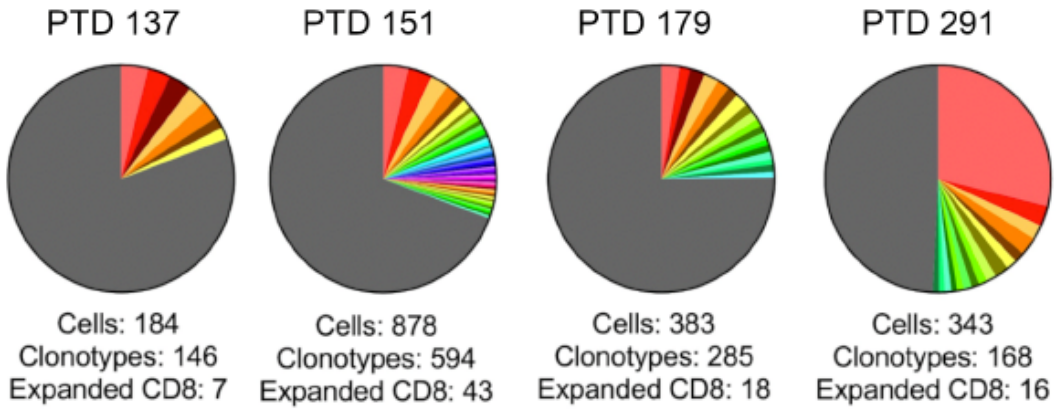


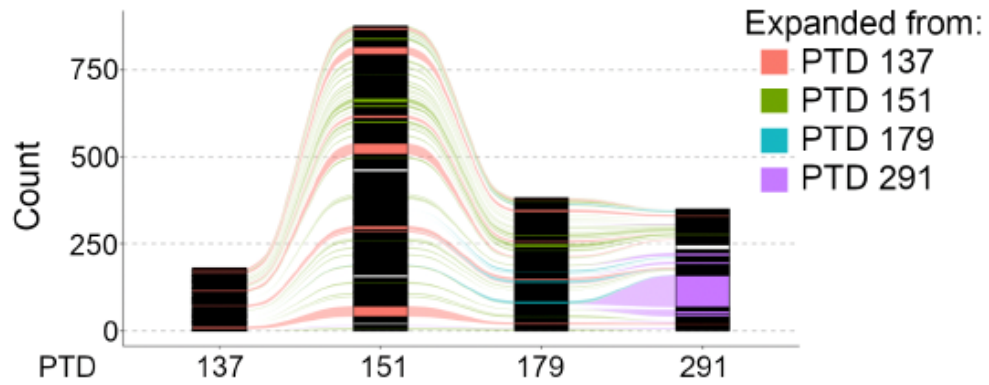
- Bela-refractory rejection associated with a dysregulated mTOR pathway
- Consistent with our prior work showing that bela-refractory rejection is responsive to everolimus, but not tacrolimus Castro-Rojas *et al.*, Transplantation 2020

Shi *et al.*, J Clin Invest 2023

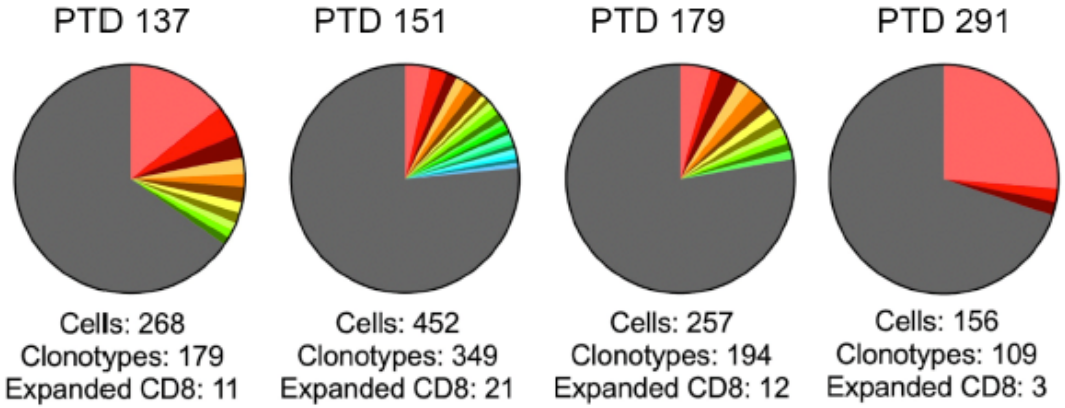
$CD8_{EXP}$ overlap in the biopsy & urine

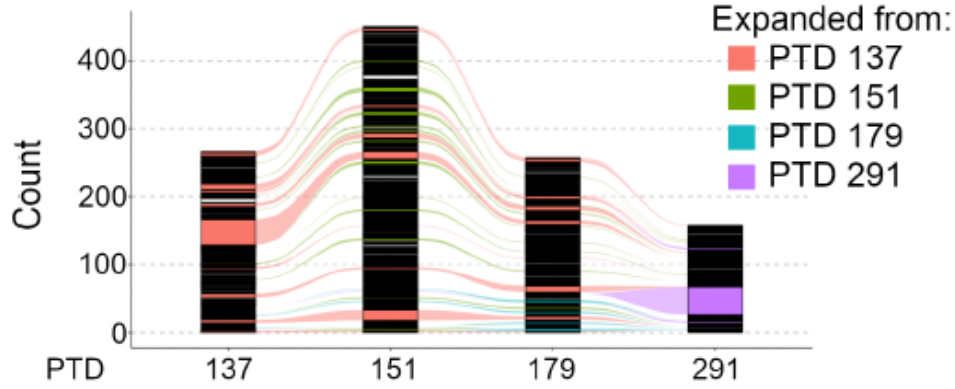
Biopsy





Urine





Shi *et al.*, J Clin Invest 2023, *in press*

Conclusions: Endpoints

- Primary endpoints with biopsy proven rejection as an endpoint have to be reconsidered
- New endpoints for AMR and ACR rejection therapy are needed
- Rejection treatment may significantly mitigate deleterious effects on graft survival
- New endpoints are needed to assess adequacy of rejection treatment
- Longer term followup of graft function in patients with rejection is needed in registration trials and assessed independently
- DSA as a secondary endpoint has some limitations, but has not as yet been adequately defined
  - Clinical setting in which DSA is first detected is a major consideration that has not yet been fully evaluated

Conclusions: Rejection Biology

- Many rejections have both cellular and antibody components
- We have hypothesized that to improve rejection outcomes both ACR and AMR must be effectively and completely treated
- Alloreactive CD8 clones that drive rejection differ markedly based on underlying maintenance immunosuppression
- ACR is mediated by an astonishingly restricted number of TCR clones
- TCR clonal populations change/adapt over time, and individual clones may disappear, or even expand and new clones may appear over time
- TCR clones exhibit a remarkable capacity to alter phenotype and gene expression with reversibility between exhaustion and activation
- In many rejections, alloreactive CD8 clones persist over time despite differing therapies
- Alloreactive CD8 clones persist in the allograft despite histologic rejection resolution
- Failure to eliminate alloreactive CD8 clones may underlie ongoing injury and allograft loss

Conclusions: Points for FDA to consider

- Requiring standard rejection treatment across all limbs of registration trials is not supported by recent data

- Personalized rejection therapy approaches have arrived, and need to be accommodated in *ongoing* and future trials

- Banff 1A ACR should not be included as part of a primary endpoint in registration trials

- New maintenance therapies should be developed along with rejection therapies tailored specifically for the rejections that arise under the new therapy

Importance of Safety Endpoints in Kidney Transplantation Trials

William E. Fitzsimmons, Pharm.D., M.S., Senior Advisor, TTC, C-Path

TTC
TRANSPLANT THERAPEUTICS CONSORTIUM
CRITICAL PATH INSTITUTE

Disclosures- William E. Fitzsimmons

Board Member- Tutela Pharmaceuticals Inc, a 501(c)(3) nonprofit, CARER Group, a 501(c)(3), and CTI Clinical Trial Services

Adjunct Professor- University of Illinois at Chicago, Colleges of Pharmacy and Medicine

Consultant- Tract Therapeutics

Why Focus on Safety Endpoints?

1. **Impact on transplant recipients**

2. Impact on death and graft loss

3. The incidence is high enough to show improvements

4. Innovative new therapies may likely be targeted to improve safety since efficacy improvement is difficult to demonstrate- i.e. can stimulate investment and innovation in transplant even if efficacy is non-inferior

My Transplanted Heart and I Will Die Soon
by: Amy Silverstein, NY Times, April 18, 2023

"Over the last almost four decades a toxic triad of immunosuppressive medicines — calcineurin inhibitors, antimetabolites, steroids — has remained essentially the same with limited exceptions.

These transplant drugs cause secondary diseases and dangerous conditions, including diabetes, uncontrollable high blood pressure, kidney damage and failure, serious infections and cancers.

Transplantation is no different from lifelong illnesses that need newer, safer, more effective medicines."

Why Focus on Safety Endpoints?

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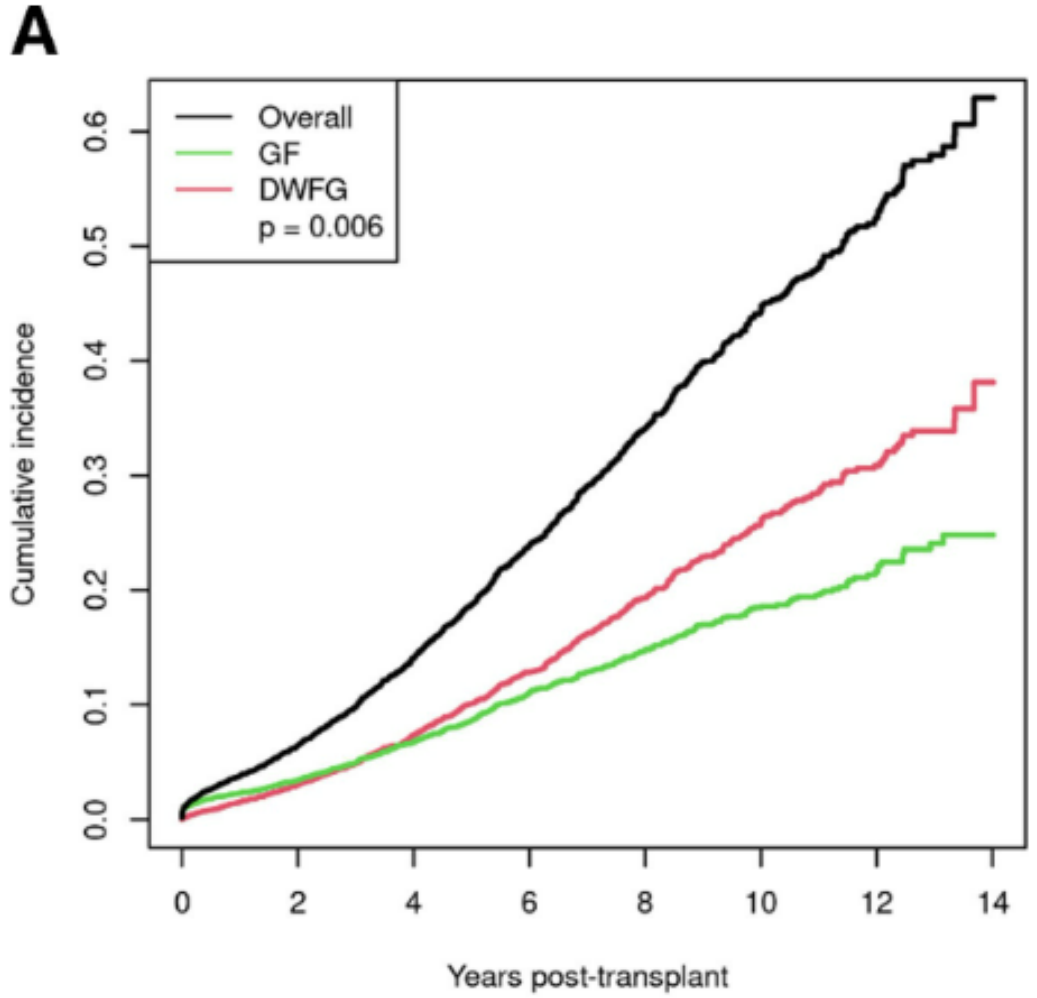
4. Innovative new therapies may likely be targeted to improve safety since efficacy improvement is difficult to demonstrate- i.e. can stimulate investment and innovation in transplant even if efficacy is non-inferior

Cumulative incidence of death with a functioning graft exceeds graft failure from 5 years onward



5,752 kidney transplants performed at the 3 Mayo Clinic centers

TABLE 2. - DWFG after solitary kidney transplantation (2006–2018)

Cause	Time after kidney transplantation			
	Total	<1 y	1–5 y	>5 y
All DWFG	691 (12.0%)	85 (12.3%)	314 (45.4%)	292 (42.3%)
Malignancy	138 (20.0%)	10 (11.8%)	66 (21.0%)	62 (21.2%)
Infection	136 (19.7%)	29 (34.1%)	63 (20.1%)	44 (15.1%)
Cardiac	87 (12.6%)	11 (12.9%)	32 (10.2%)	44 (15.1%)
Other	74 (10.7%)	20 (23.5%)	31 (9.9%)	23 (7.9%)
Unknown	256 (37.0%)	15 (17.6%)	122 (38.9%)	119 (40.8%)

The causes of DWFG are listed by cause and by the time that they occurred with respect to the kidney transplantation.
DWFG, death with a functioning graft.

Merzkani, Massini A.; Bentall, Andrew J.; Smith, Byron H.; Benavides Lopez, Xiomara; D'Costa, Matthew R.; Park, Walter D.; Kremers, Walter K.; Issa, Naim; Rule, Andrew D.; Chakkera, Harini; Reddy, Kunam; Khamash, Hasan; Wadei, Hani M.; Mai, Martin; Alexander, Mariam P.; Amer, Hatem; Kukla, Aleksandra; El Ters, Mireille; Schinstock, Carrie A.; Gandhi, Manish J.; Heilman, Raymond; Stegall, Mark D.
Transplantation Direct8(2):e1273, February 2022.
doi: 10.1097/TXD.0000000000001273

Graft failure can be caused by toxicity of immunosuppression

Merzkani MA et al- Mayo Clinics Transplantation Direct 8(2):e1273, February 2022

TABLE 3. - Causes of graft failure by time after kidney transplantation

Cause	Time after kidney transplantation			
	Total	<1 y	1–5 y	>5 y
Total	553 (100%)	131 (23.7%)	235 (42.5%)	188 (33.8%)
Alloimmune	214 (38.7%)	16 (12.2%)	117 (49.8%)	81 (43.3%)
Glomerular diseases	103 (18.6%)	18 (13.7%)	41 (17.4%)	44 (23.5%)
Renal tubular injuries	77 (13.9%)	12 (9.2%)	41 (17.4%)	24 (12.8%)
Primary dysfunction/surgical	79 (14.3%)	79 (60.3%)	0 (0.0%)	0 (0.0%)
BK nephropathy	24 (4.3%)	4 (3.1%)	10 (4.3%)	10 (5.3%)
Unknown/Other	56 (10.1%)	2 (1.5%)	26 (11.1%)	28 (15.0%)
Number at risk at the beginning of the time period	5752	5752	5396	3716

Graft failure (not due to death) by category was determined by an adjudication process in which 2 or more expert nephrologists determined the cause based on chart review. The table also shows the causes of graft loss with respect to time after kidney transplantation and the number of patients followed at the beginning of the time period.

Contribution of Immunosuppression to Death and Graft Loss

Leading Causes of Death with a Functioning Graft

- Cardiovascular (stroke, CHD, DM)
- Infection
- Cancer

Leading Causes of Death-Censored Graft Loss

- Rejection
- Recurrent Disease
- BK Nephropathy
- Nephrotoxicity/Renal Tubular Injuries
- Primary Dysfunction/Surgical

Impacted by immunosuppression

Why Focus on Safety Endpoints?

1. Impact on transplant recipients

2. Impact on death and graft loss

3. The incidence is high enough to show improvements

4. Innovative new therapies may likely be targeted to improve safety since efficacy improvement is difficult to demonstrate- i.e. can stimulate investment and innovation in transplant even if efficacy is non-inferior

Most Common Adverse Events based on approved U.S. labels of Envarsus XR, ASTAGRAF XL, and Nulojix

	Envarsus XR (tacrolimus extended release)	Astagraf XL (tacrolimus extended release)	Nulojix (belatacept)
Diarrhea	31%	45%	39%
Anemia	26%	33%	45%
UTI	25%	16%	37%
Hypertension	23%	28%	32%
Diabetes	21%	36%	5%
SERIOUS INFECTIONS	26%	22%	24%

Why Focus on Safety Endpoints?

1. Impact on transplant recipients

2. Impact on death and graft loss

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4. Innovative new therapies may be targeted to improve safety since efficacy improvement is difficult to demonstrate- i.e. can stimulate investment and innovation in transplant even if efficacy is non-inferior

Since adverse events are included in the current FDA approved labels, can’t companies already actively promote safety superiority?

Nulojix (belatacept), Envarsus XR and ASTAGRAF XL (tacrolimus extended release) Labels in U.S.

“Studies 1 and 2 were not designed to support comparative claims for NULOJIX for the adverse reactions reported in this table. “

“Study 1 was not designed to support comparative claims of ENAVARSUS XR compared to tacrolimus [immediate-release] capsules for the adverse reactions reported in this table.”

“Study 1 was not designed to support comparative claims of ASTAGRAF XL compared to tacrolimus immediate-release product for the adverse reactions reported in this table. “

How do we design a trial to support comparative claims?

FDA Guidance on Secondary Endpoints-Applying efficacy concepts to hypothesis testing of secondary safety endpoints*

"Positive results on the secondary endpoints can be interpreted only if there is first a demonstration of a treatment effect on the primary endpoint family"

"In general, it may be desirable to limit the number of secondary endpoints,..."

*Multiple Endpoints in Clinical Trials Guidance for Industry OCTOBER 2022

Safety Endpoints-Operational aspects

-Predefine the secondary safety endpoint(s)

-Collect safety endpoint rigorously and systematically in all patients as defined by protocol, not in a typical spontaneous adverse event fashion

-Use established definitions and endpoints from trials and approvals of other therapeutics

-Perform hierarchical statistical testing after testing for the primary efficacy endpoint – appropriately control for multiplicity and Type I error

Safety Endpoints in Kidney Transplant-Clearly Established

Safety Event	Endpoint
Diabetes	Hemoglobin A1c and OGTT
Hypertension	Blood pressure
Hyperlipidemia	LDL-C
Infection	Plasma CMV DNA
Leukopenia	WBC and differential
Anemia	Hemoglobin
Weight Gain/Obesity	Body weight

Safety Endpoints in Kidney Transplant-Second Generation

Safety Event	Endpoint
Infection	Plasma BK viremia
PTLD	Plasma Epstein-Barr Virus DNA
Diarrhea	Stool count and stool form (Bristol Stool scale)
Insomnia	Polysomnography (LPS, WASO)

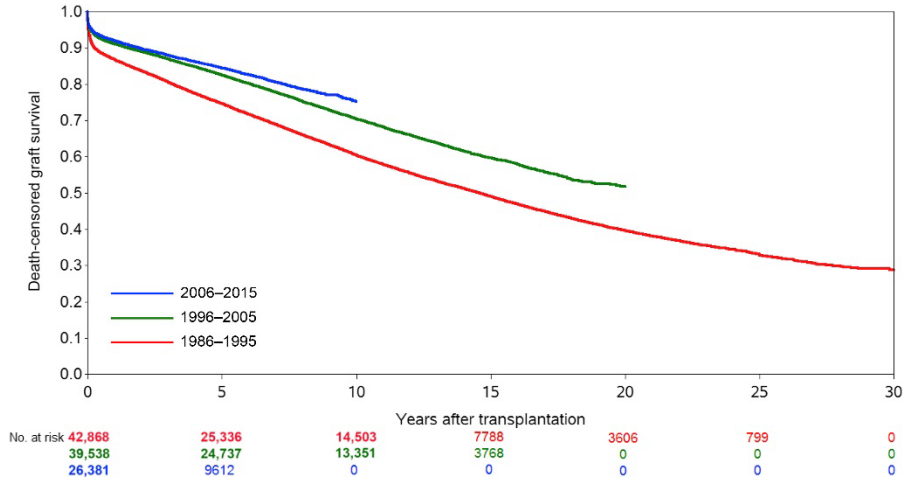
Summary- Safety Endpoints in Kidney Transplant

Adverse events contribute to both death and graft loss

Objective, quantitative safety endpoints are established for diabetes, hematologic, infection, and cardiovascular adverse events

Prospective planning and interactions between sponsors, investigators, patients and regulators will facilitate incorporation in trials

Innovation in transplant immunosuppression could include non-inferior efficacy failure, superior iBOX and superior safety in comparison to SOC



PANEL DISCUSSION/AUDIENCE Q&A

SESSION 4: PERSONALIZED IMMUNOSUPPRESSION / ENRICHMENT AS A TOOL IN TRIAL DESIGN

Using biomarkers as part of enrichment strategies for clinical trials in transplantation

Peter S. Heeger, M.D.
Professor of Medicine, Surgery and Biomedical Sciences
Director, Transplant Immunology Research
Comprehensive Transplant Center
Cedars-Sinai Medical Center, Los Angeles CA

Cedars Sinai

FDA

University of Manitoba

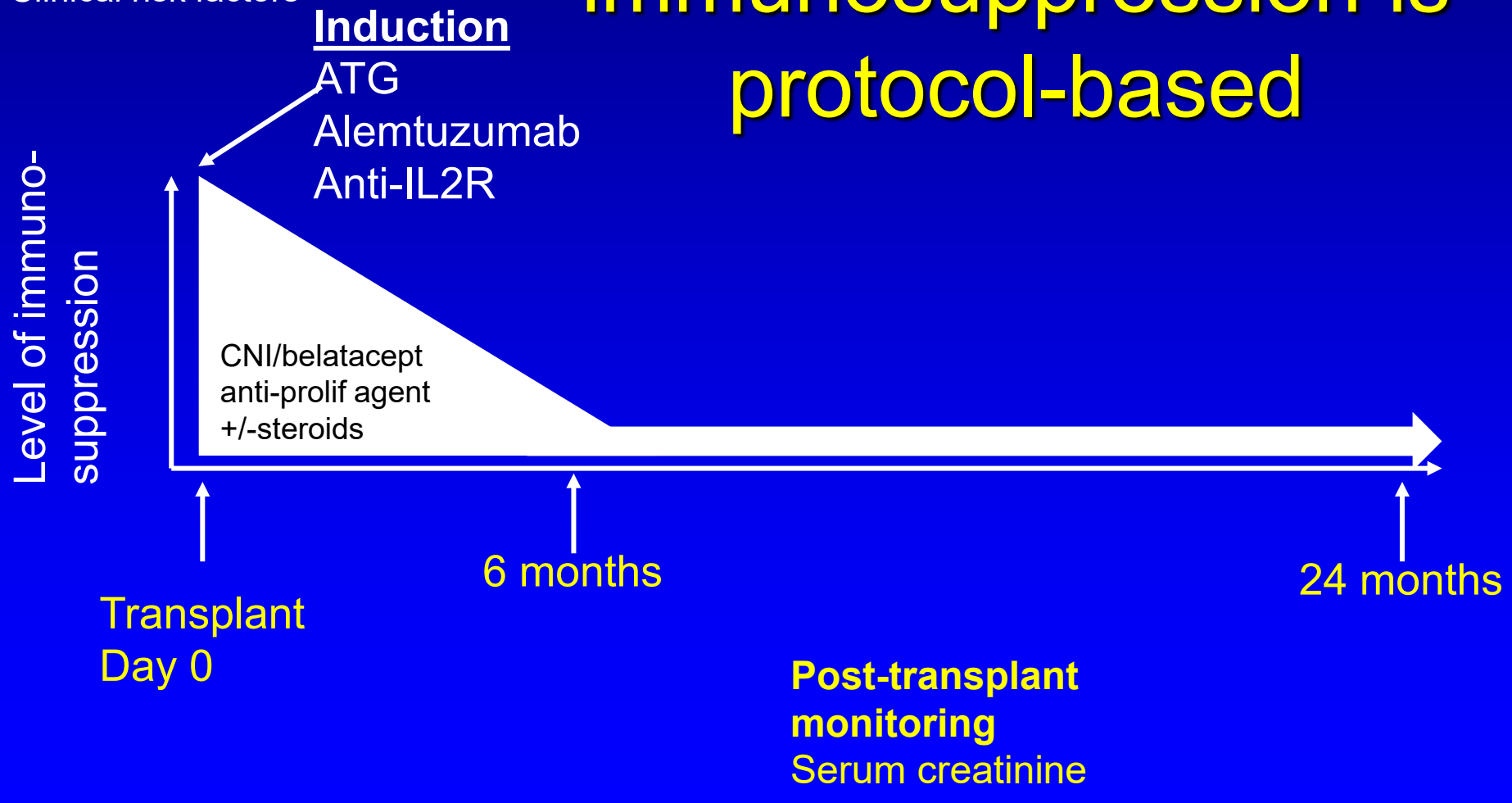
Disclosures

- Faculty: Peter Heeger

- Relationships with commercial interests: none
- Speakers Bureau/Honoraria: None
- Consulting Fees: None
- Other: None

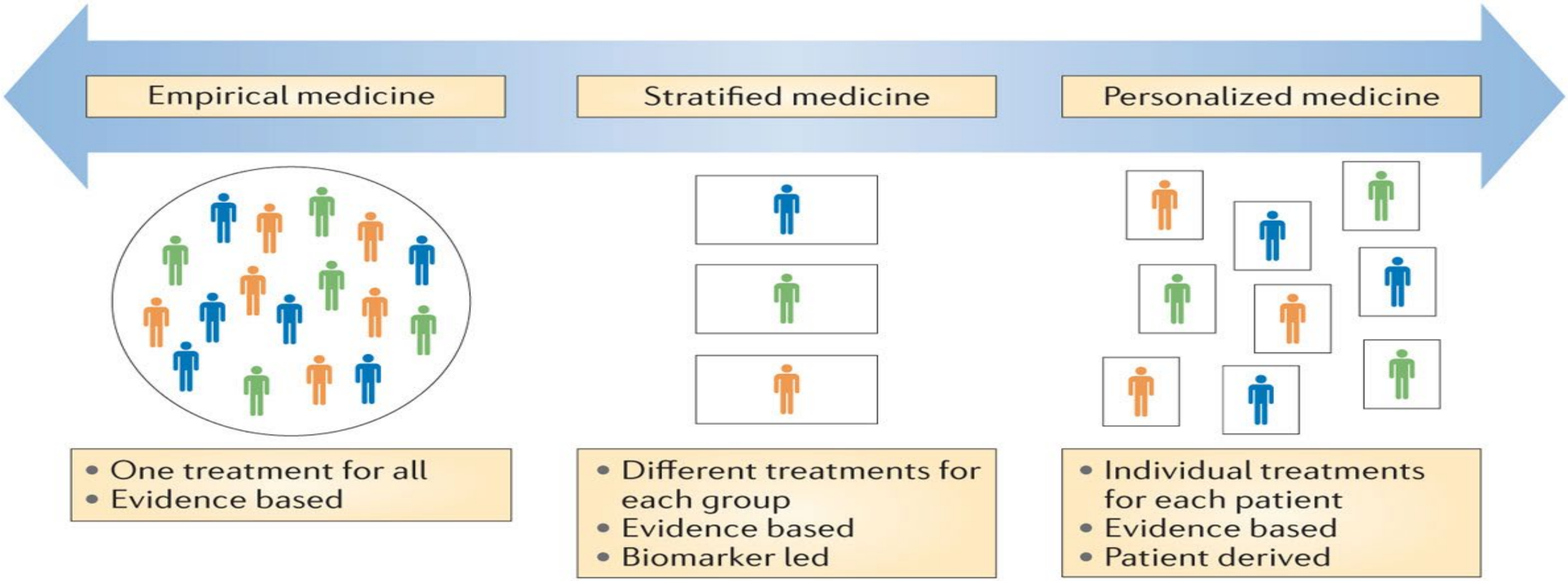
Current approach to transplant immunosuppression is protocol-based

Pre-transplant
Risk assessment
HLA typing
Cross matching
Implantation biopsy
Clinical risk factors



Post-transplant monitoring
Serum creatinine

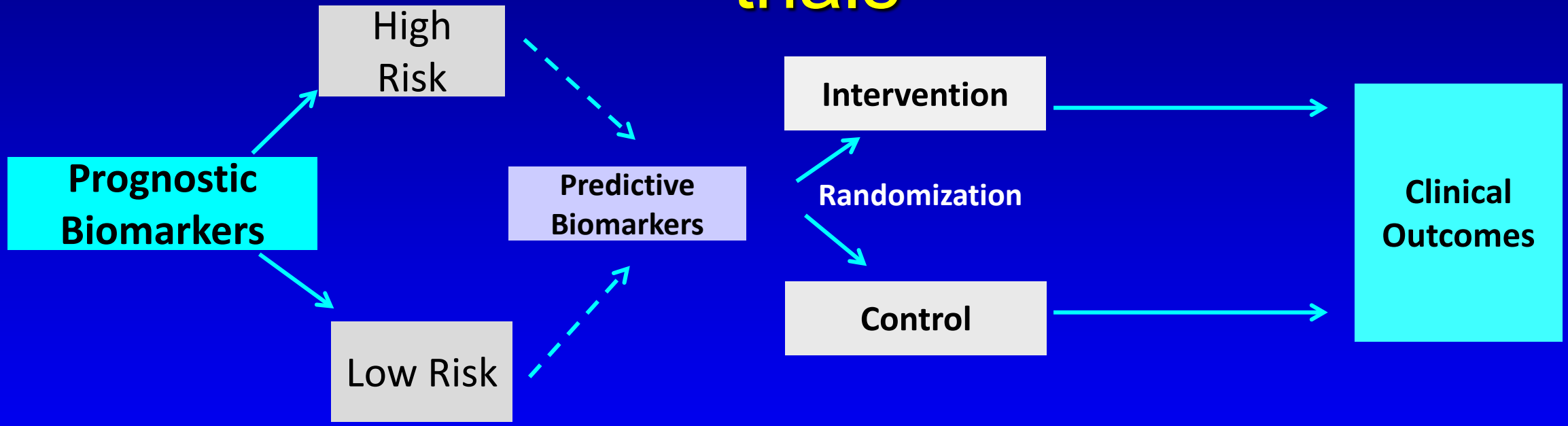
Goal is to move toward individualized therapy



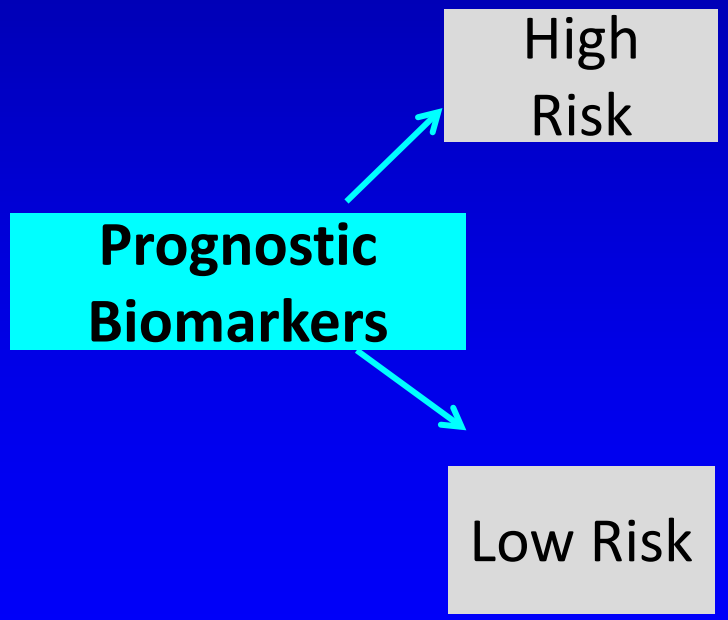
Potential Impact of Prognostic Biomarkers on Future Transplant Trials

Problems with Current Trial Design	Defining approaches to stratify patients based on risk	Type of Biomarkers and their Impact on transplant Trials
Enrollment of large proportion of low-risk patients who do not reach progression endpoints (BPAR, eGFR)	**Identify patients at high risk of reaching clinically relevant endpoints: baseline biomarkers**	**Prognostic Biomarkers:** Used as *enrichment strategy* for enrollment of high-risk patients in clinical trials leading to studies with higher power to detect change

Prognostic and Predictive Biomarkers Drug development tools within clinical trials



Example of using clinical risk factors as an enrichment strategy in transplantation: ischemia reperfusion injury



- Ischemia Reperfusion Injury (IRI) is a crucial driver of the poorer outcomes observed after kidney transplantation
- High risk populations include recipients of deceased donor kidneys particularly those with
  - prolonged cold ischemia times ≥24hr
  - elevated Serum Cr ≥ 2.5mg/dl at death
  - donors >65 years
  - need for dialysis prior to donation
  - donation after cardiac death (DCD)

Design of IRI trials involve enrichment for patients at high risk for developing IRI

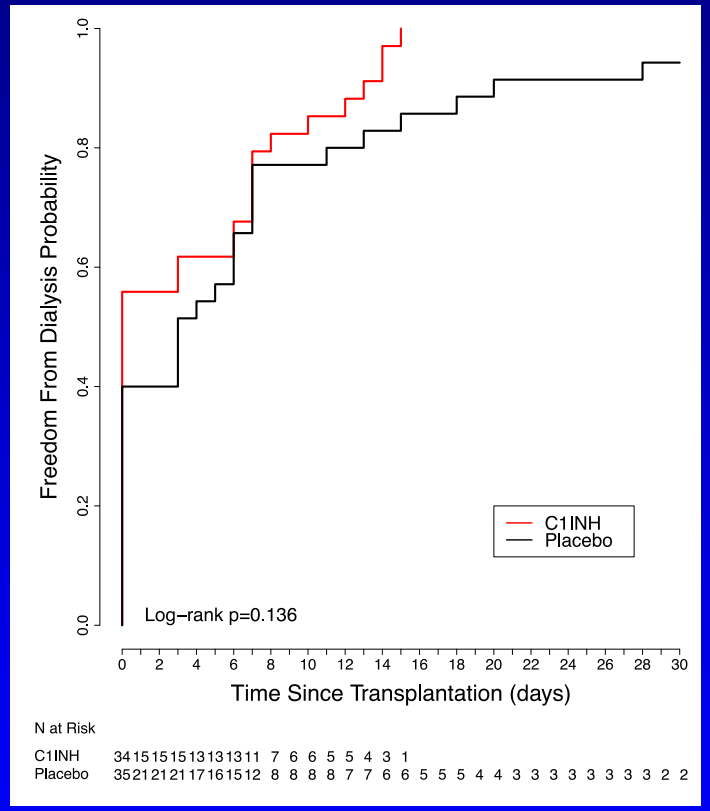
- Choose enrollment criteria that include accepted clinical risk factors that define high risk for developing IRI
  - Would not include all transplant recipients, living and deceased because this would dilute the chance of observing an effect of the intervention
  - Randomize the enriched population to experimental vs control arm
  - Assess outcome

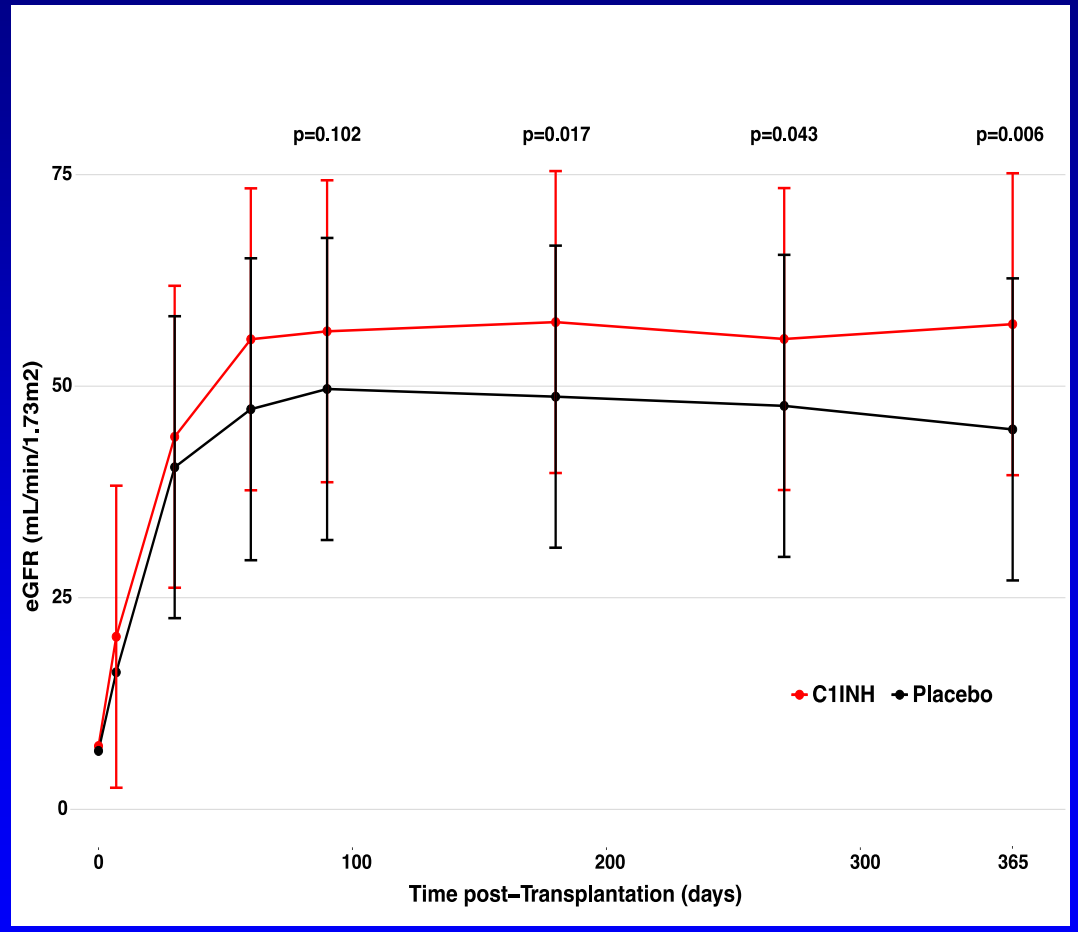
A phase I/II, double-blind, placebo-controlled study assessing safety and efficacy of C1 esterase inhibitor for prevention of delayed graft function in deceased donor kidney transplant recipients

Stanley C. Jordan[1] | Jua Choi[1] | Olivier Aubert[2] | Mark Haas[3] | Alexandre Loupy[2] | Edmund Huang[1] | Alice Peng[1] | Irene Kim[1] | Sabrina Louie[1] | Noriko Ammerman[1] | Reiad Najjar[1] | Dechu Puliyanda[1] | Ashley Vo[1]

Am J Trans 2018

- Building on preclinical data implicating the Complement activation as a key mechanistic driver of IRI, Stan Jordan's group at Cedars tested impact of C1 esterase inhibitor on outcomes in patients at high risk for IRI
- **Enrichment strategy: deceased donor, high KDPI, long CIT, high donor terminal Cr, others**
- Randomized blinded 2 arm study n=35/group
- C1INH (Berinert®) given i.v. (systemically) pre op and 24 h post op vs Saline
- Induction with alemtuzumab (highly sensitized) or thymoglobulin (T cell depleting) then standard immunosuppression (TAC MMF Pred)





Left. No effect on DGF, trend toward decreased need for dialysis during the 1st month post-transplant and (right) a significant improvement in eGFR at 1 year compared to placebo.

C1INH DGF Trial 3.5 Year Data

What are the 3-year outcomes of an RCT assessing the safety

CJASN

Together, these findings suggest peri-transplant C1 INH administration to kidney transplant recipients at high risk for IRI can improve allograft function independent of DGF

Supports the need for a larger, multicenter clinical trial

Will be important to carefully define the enrollment criteria to enrich for subjects at high risk so as to optimize chances of detecting an effect of the intervention

Conclusion Treatment of patients at risk for ischemia-reperfusion injury and delayed graft function with C1 esterase inhibitor was associated with lower incidence of graft failure.

Edmund Huang, Ashley Vo, Jua Choi, et al. ***Three-Year Outcomes of a Randomized, Double-Blind, Placebo-Controlled Study Assessing Safety and Efficacy of C1 Esterase Inhibitor for Prevention of Delayed Graft Function in Deceased Donor Kidney Transplant Recipients.*** CJASN doi: 10.2215/CJN.04840419. **Visual Abstract by Beatrice Concepcion, MD**

Biomarkers vs in vitro companion diagnostic device

- Biomarkers are anatomic, physiologic, biochemical, or molecular parameters that indicate, or are associated with an alteration in physiology and are of clinical significance (this doesn't necessarily mean they are clinically useful)
  - Surrogate Markers can be defined as biomarkers that have established clinical utility
  - Surrogate Endpoints are biomarkers used (in clinical trials) to evaluate the safety or effectiveness of a therapy and serve as alternatives to traditional endpoints.
- In vitro companion diagnostic device (FDA guidelines 2014):is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product.
  - Example FDA approved HER-2 tests to determine whether a patient may be a candidate for Herceptin (trastuzumab) therapy, which is indicated for treatment of metastatic breast cancer and gastric cancer.

FDA guidelines

- FDA approval is required to use/test a candidate in vitro companion diagnostic device in the context of a clinical trial for a particular context of use
- Information about the planned use of an in vitro companion diagnostic device and its use in clinical trials should be included in an investigational submission. This information will help FDA understand and provide advice on how the IVD device will be used to enroll subjects into the trial(s) and how the test will be validated for use.

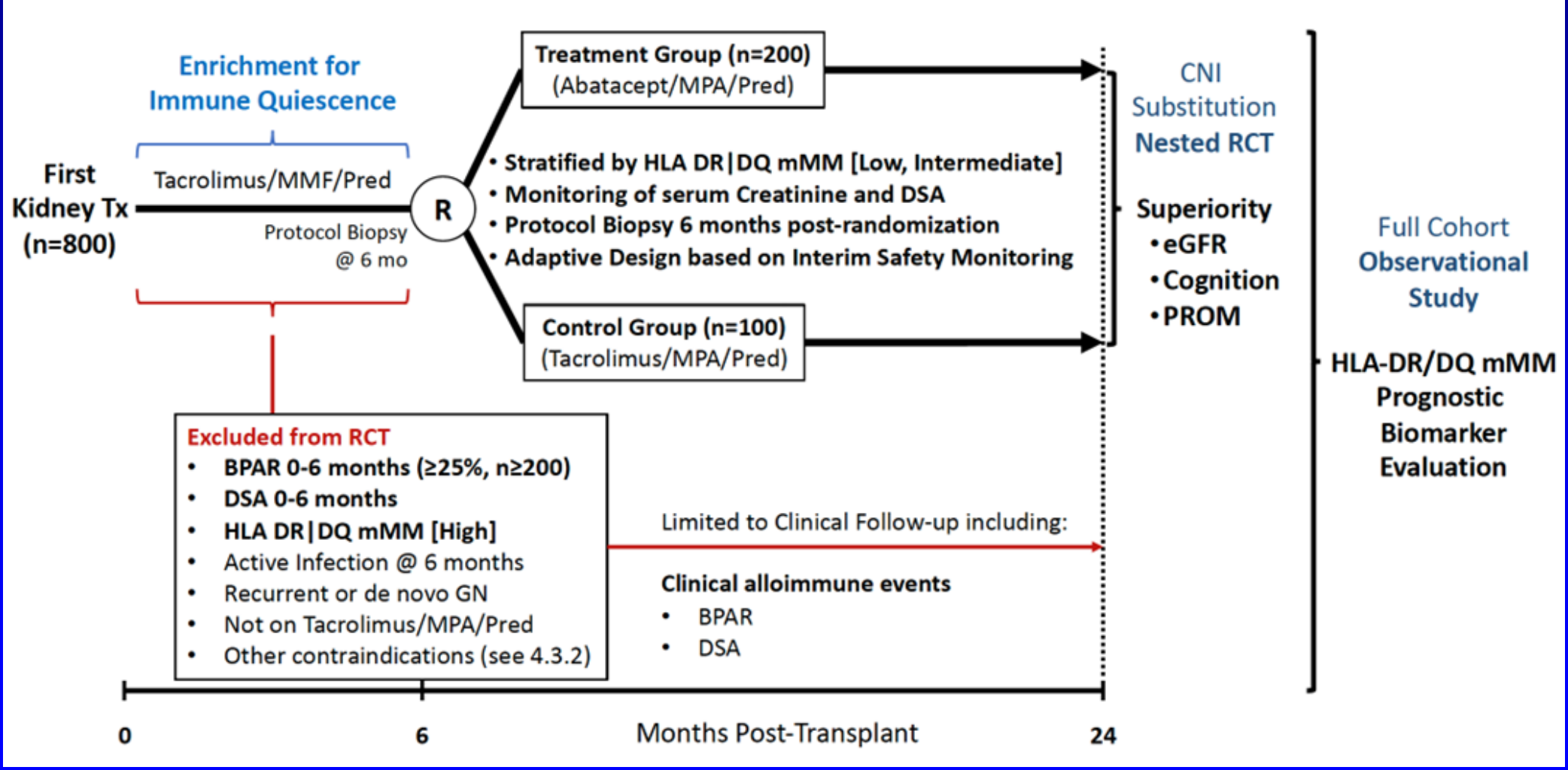
Example HLA DR/DQ molecular mismatch (mMM)

- Retrospective data indicate HLA DR/DQ mMM
  - Can stratify kidney transplant recipients in high, intermediate and low risk for developing posttransplant immune events (DSA, ABMR, TCMR).
  - Prospective validation required to provide further evidence that this approach is a valid PROGNOSTIC biomarker
  - Can identify subjects at low risk for immune events during TAC withdrawal (CTOT19).
  - Prospective study required to test the utility of HLA DR/DQ mMM as a PREDICTIVE biomarker
- HLA DR/DQ mMM has been submitted to the FDA biomarker qualification program that would permit it to be used as an in vitro companion diagnostic device in clinical trials

Assessment of biomarker guided CNI substitution in kidney transplantation (ABCs)

- Designed to
  - Prospectively assess PROGNOSTIC utility of HLA DR/DQ mMM in kidney transplantation (risk assessment)
  - Prospectively test PREDICTIVE utility of HLA DR/DQ mMM in kidney transplantation
  - Test hypothesis that stable kidney transplant recipients with low/intermediate HLA DR/DQ mMM (enrichment) can safely switch from TAC to abatacept 6 mo posttransplant resulting in improved allograft function.

ABC trial design



Summary and conclusions

Collaborators

Cedars-Sinai

- Stan Jordan
- Irene Kim
- Jun Shoji
- Justin Steggerda
- Sanjeev Kumar
- Ananth Karumanchi
- Simon Knott
- Michel Zamojskiy
- Sindhu Chandran
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Tarek Alhamad, Wash U

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Funded By NIAID

What enrichment tools exist in kidney transplantation trials?

HLA Molecular Mismatch

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University of Manitoba, Winnipeg, Canada

FDA

University of Manitoba

Health Sciences Centre Winnipeg

Shared health Soins communs Manitoba

Conflicts

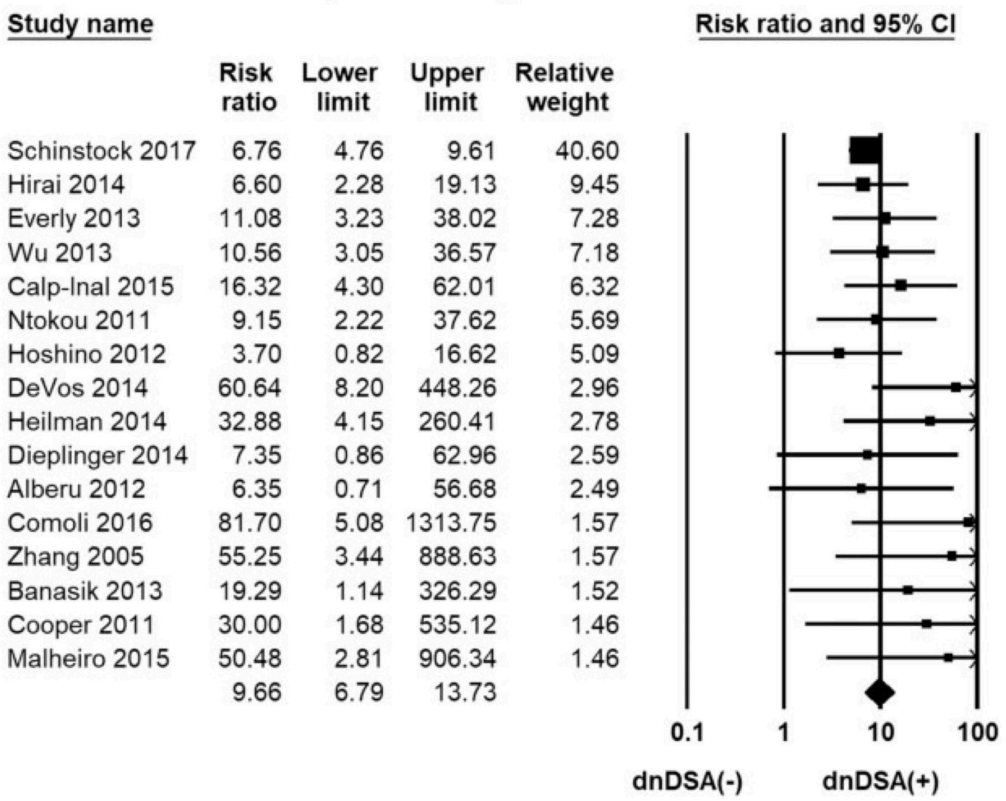
I have **no** financial relationships with commercial interests to disclose

AND

My presentation **does not include** a discussion of off-label or investigational use.

De novo Donor Specific Antibody Development correlates with ABMR and Graft Loss in Renal Transplantation

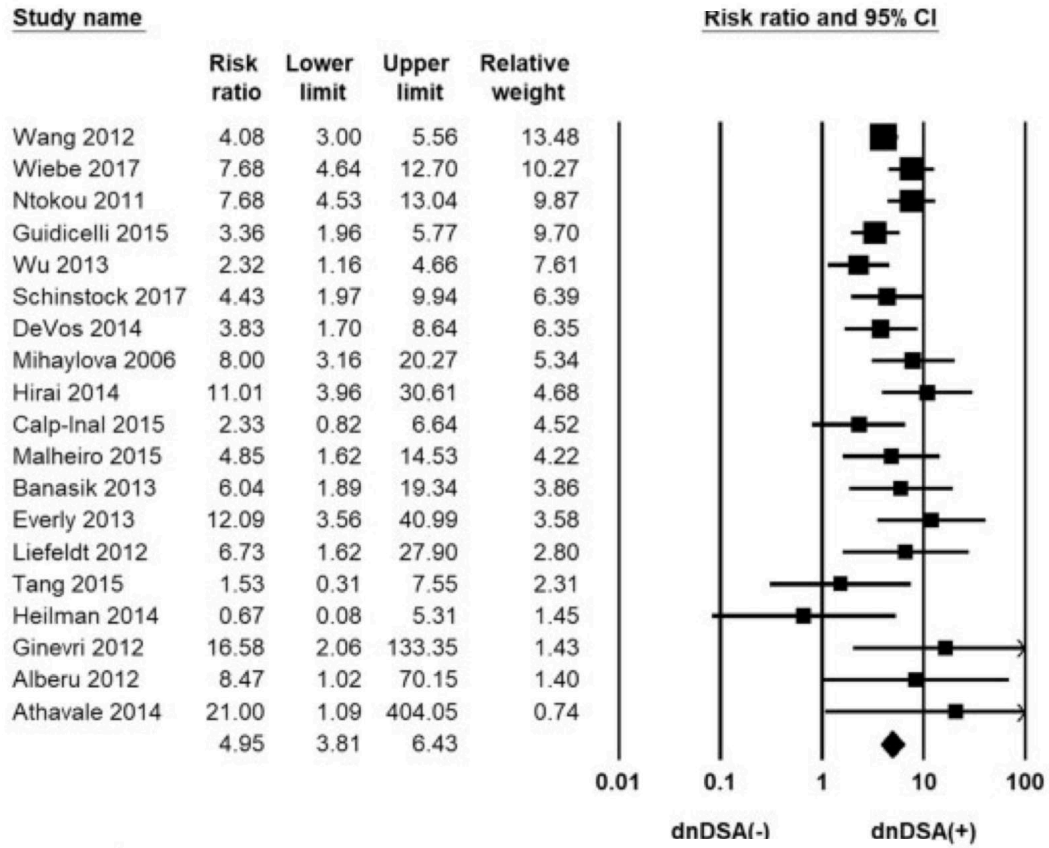
Antibody-mediated Rejection (ABMR)



Study name	Risk ratio	Lower limit	Upper limit	Relative weight
Schinstock 2017	6.76	4.76	9.61	40.60
Hirai 2014	6.60	2.28	19.13	9.45
Everly 2013	11.08	3.23	38.02	7.28
Wu 2013	10.56	3.05	36.57	7.18
Calp-Inal 2015	16.32	4.30	62.01	6.32
Ntokou 2011	9.15	2.22	37.62	5.69
Hoshino 2012	3.70	0.82	16.62	5.09
DeVos 2014	60.64	8.20	448.26	2.96
Heilman 2014	32.88	4.15	260.41	2.78
Dieplinger 2014	7.35	0.86	62.96	2.59
Alberu 2012	6.35	0.71	56.68	2.49
Comoli 2016	81.70	5.08	1313.75	1.57
Zhang 2005	55.25	3.44	888.63	1.57
Banasik 2013	19.29	1.14	326.29	1.52
Cooper 2011	30.00	1.68	535.12	1.46
Malheiro 2015	50.48	2.81	906.34	1.46
	9.66	6.79	13.73	

RR 9.66 (6.79-13.73)

Overall Graft Loss

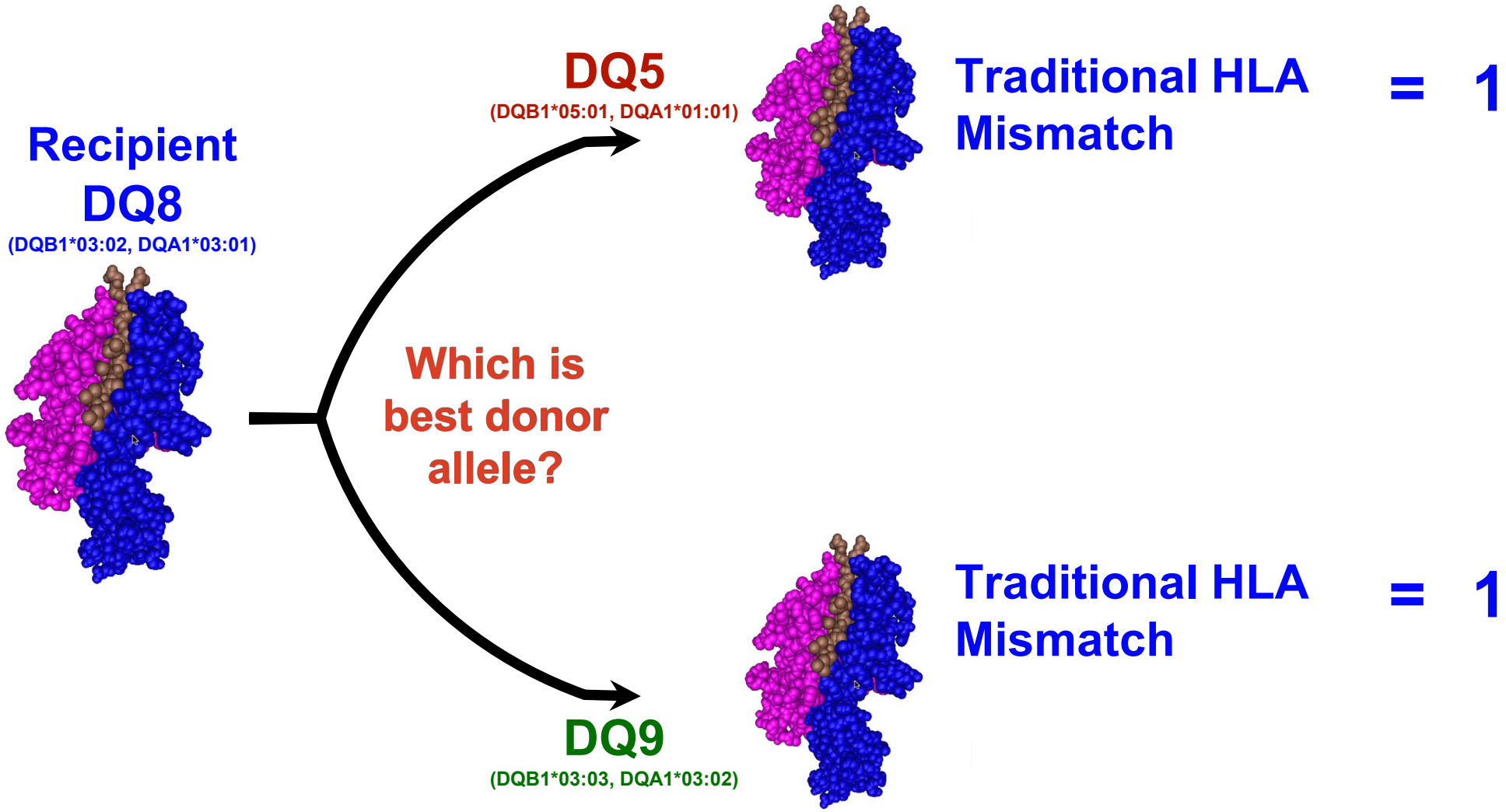


Study name	Risk ratio	Lower limit	Upper limit	Relative weight
Wang 2012	4.08	3.00	5.56	13.48
Wiebe 2017	7.68	4.64	12.70	10.27
Ntokou 2011	7.68	4.53	13.04	9.87
Guidicelli 2015	3.36	1.96	5.77	9.70
Wu 2013	2.32	1.16	4.66	7.61
Schinstock 2017	4.43	1.97	9.94	6.39
DeVos 2014	3.83	1.70	8.64	6.35
Mihaylova 2006	8.00	3.16	20.27	5.34
Hirai 2014	11.01	3.96	30.61	4.68
Calp-Inal 2015	2.33	0.82	6.64	4.52
Malheiro 2015	4.85	1.62	14.53	4.22
Banasik 2013	6.04	1.89	19.34	3.86
Everly 2013	12.09	3.56	40.99	3.58
Liefeldt 2012	6.73	1.62	27.90	2.80
Tang 2015	1.53	0.31	7.55	2.31
Heilman 2014	0.67	0.08	5.31	1.45
Ginevri 2012	16.58	2.06	133.35	1.43
Alberu 2012	8.47	1.02	70.15	1.40
Athavale 2014	21.00	1.09	404.05	0.74
	4.95	3.81	6.43	

RR 4.95 (3.81-6.43)

Sharma et al. NDT 2018 Aug 1;33(8):1472-1480

Heterogeneity HLA Antigen MM



Wiebe et al. Curr Opin Nephro Hypertens 2020 Nov;29(6):630-635

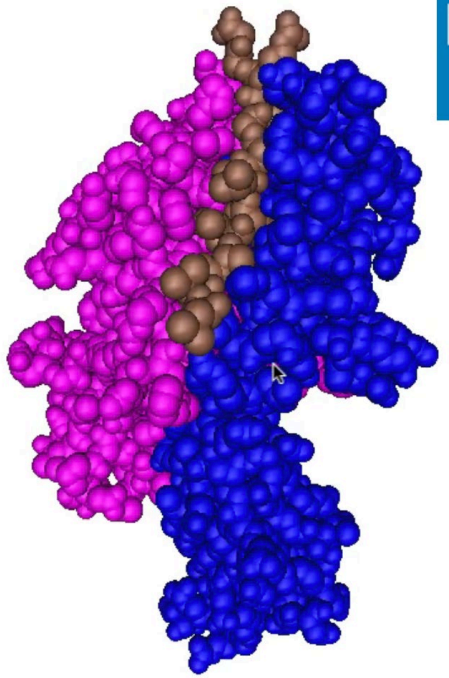
IPD - IMGT/HLA

Overview | IMGT/HLA | KIR | MHC | HPA | ESTDAB | Contact | Support

Numbers of HLA Alleles

HLA Class I Alleles	26,341
HLA Class II Alleles	11,175
HLA Alleles	37,516

https://www.ebi.ac.uk/ipd/imgt/hla/



FDA

University of Manitoba

NCBI

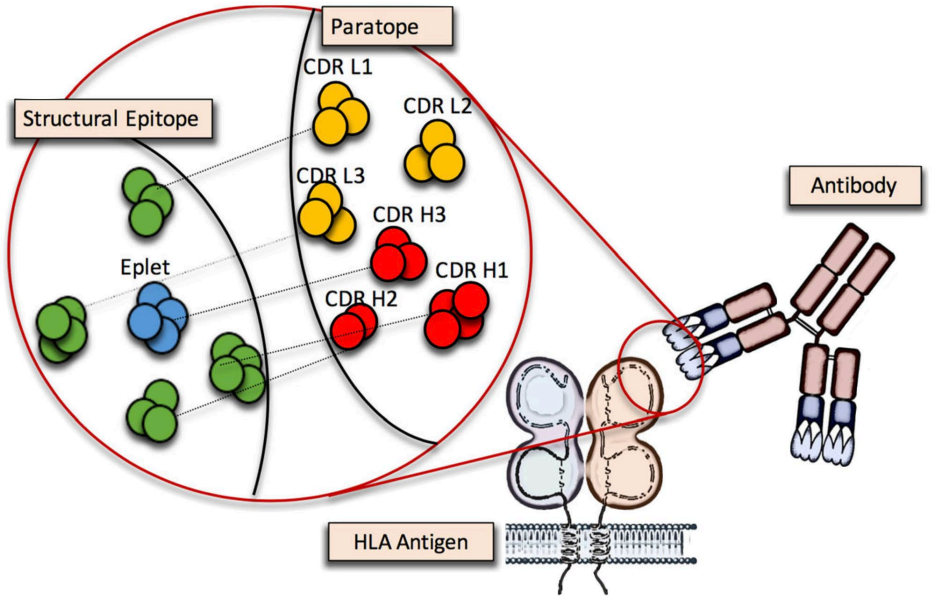
dbMHC Sequence Alignment Viewer

NCBI Resources Projects Accounts External Links Contact Us

Download/3D | EntrezGene | Show Region | DNA | Protein | Diff | SNPs | FASTA | Help

Alleles | HLA-DQB1 | Intr/Exon | -32 - 238 | Exons | Codon | Code | Reference: | Reference

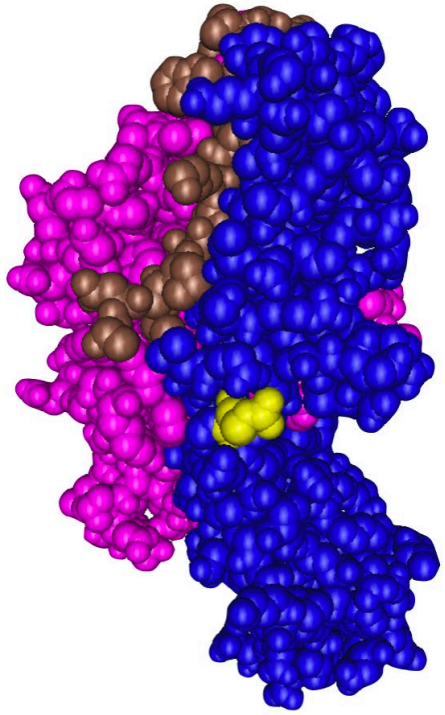
<< <C> >>	Exon1 | Exon2							Exon2 |
Codon Nr.		40	50	60	70	80	90	
DQB1*03:01:01:01	DQ7	IYNREEYARF	DSDVEVYRAV	TPLGPPDAEY	WNSQKEVLER	TRAELDTVCR	HNYQLELRTT	LQRRV
DQB1*03:02:01	DQ8	----------	----G-----	------A---	----------	----------	----------	-----
DQB1*03:03:02:01	DQ9	----------	----G-----	----------	----------	----------	----------	-----
DQB1*05:01:01:01	DQ5	-------V--	----G-----	--Q-R-V---	---------G	A--SV-R---	---EVAY-GI	-----



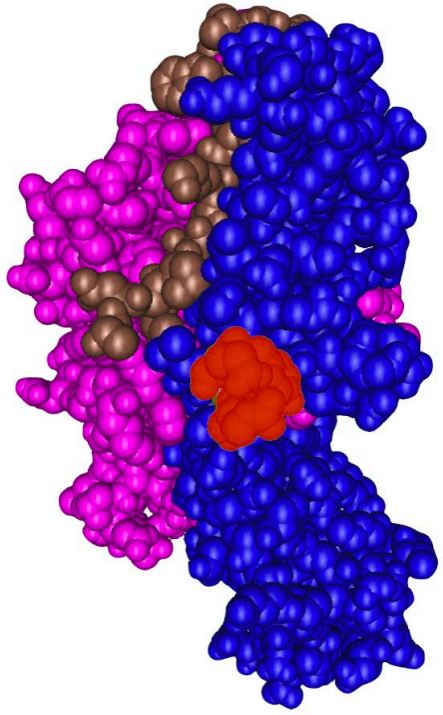
Pediatr Nephrol (2017) 32:1861-69

New Terms

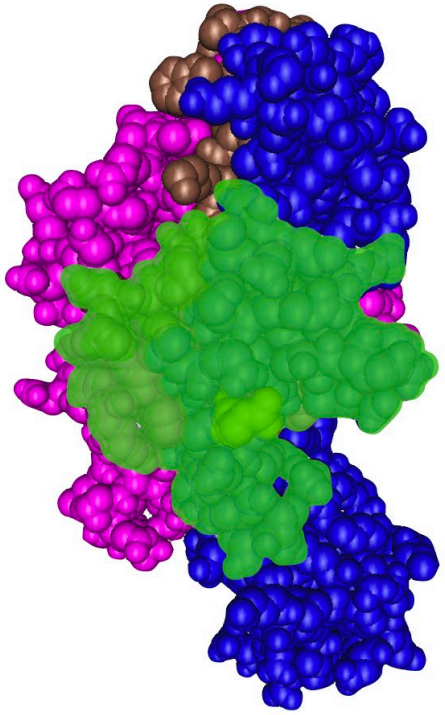
- HLA eplet Mismatch
- HLA molecular mismatch



Polymorphic amino acid



Eplet
3Å radius

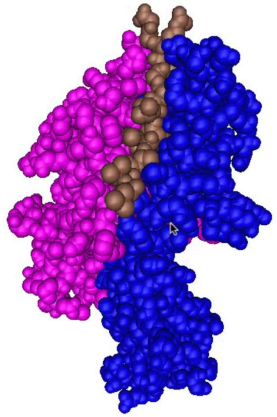


Epitope
15Å radius

Wiebe et al. AJT 2019 19:1708-19

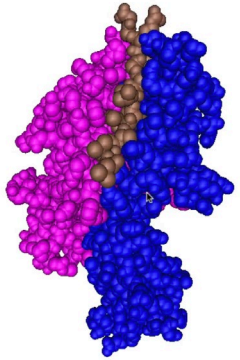
Heterogeneity HLA Antigen MM

Recipient
DQ8
(DQB1*03:02, DQA1*03:01)



Which is best donor allele?

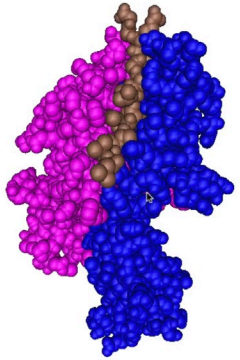
DQ5
(DQB1*05:01, DQA1*01:01)



Traditional HLA Mismatch = 1

Eplet Mismatches = 27

DQ9
(DQB1*03:03, DQA1*03:02)



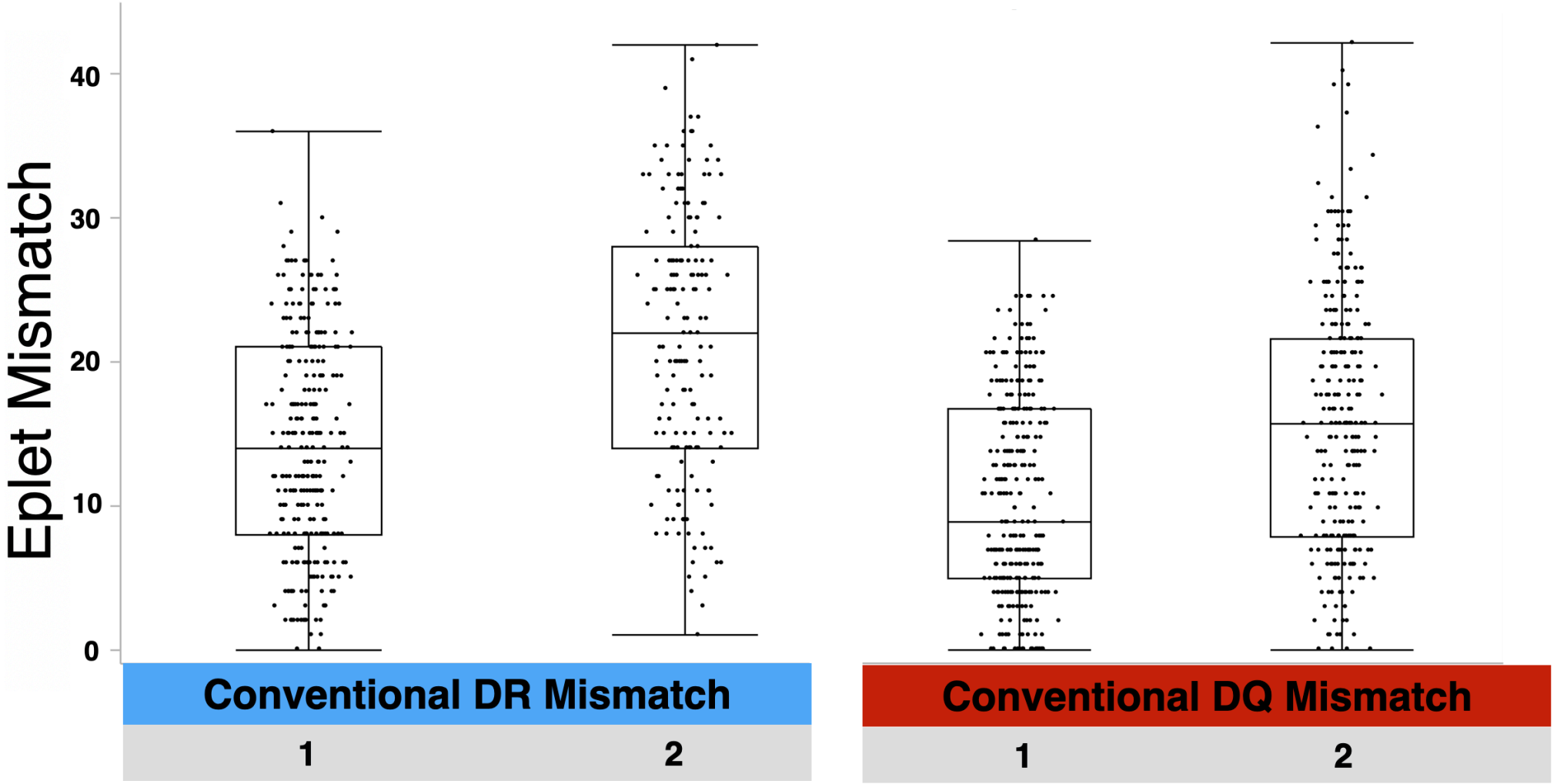
Traditional HLA Mismatch = 1

Eplet Mismatches = 2

Wiebe et al. Curr Opin Nephro Hypertens 2020 Nov;29(6):630-635

Wide Range of Eplet Mismatches for each Antigen Mismatch

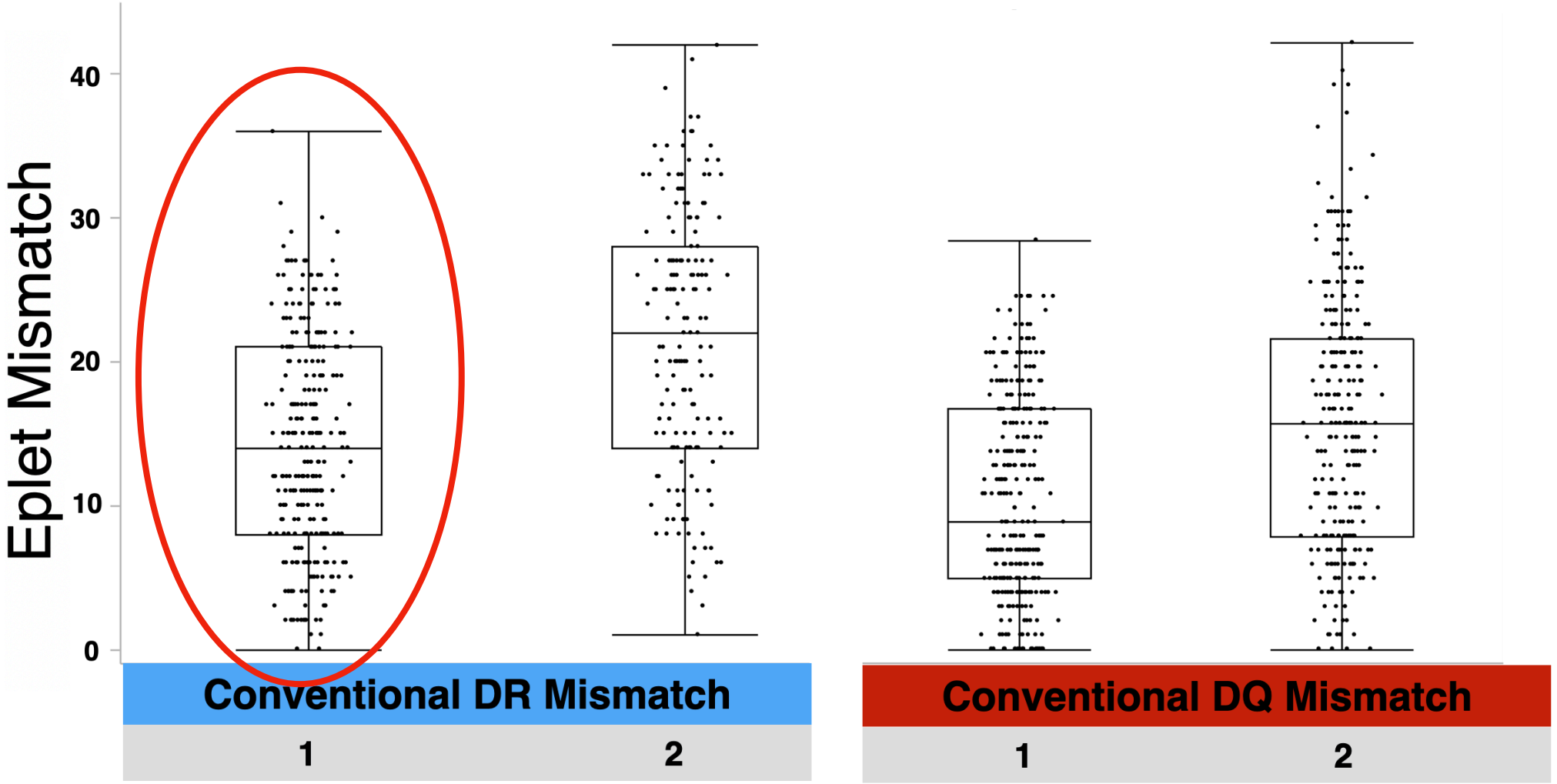
n=596



Wiebe et al. JASN 2017 Nov;28(11):3353-62

Wide Range of Eplet Mismatches for each Antigen Mismatch

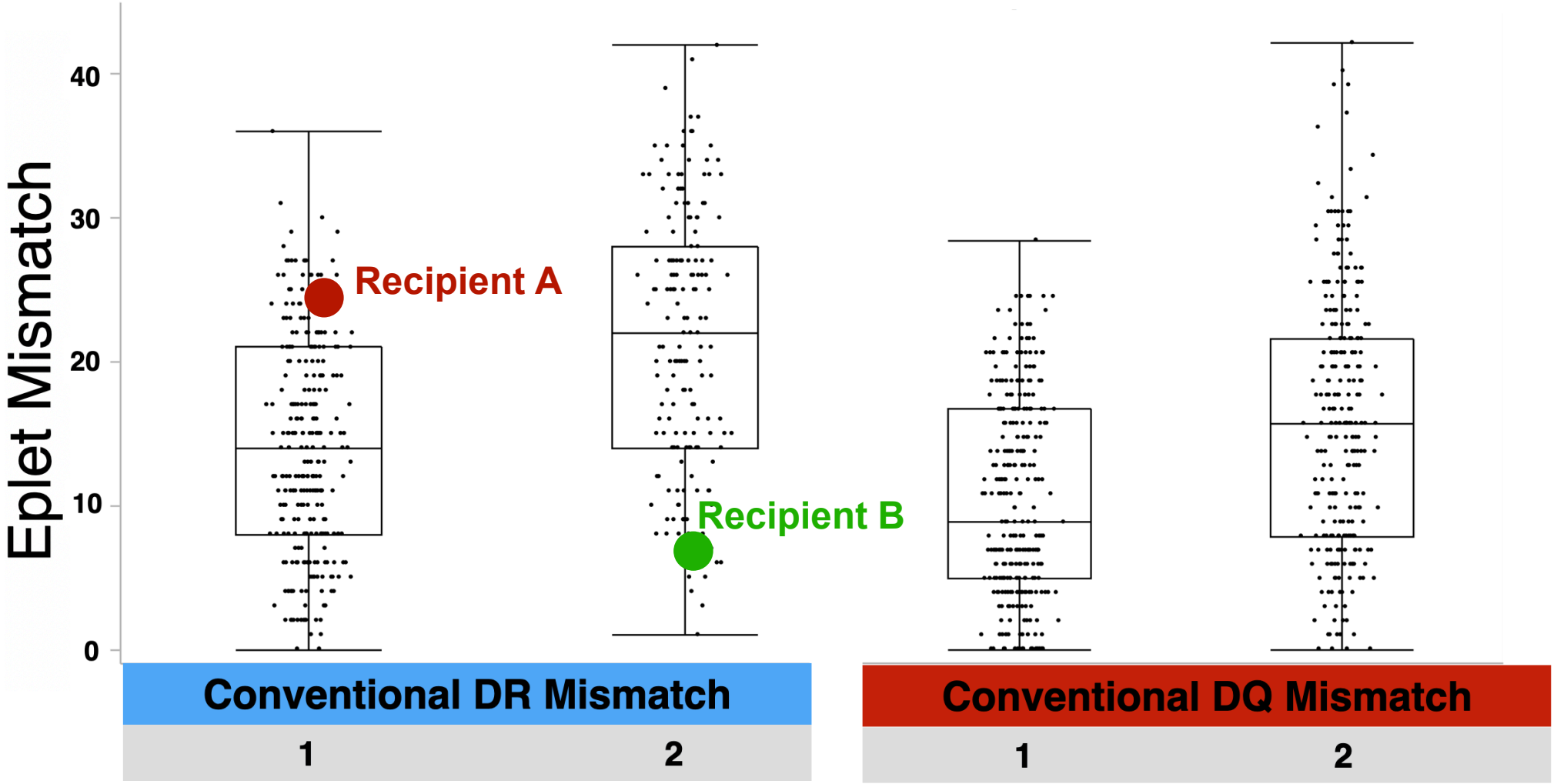
n=596



Wiebe et al. JASN 2017 Nov;28(11):3353-62

Wide Range of Eplet Mismatches for each Antigen Mismatch

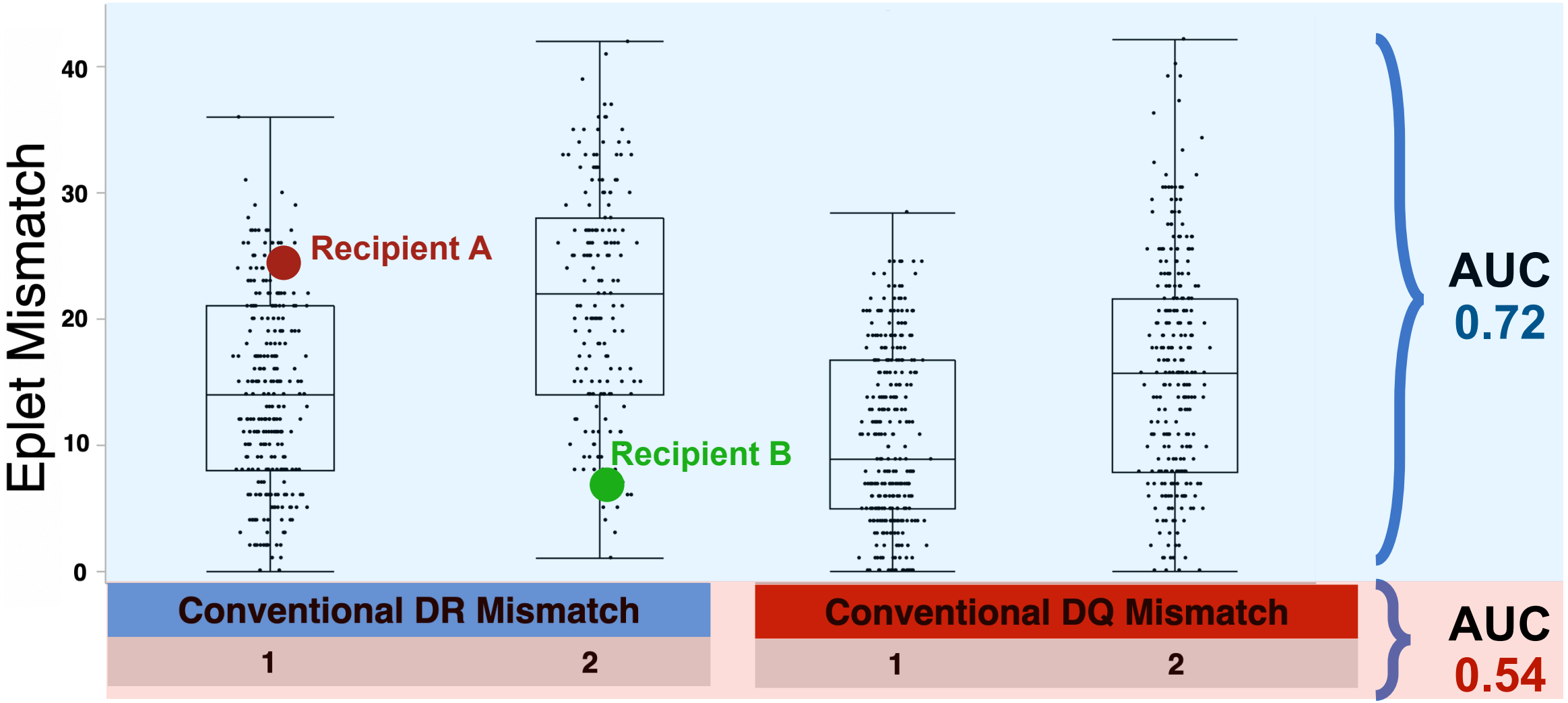
n=596



Wiebe et al. JASN 2017 Nov;28(11):3353-62

Wide Range of Eplet Mismatches for each Antigen Mismatch

n=596



Wiebe et al. JASN (2017) 28: 3353–62 Wiebe et al., AJT (2019) 19:1708-1719

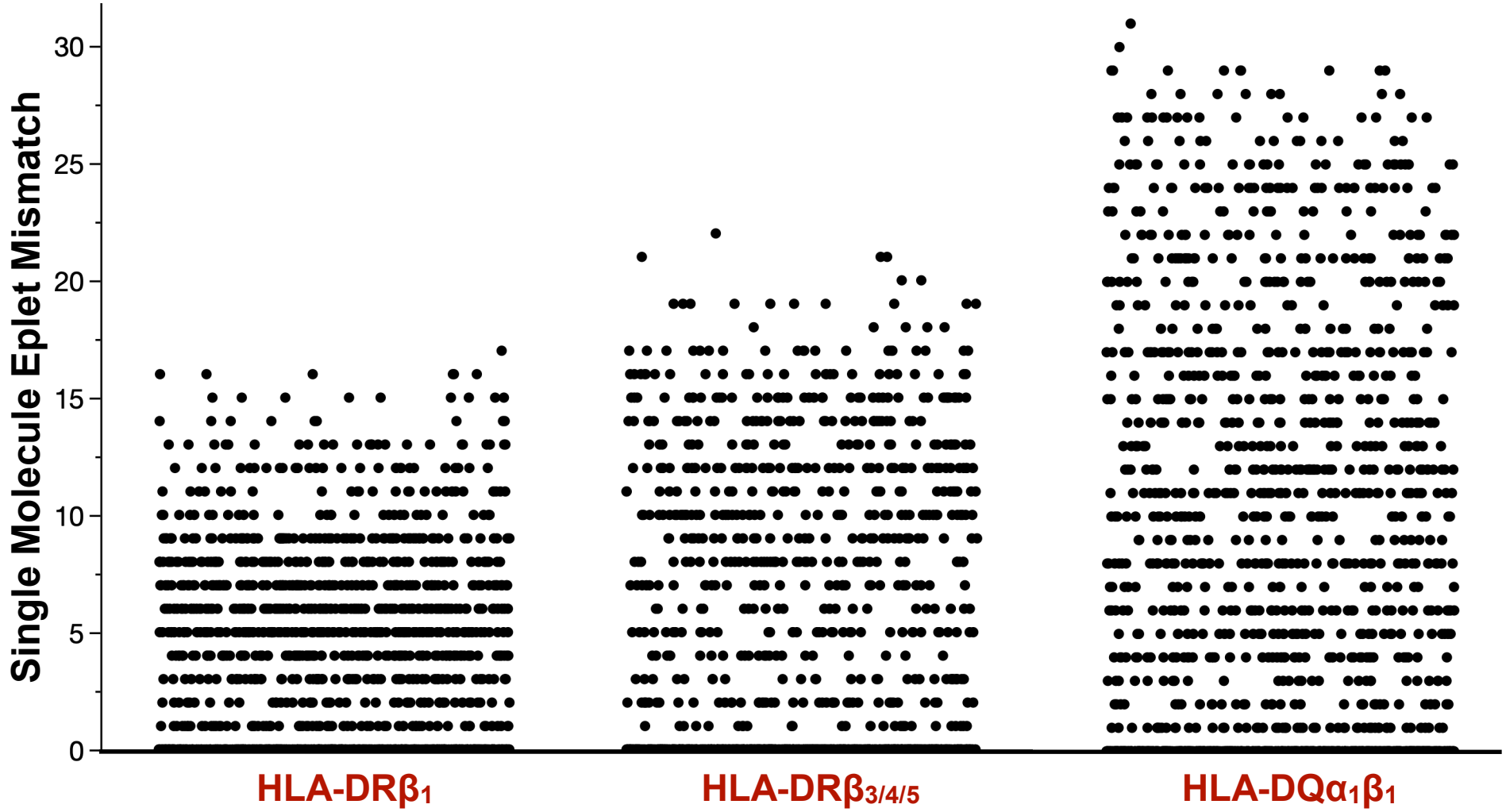
Single Molecule Molecular Mismatch

HLA Class II Single Molecule Eplet Mismatch Scores

n=784 recipients

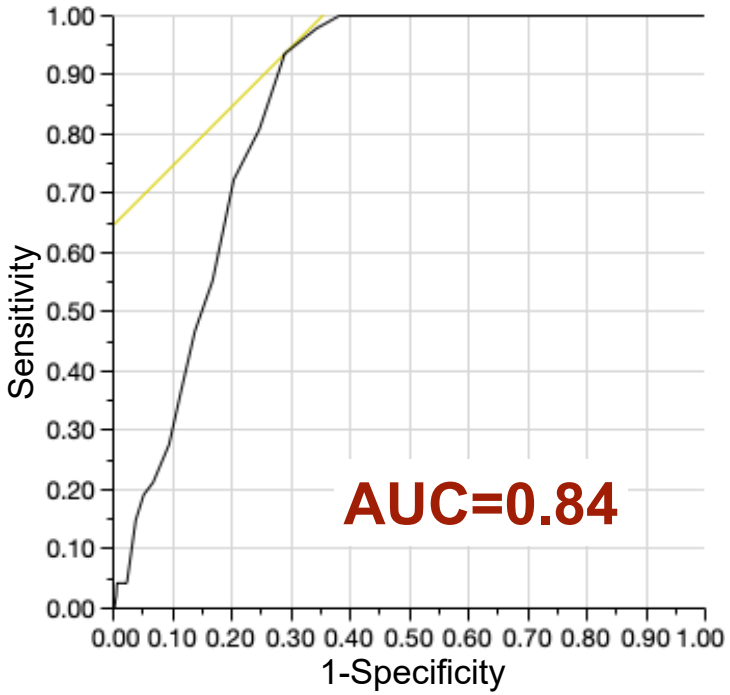
n=4,704 molecules

Which molecules result in dnDSA development post-transplant?



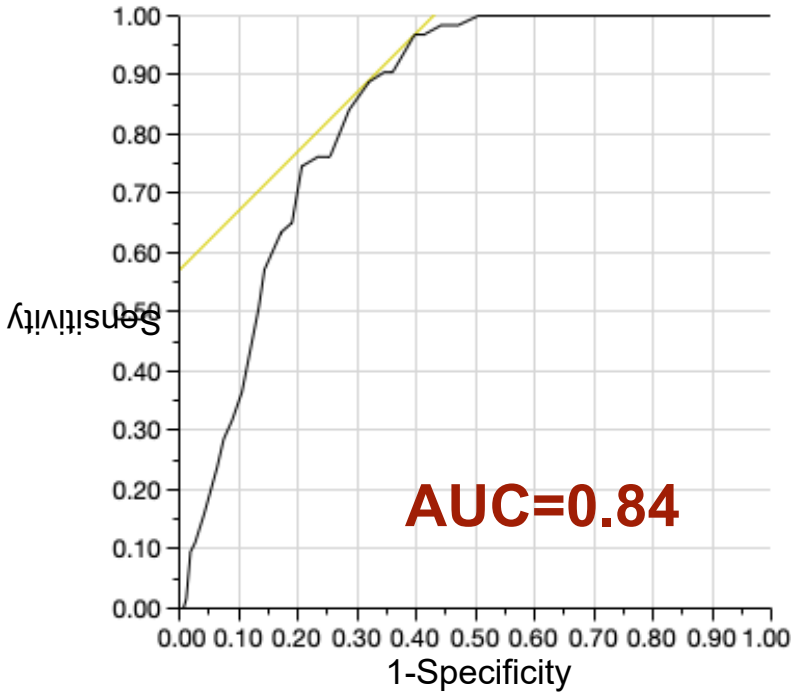
ROC Curves for dnDSA development

HLA-DR



HLA-DR ≥7

HLA-DQ

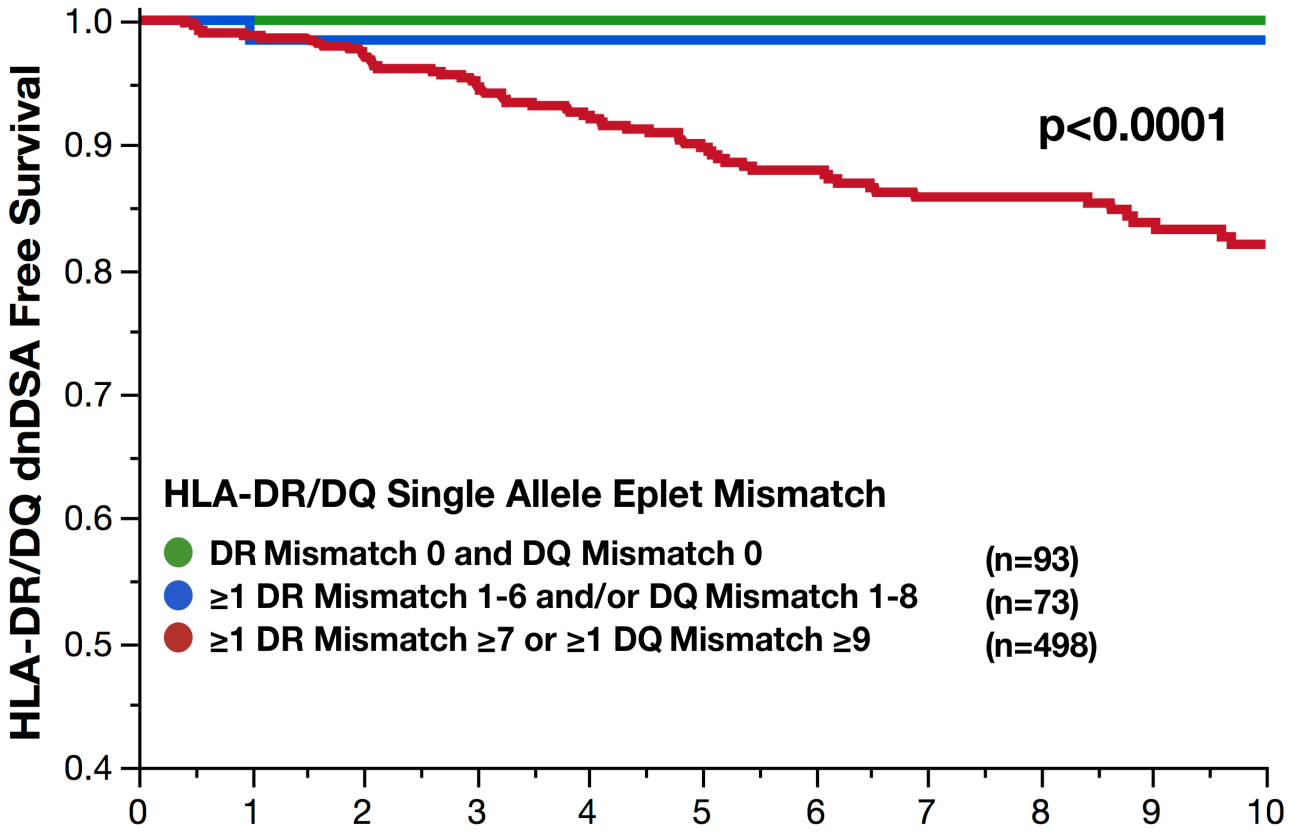


HLA-DQ ≥9

Traditional HLA
Antigen mismatch
AUC = 0.54-0.58

Wiebe et al. AJT 2019 Jun;19(6):1708-19

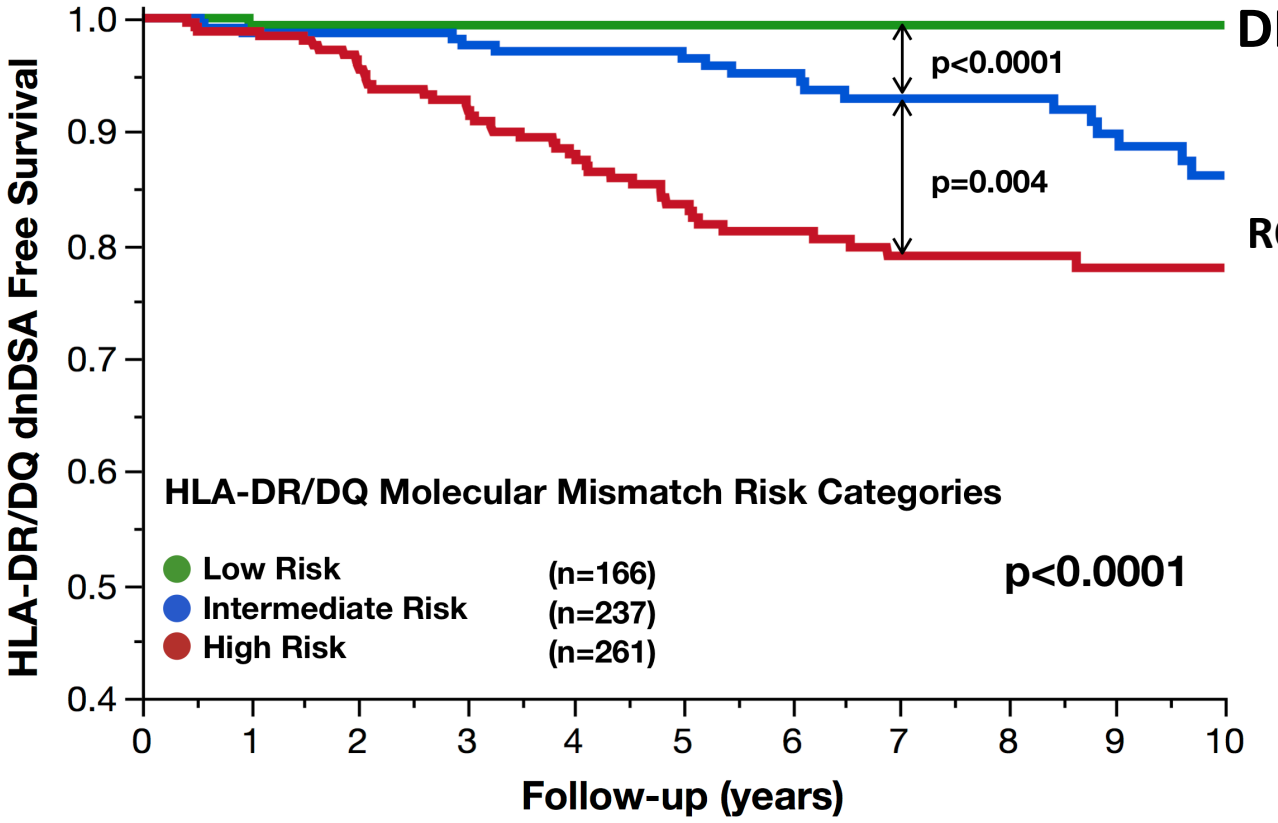
Aggregate Risk at the Level of the Patient



DR<7, DQ<9 Low Risk (25%)

Wiebe et al. AJT 2019 Jun;19(6):1708-19

Aggregate Risk at the Level of the Patient



DR<7, DQ<9 Low Risk (25%)

ROC

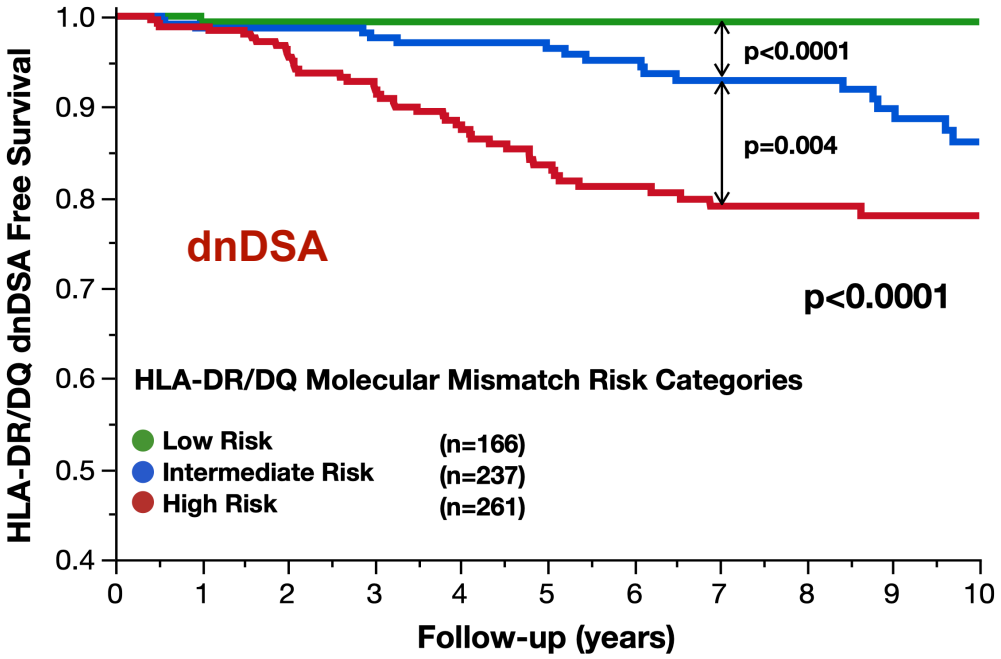
DQ<15 Intermediate Risk (35%)

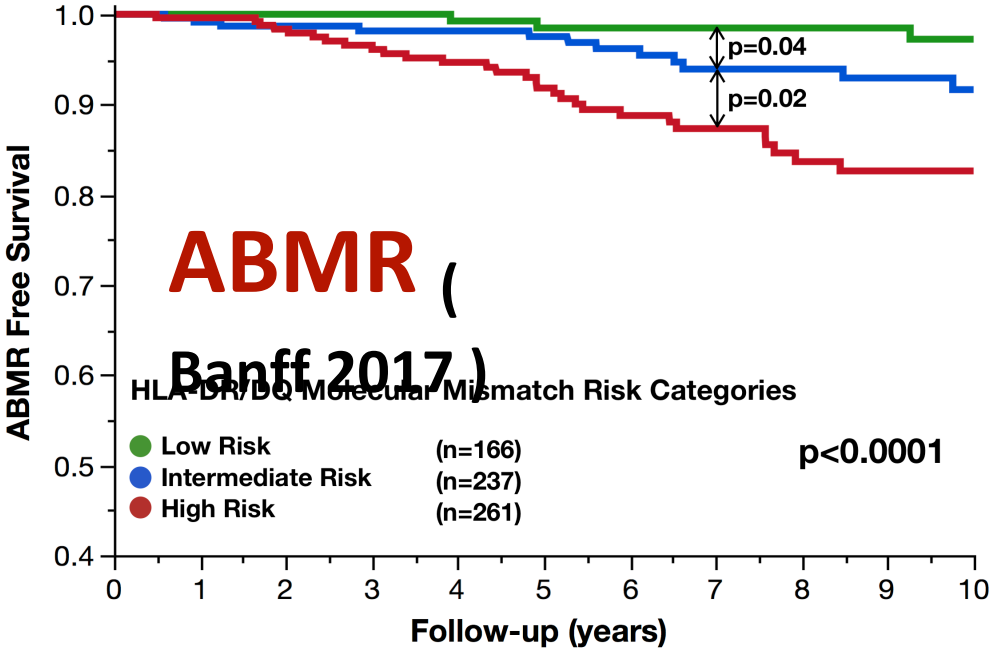
DQ<15 High Risk (40%)

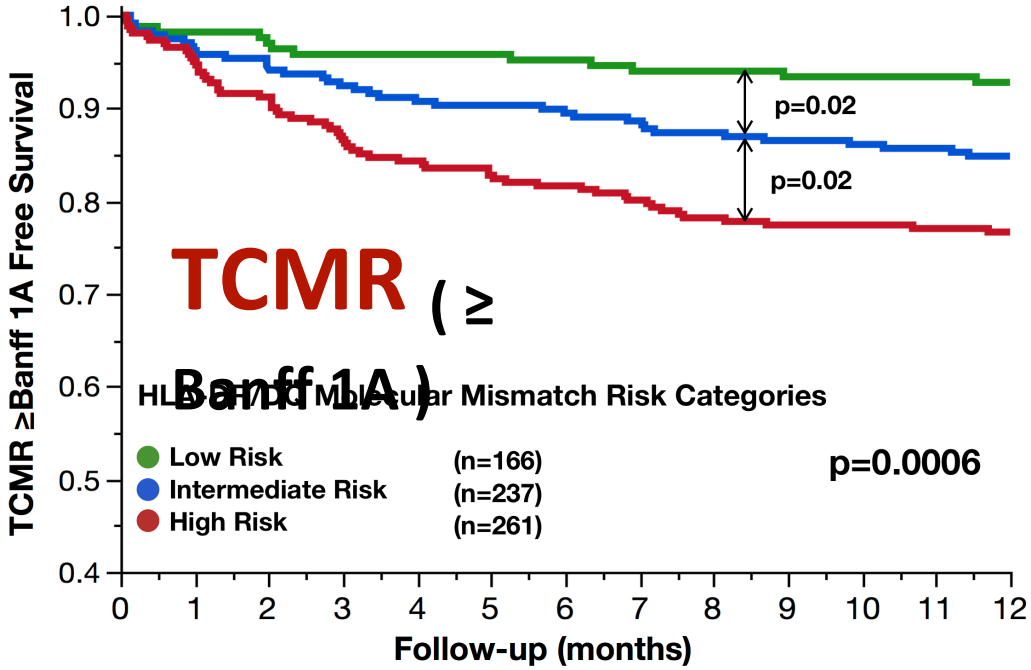
Wiebe et al. AJT 2019 Jun;19(6):1708-19

HLA Single Molecule Eplet Mismatch Alloimmune risk categorization

Wiebe et al. AJT 2019 Jun;19(6):1708-19

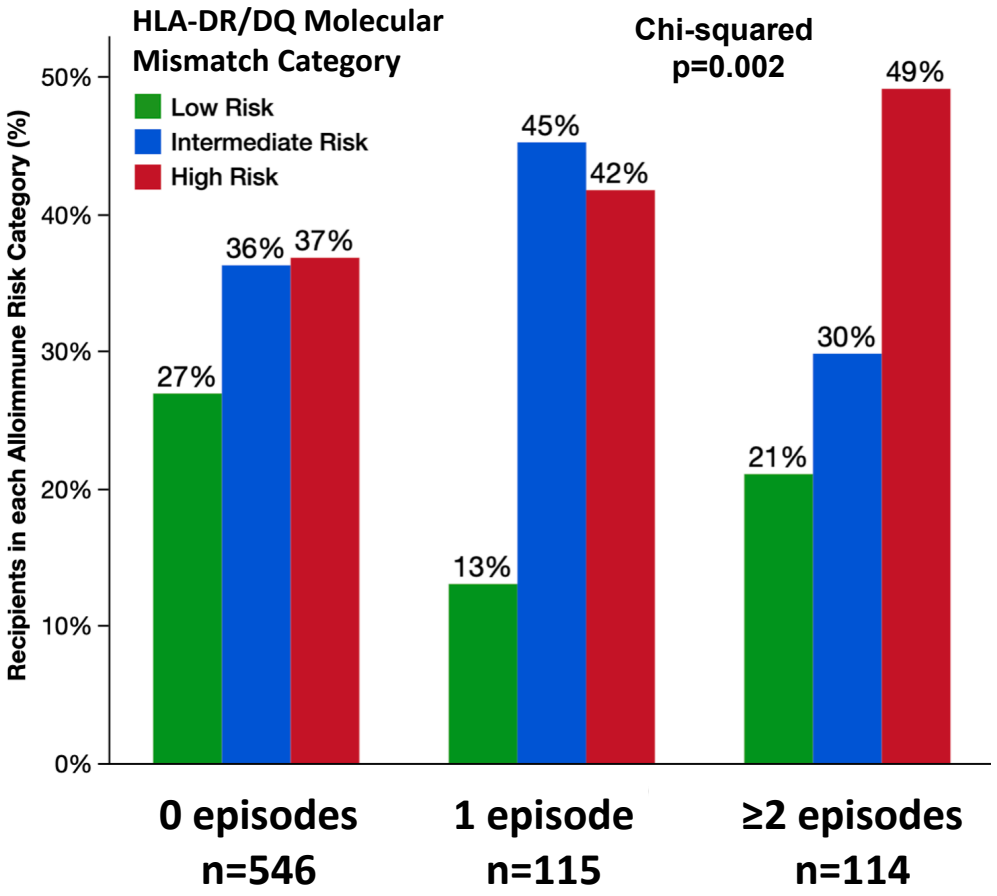






The negative impact of T-cell mediated rejection on renal allograft survival in the modern era

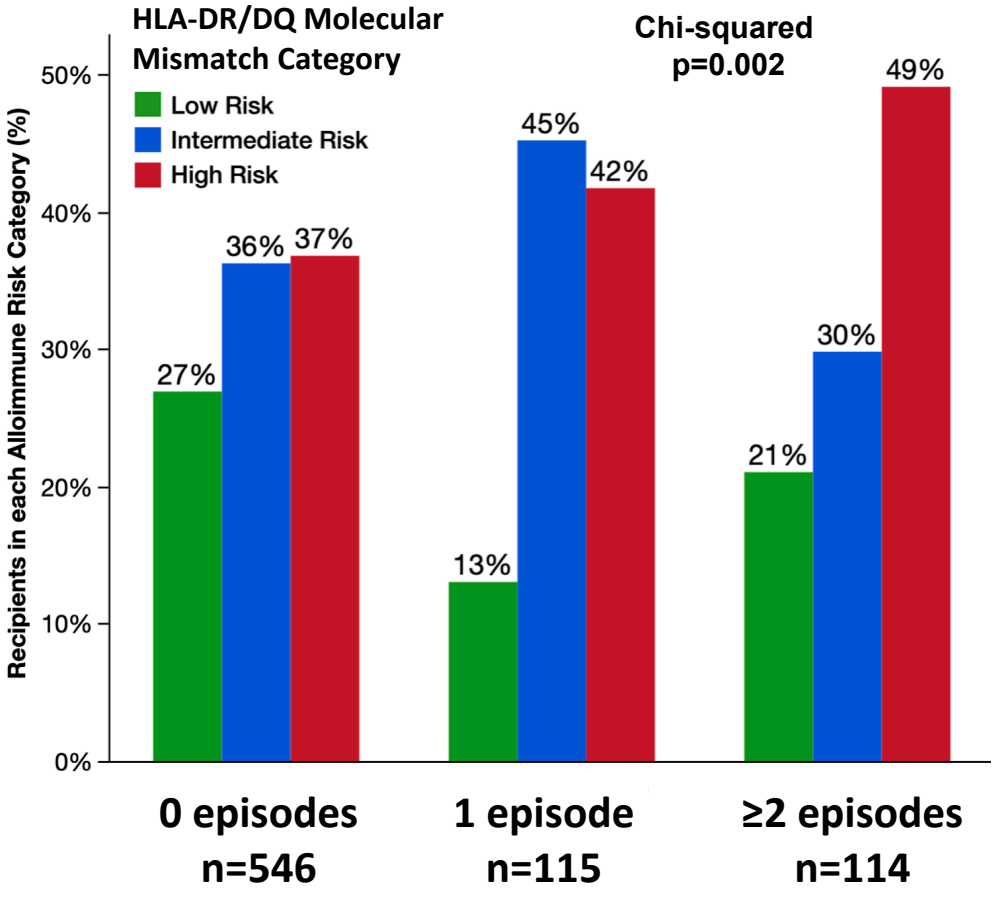
Rampersad et al. AJT (2022) 22: 761-771



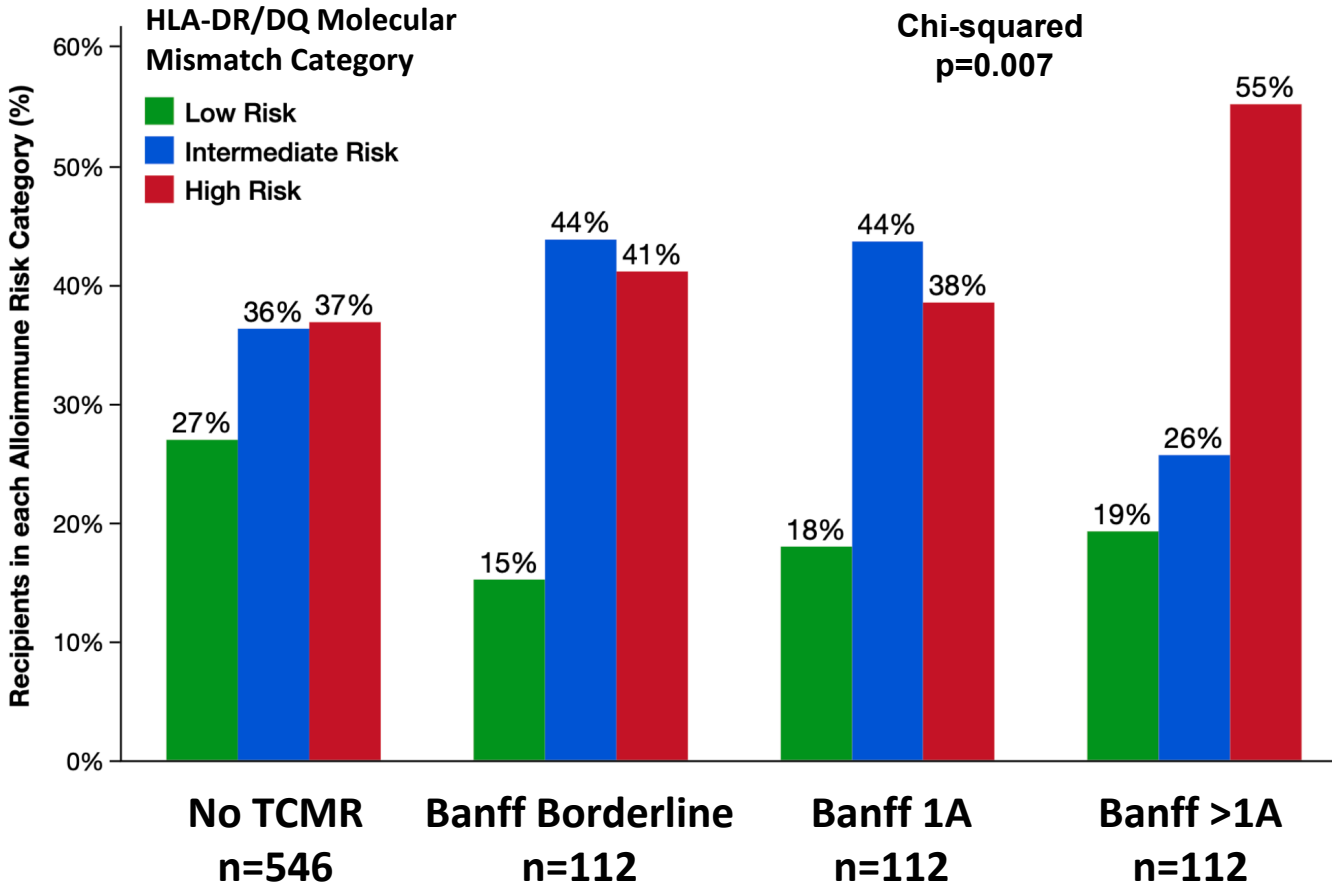
Total number of **TCMR episodes** per recipient

The negative impact of T-cell mediated rejection on renal allograft survival in the modern era

Rampersad et al. AJT 2022 Mar;22(3):761-771



Total number of **TCMR episodes** per recipient



Recipients **most severe TCMR** grade

Single Molecule Molecular Mismatch

Validation

Adequate Tacrolimus Exposure Modulates the Impact of HLA Class II Molecular Mismatch: A Validation Study in an American Cohort

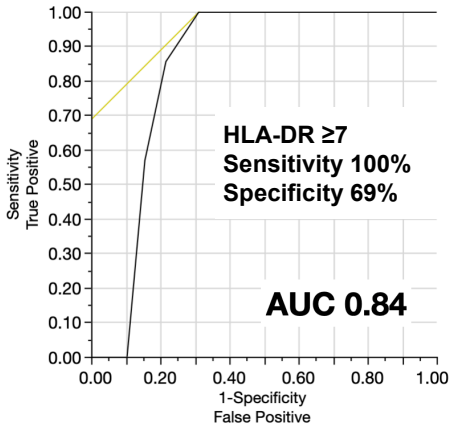
Davis et al. AJT 2020 p.322-328

n=444

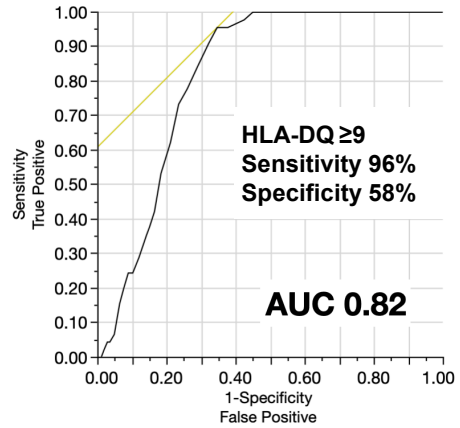
	65%	71%
	20%	1-3%
	13%	1-3%
	2%	9%
	<1%	16%

Risk Category	Manitoba	Denver
Low	25%	27%
Intermediate	35%	34%
High	40%	39%

HLA-DRβ1/3/4/5



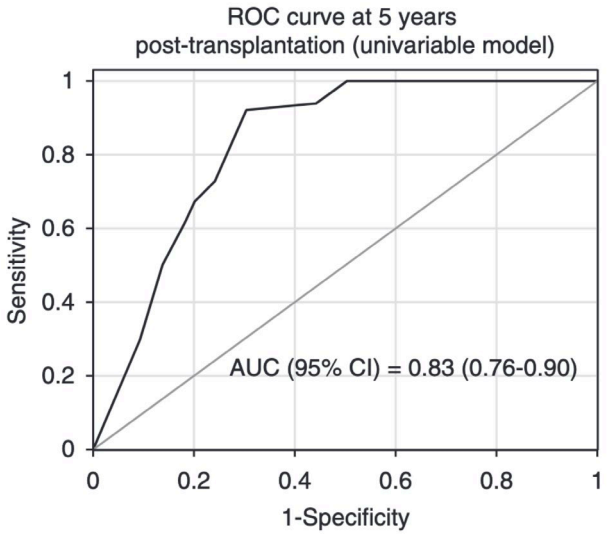
HLA-DQα/β



Multivariate Correlates of dnDSA Free Survival

	Hazard Ratio (95% CI)	p value
Recipient age (yrs)	0.96 (0.94, 0.98)	0.0001
Deceased donor	2.74 (1.47, 5.1)	0.002
Mean tacrolimus (0-12)		
<6.0 ng/ml	2.34 (1.05, 5.22)	0.04
6.0-7.9 ng/ml	1.09 (0.54, 2.18)	0.81
Alloimmune Risk Category		
Intermediate vs. Low	15.39 (2.01, 118.09)	0.009
High vs. Low	23.81 (3.17, 178.66)	0.002

Eplet Mismatch Load and *De Novo* Occurrence of Donor-Specific Anti-HLA Antibodies, Rejection, and Graft Failure after Kidney Transplantation: An Observational Cohort Study



n=926

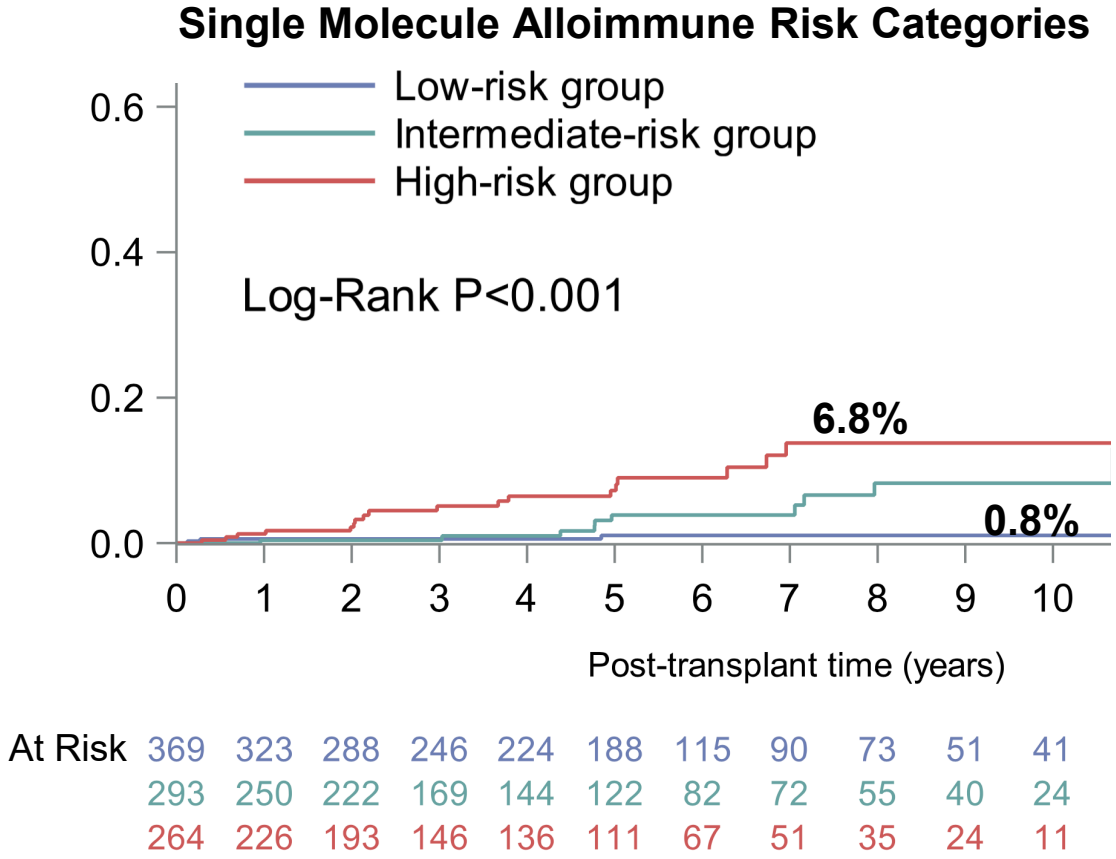
	98%
	<1%
	<1%
	<1%

Modification

analyzed

Risk Category	Manitoba	Denver	Lueven
Low	25%	27%	40%
Intermediate	35%	34%	32%
High	40%	39%	28%

eplets



Senev et al. JASN (2020) 31:2193-2204

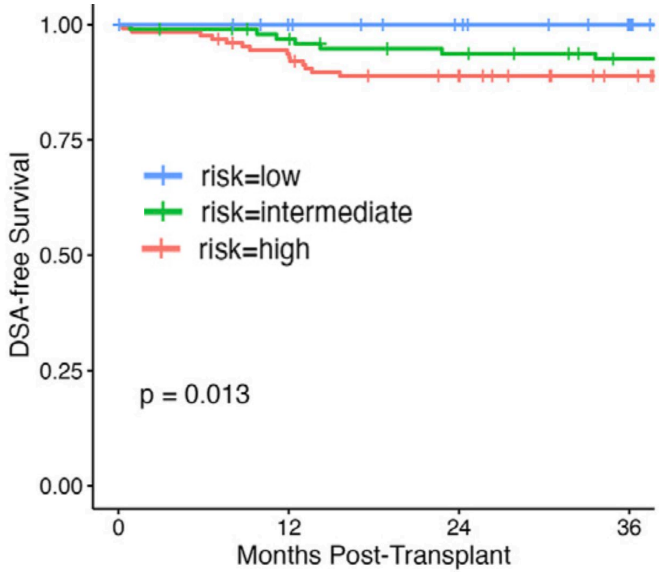
HLA-DR|DQ Molecular Mismatch Score

Prognostic Biomarker for Immunosuppressive Minimization (EMORY Cohort)

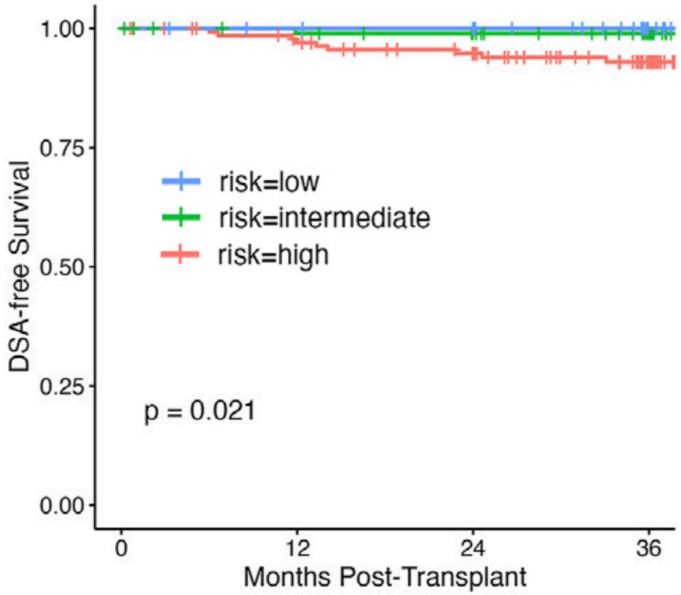
n=586

	35%
	4%
	57%
	4%

Tacrolimus Cohort



Belatacept Cohort



Risk Category	Manitoba	Denver	Emory	Lueven
Low	25%	27%	21%	40%
Intermediate	35%	34%	33%	32%
High	40%	39%	46%	28%

Johnson et al AJT (2023) In Press

Low-Risk by Single-Molecule Molecular Mismatch - Studies to date

Study	Low-Risk Group	dnDSA development
Wiebe et al., AJT (2019) 19(6):1708	166/664 (25%)	1%
Davis et al. AJT (2020); 21(1):322	119/444 (27%)	2%
Senev et al. JASN (2020) 31(9):2193	369/926 (40%)	1%
Johnson et al. (2023) in press	124/298 (21%)	0%
	778/2332 (33%)	0-2%

National Kidney Registry Living Donor Results

	0 EMM + Low EMM	Med EMM + High EMM	Totals
1 Year Kits Mailed	77	78	155
1 Year Kits Outstanding	39	42	81
1 Year Screenings Completed	38	36	74
1 Year De Novo DSA**	0	8	8
% 1 Year De Novo DSA**	0%	22%	

***confirmed by lab director, 1,000 MFI Cutoff*

To learn more about the Kidney for Life Initiative please visit the website at www.kidneyforlife.org.

https://www.kidneyregistry.org/wp-content/uploads/2022/08/nkr-outcomes-2022-Q2_v6.pdf

HLA Single Molecule Molecular Mismatch

- ☑ Fast - Can be done in 5 minutes
- ☑ Inexpensive
- ☑ Widely available
- ☑ Non-invasive
- ☑ Statistically robust
- ☑ Correlates with outcomes of interest - TCMR & ABMR
- ☑ Biologic plausibility
- ☑ Available at the time of transplant

Summary

- HLA molecular mismatch is a **more precise** way of evaluating the degree of mismatch between donors and recipients

- **Molecular Mismatch is a prognostic biomarker of:**
  - dnDSA development
  - TCMR (including Borderline TCMR and Recurrent / Persistent TCMR)
  - ABMR
- Molecular Mismatch is **independent** of recipient age and immunosuppression adequacy

Applications for HLA molecular mismatch risk assessment

- **Clinical Trials**
  - Stratification and adaptive design
  - Enrichment
- **Monitoring**
  - Identifying recipients who need more intense monitoring
    - Surveillance for DSA, histology, etc

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PANEL DISCUSSION/AUDIENCE Q&A

SESSION 5: WORKSHOP TAKEAWAYS & WRAP UP