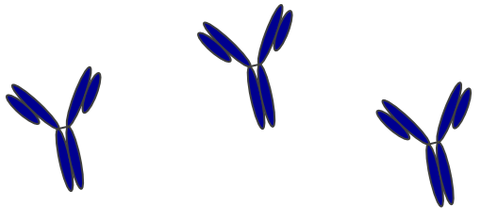
DSA Positive and then – To biopsy or not?

Banff – SCT 2017

29 March 2017



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Relevant Financial Relationship Disclosure Statement

Peter Nickerson, University of Manitoba, Winnipeg, Canada

Consultant for Astellas, GSK, Novartis and Vitaeris

AND

My presentation does include discussion of off-label or investigational use of drugs

Index Case – 2008 implemented DSA screening post-transplant

37 yr old Caucasian male, ESRD due to GN, on HD x 6 yrs

2006 Deceased Donor Transplant [Donor age 26, KDPI 10]

Cross-match **Negative (no pre-transplant donor specific Ab)**

HLA mismatch **0**A **2**B **2**DR **2**DQ

Tacrolimus (**target C_0 ≥ $10_{0\text{-}3\ \text{months}}$ $8_{4\text{-}6\ \text{months}}$ $6_{6+\ \text{months}}$** ng/ml)

MMF 1 g bid, Prednisone tapered to 5 mg qd

First Year Clinical Course

No DGF**, No** Acute Rejection, **No** BKV or CMV viremia

Surveillance Biopsy (6 months) – **no acute inflammation**

$eGFR_{CKD\text{-}EPI}$ **74 [66 – 82]** ml/min/1.73m^2

37 yr old Caucasian male, 1st SCD kidney transplant

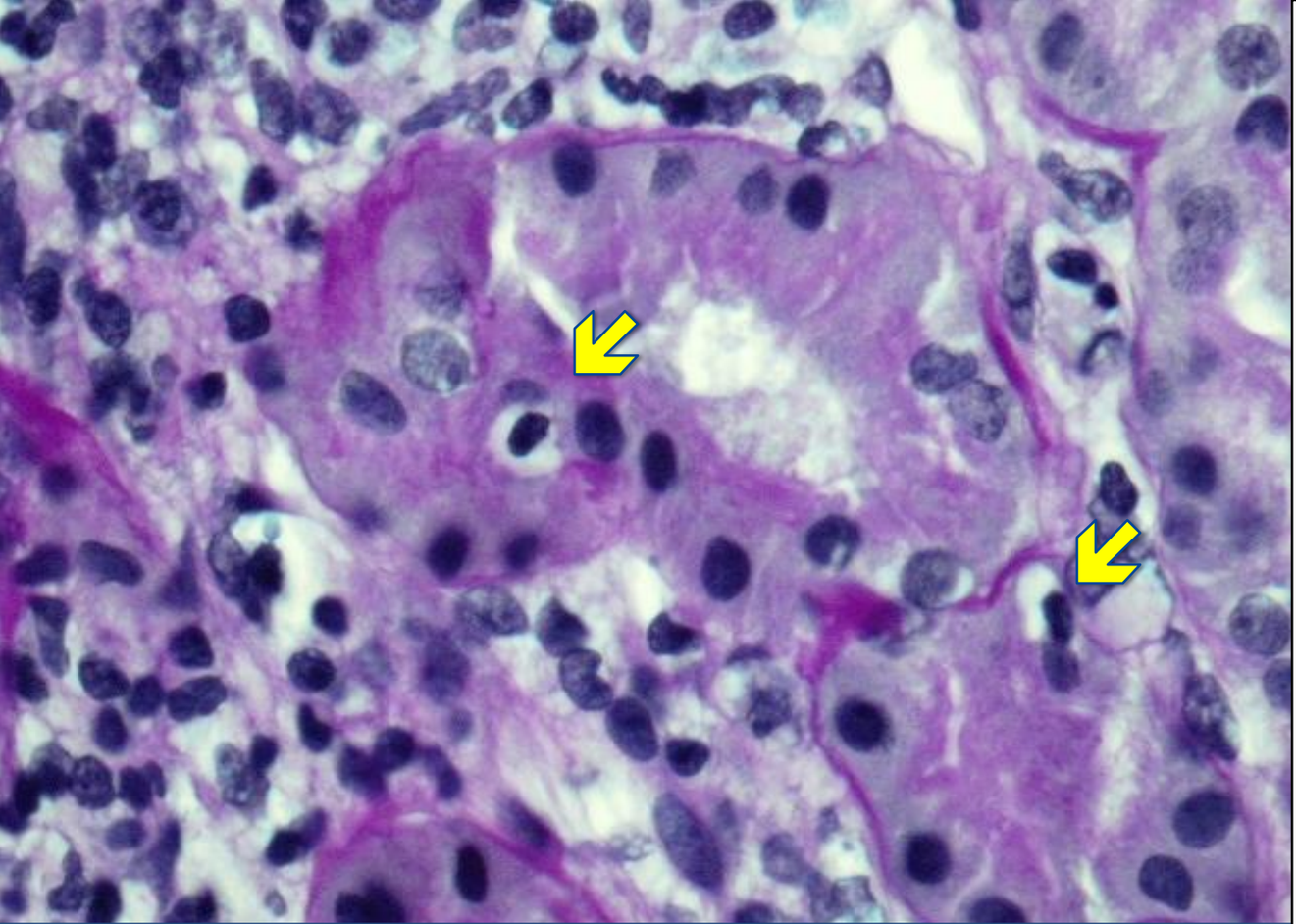
24 month Serum Screen → *de novo* Class II DSA (DQ4)

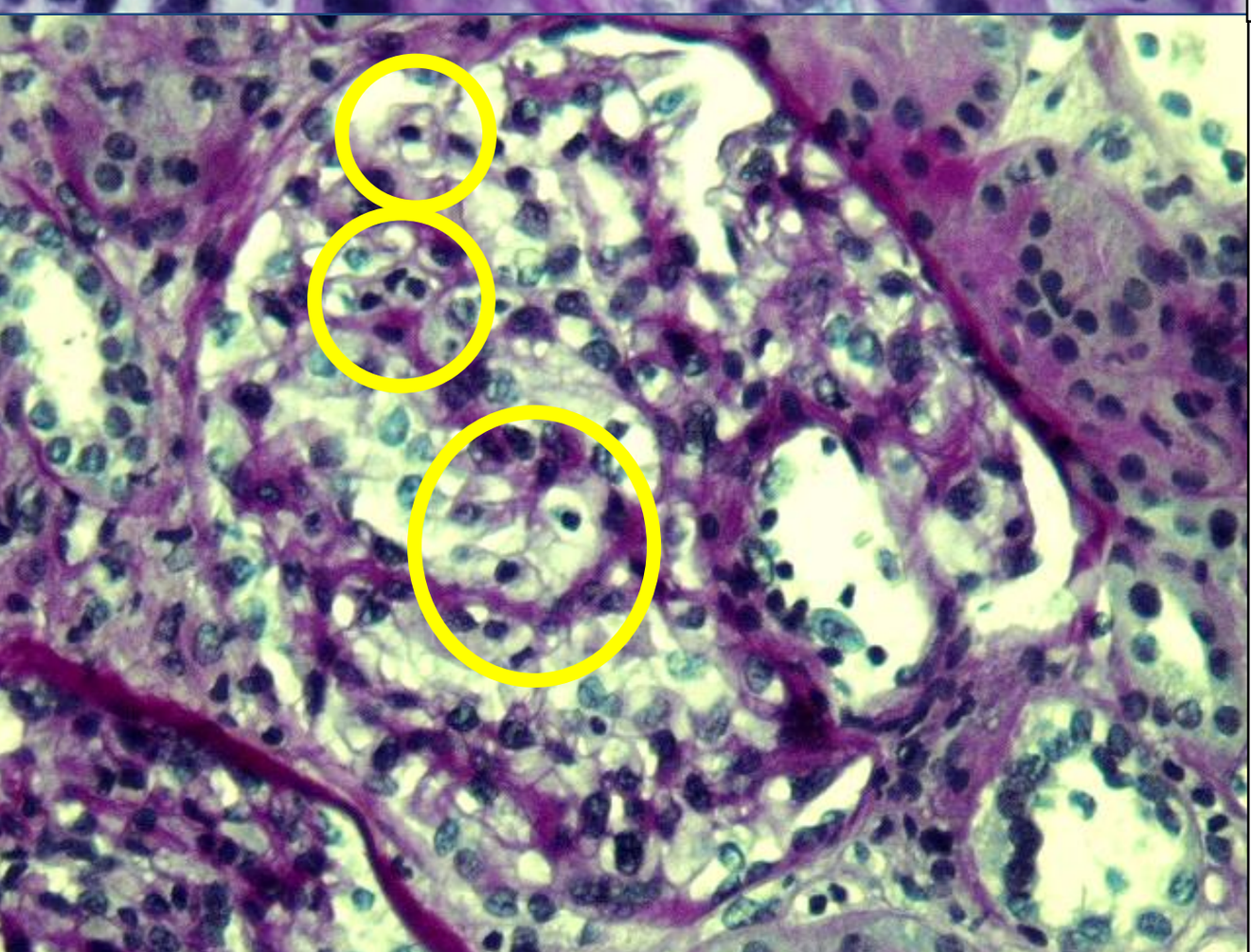
Serum Screen at 1, 2, 3, 6, 12, and 18 months **negative for DSA**

Tacrolimus (C_0=**6.4** ng/ml, nadir **5.0** at 18 mo), MMF 750 mg bid, Pred 5 mg qd

Creatinine **108** umol/L (**1.2** mg/dL), Proteinuria **<150 mg/24hr**

$eGFR_{CKD\text{-}EPI}$ **74** ml/min/1.73m^2





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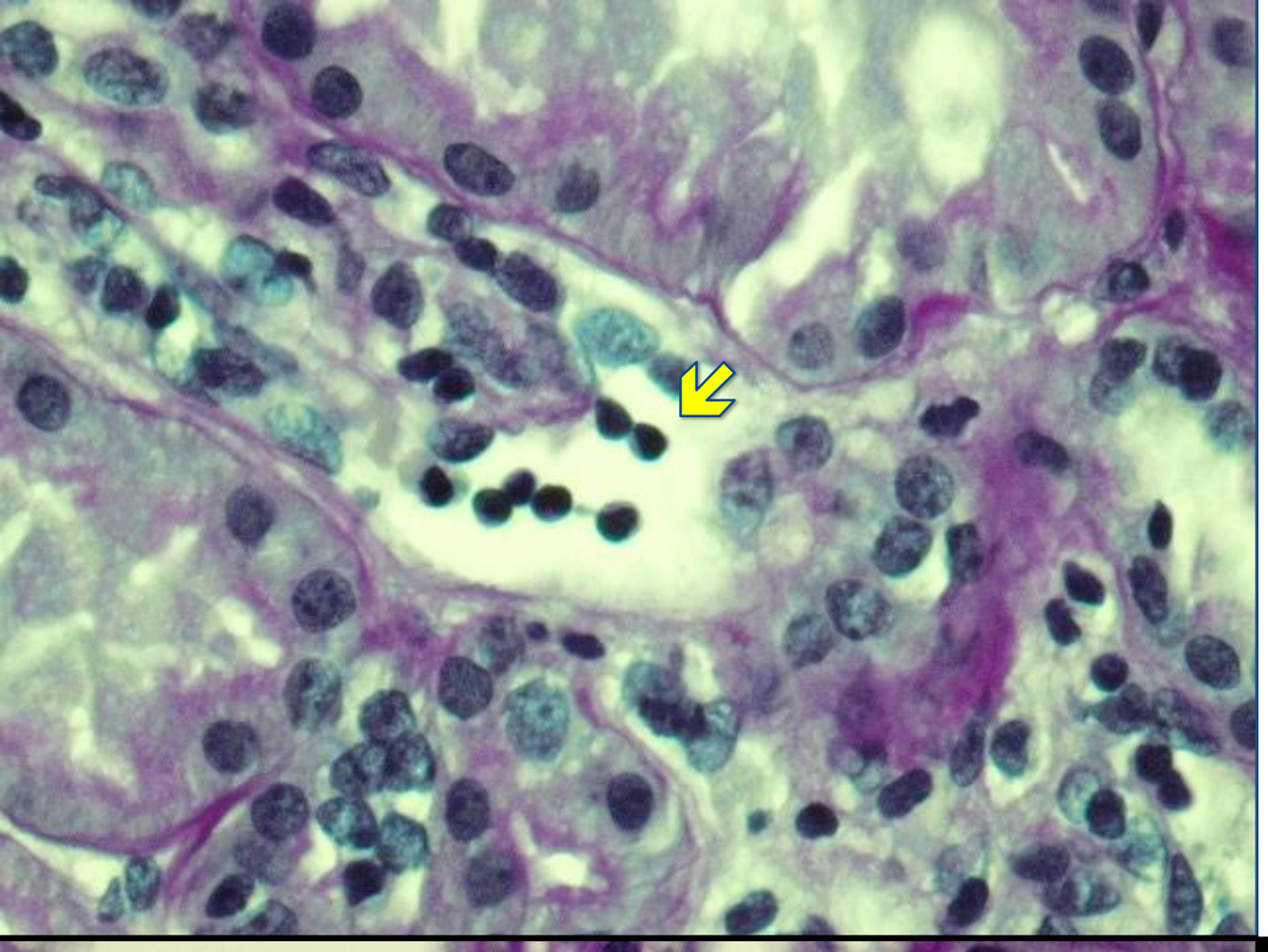
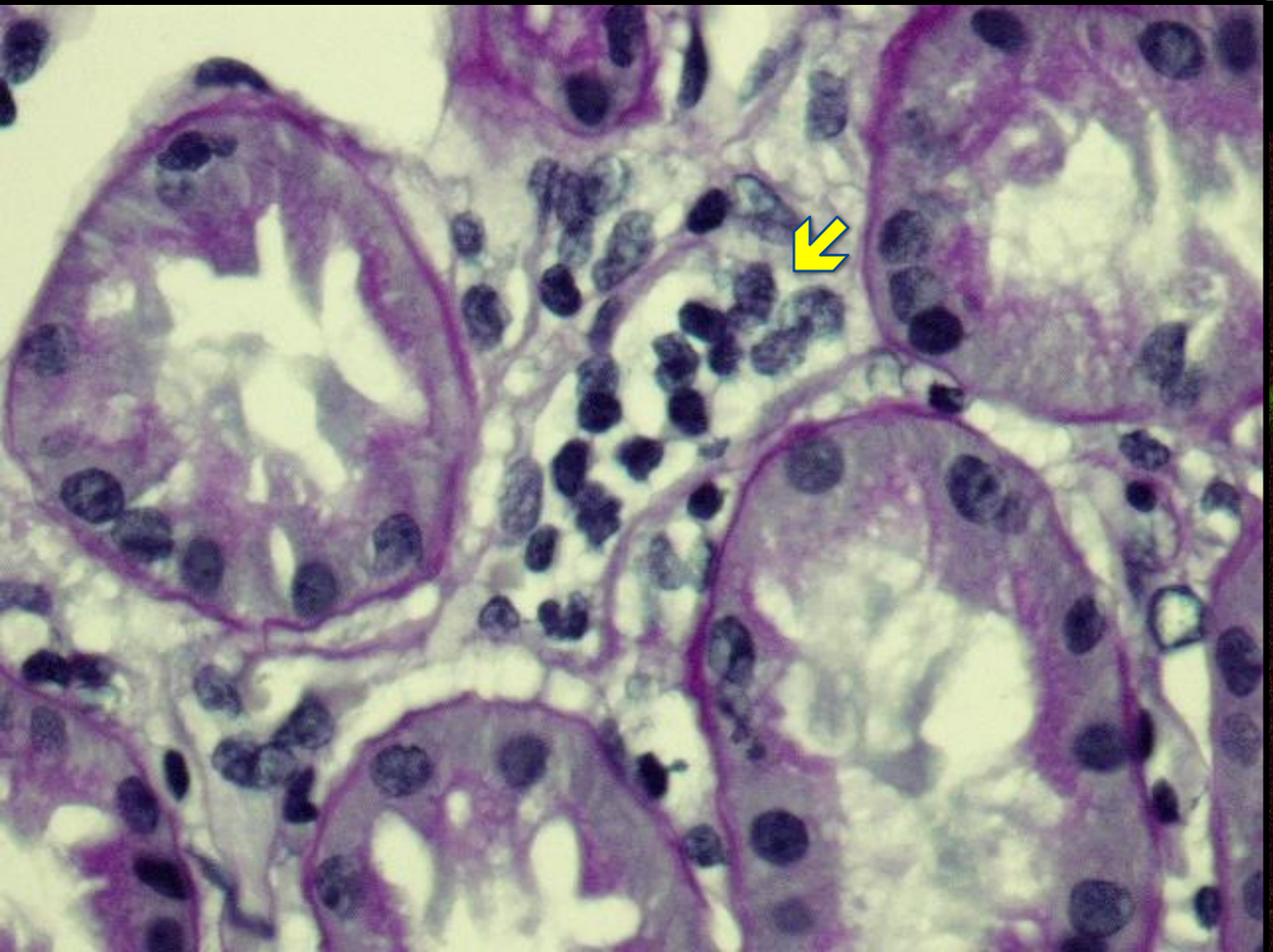
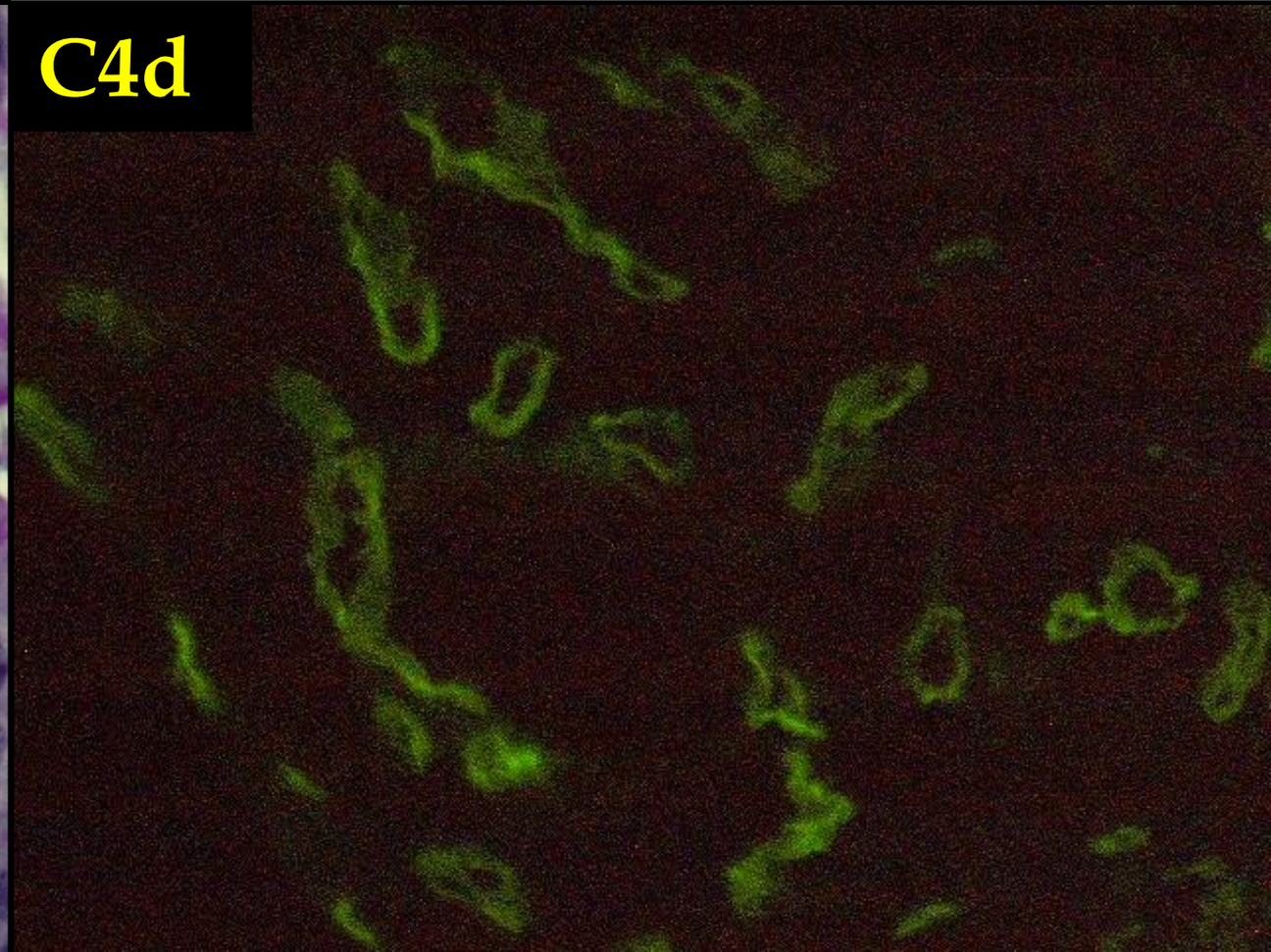
Mild lymphocytic tubulitis (i1 t1 ci0 ct1)

Subclinical Borderline TCMR (Banff 2007)

Mild Tx Glomerulitis (**g1 cg0**)
with mononuclear cells







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Peritubular Capillaritis (ptc2):

Diffuse moderate mononuclear inflammatory cell accumulation

PTCs diffuse C4d +

"Subclinical ABMR" (Banff 2013)

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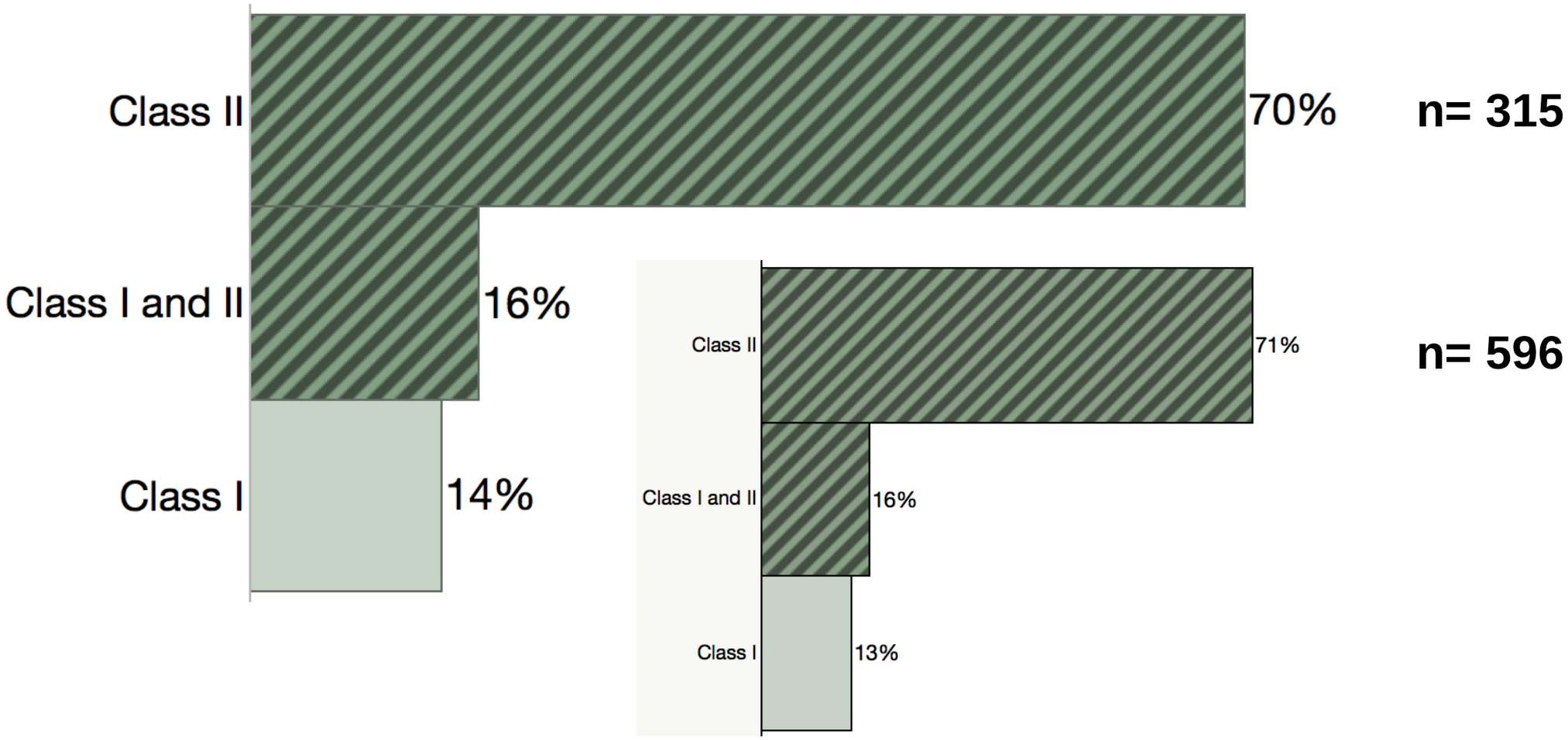
De novo DSA and Outcomes

Etiology and Natural History

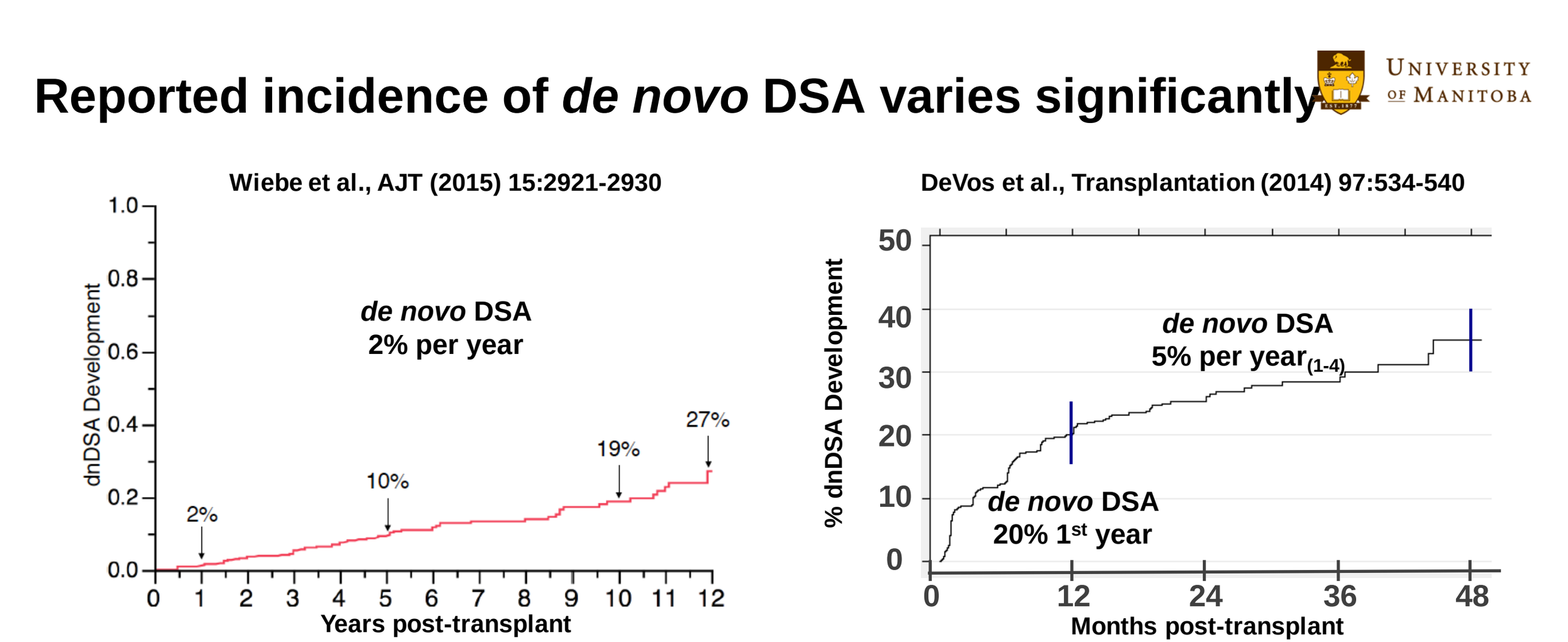
Class II is the dominant de novo DSA



Only 1 patient with an isolated Class I dnDSA has resulted in graft failure, out of 596 transplants

Wiebe et al., Am Journal Transplant (2012) 12: 1157

Reported incidence of *de novo* DSA varies significantly



Ref.	1st Tx	Defn to Rule out Pre-Tx DSA	"*de novo*" DSA		
			1st Mo	1st Yr	>1st Yr
Cooper	n.a.	FCXM	15.6%	27.0%	0% yr 2
DeVos	93%	>2000 MFI	8.0%	20.0%	5.0%/yr
Heilman	91%	>1000 MFI	8.2%	17.6%	n.a.
Everly	100%	>1000 MFI	3.0%	11.0%	2.3%/yr
Wiebe	95%	>500 MFI	0.0%	2.0%	2.0%/yr

TCMR correlates with subsequent de novo DSA / ABMR

Early clinical TCMR (<1yr) linked to development of *de novo* DSA / ABMR

Hourmant et al., JASN (2005) 16:2804-2812
Wiebe et al., AJT (2012) 12:1157-1167
Liefeldt et al., AJT (2012) 12:1192-1198
El Ters et al., AJT (2013) 13:2334-2341
Chemouny et al., Transplantation (2015) 99:965-972
Yamamoto et al., Transplantation (2015) 100:2194-2202
Schinstock et al., AJT (2017) ePub

Early Subclinical tubulointerstitial inflammation

Linked to → ***de novo* DSA**

Wiebe et al., AJT (2012) 12:1157-1167
El Ters et al., AJT (2013) 13:2334-2341
Garcia-Carro et al., Transplantation (2016) ePub

Linked to → **Chronic Antibody-Mediated Rejection**

(TG, PTC BM multi-layering; C4d+; DSA)

Moreso et al., Transplantation (2012) 93:41-46

Patients with de novo DSA have early (0-6 month) TCMR with more intense PTC inflammation

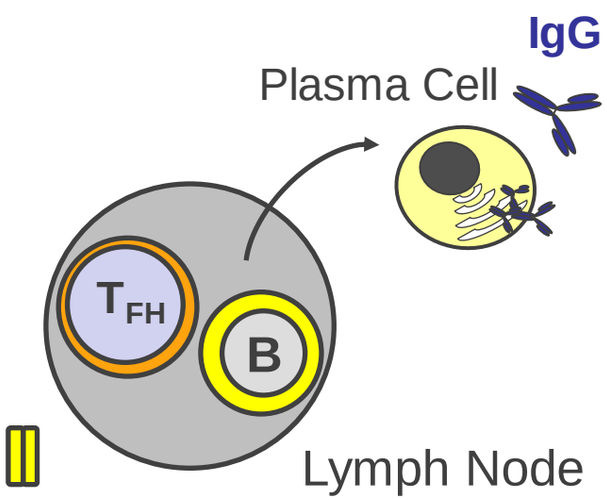
Wiebe et al. AJT (2012) 12:1157

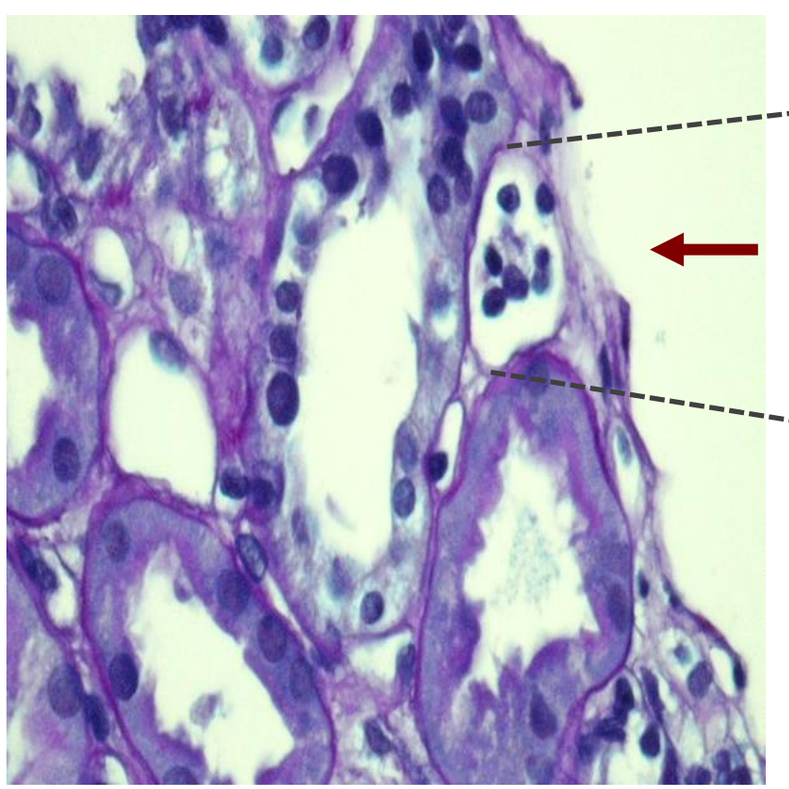
TCMR PTC score

2.0 *de novo* DSA

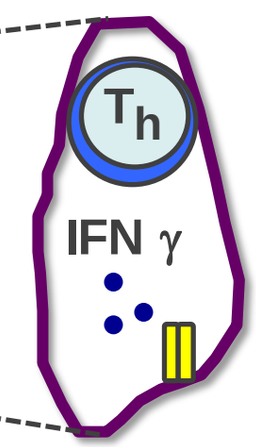
1.0 No DSA

p <0.05



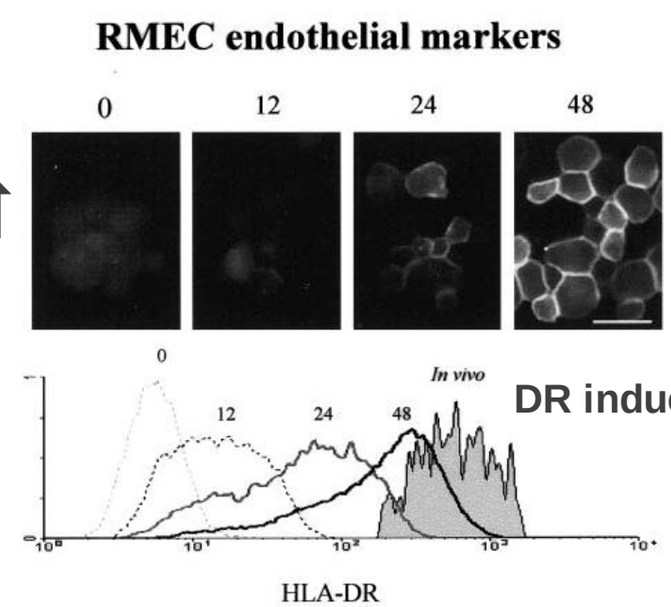


PTC 2



Shed MHC II

MHC II

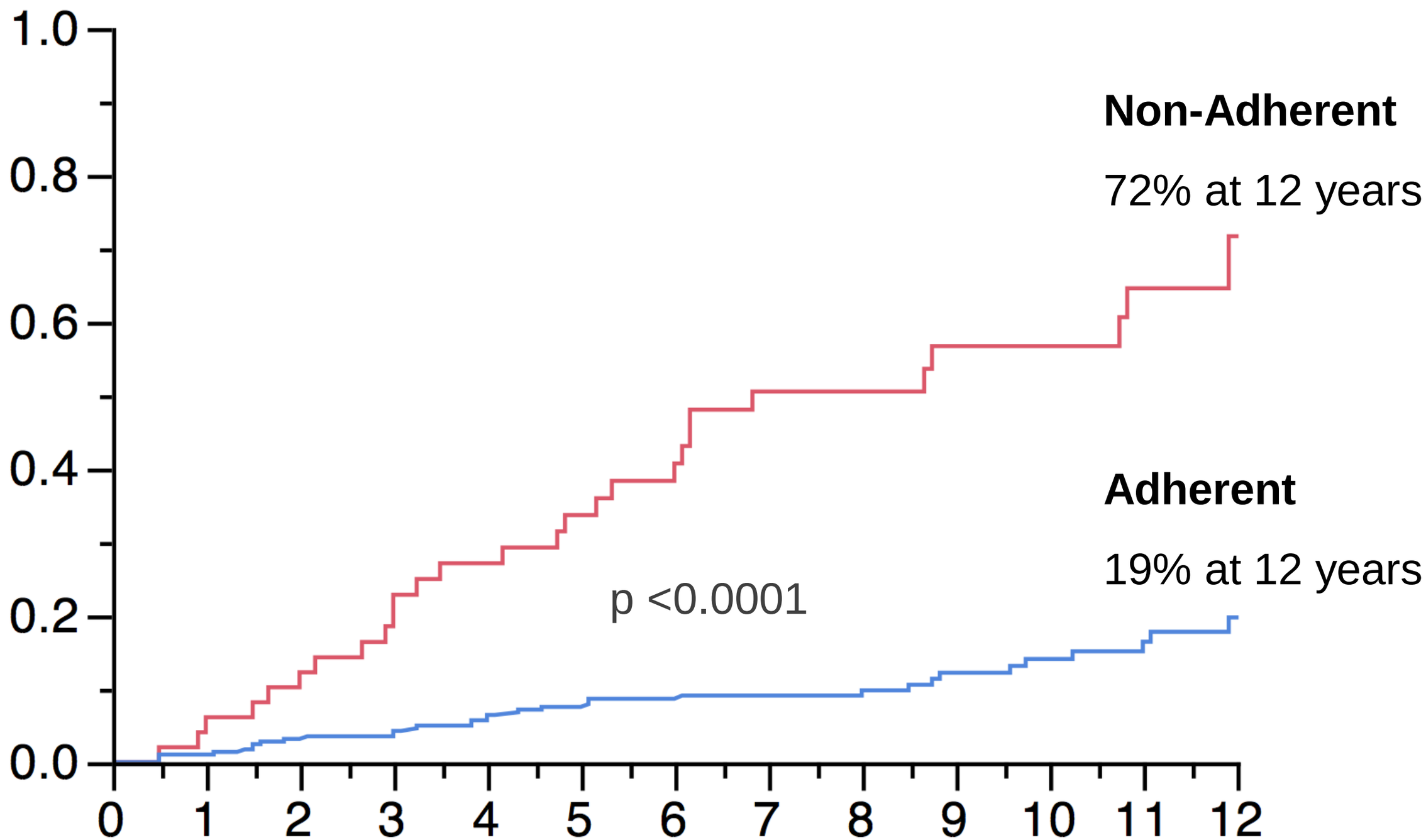


DR induction by IFN γ

Gibson et al. AJT (2008) 8:819

Muczynski et al. JASN (2003) 14:1336

Non-Adherence is a major risk factor for *de novo* DSA



Wiebe et al., AJT (2015) 15: 2921-2930

Independent Correlates for *de novo* DSA

de novo DR DSA	p value	OR
DR$\beta_{1/3/4/5}$ MM	0.002	2.14†
TCMR preceding dnDSA	0.002	2.38†
Non-Adherence	0.002	5.30

† per unit change

de novo DQ DSA	p value	OR
DQ$\alpha\beta$ MM	0.01	1.62†
Recipient Age	0.03	0.97†
Non-Adherence	<0.0001	9.53

Wiebe et al AJT 2012; 12: 1157-1167

De Novo DSA and Graft Dysfunction

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Estimated eGFR Rate of Decline (ml/min/1.73m^2/year)

	Adult Recipients		
	Stable	**dnDSA**	**p value**
Pre dnDSA	-0.43 (3.55)	-1.76 (3.60)	0.0046
Post dnDSA	n/a	-2.96 (3.52)	n/a
	n/a	<0.0001	

	Subclinical-dnDSA	Clinical-dnDSA	p value
Pre dnDSA	-1.89 (4.29)	-1.63 (4.79)	0.8404
Post dnDSA	-2.74 (4.29)	-2.63 (4.92)	0.9322
	<0.0001	0.0003	

Rowe et al. J. Genontology (1976)

Healthy Men (n=293)

Age (Years)	eGFR decline (ml/min/1.73m^2/year)
17-84	**-0.90 ± 3.08**
25-34	**-1.09 ± 3.13**
35-44	**-0.11 ± 2.88**
45-54	**-0.73 ± 2.92**

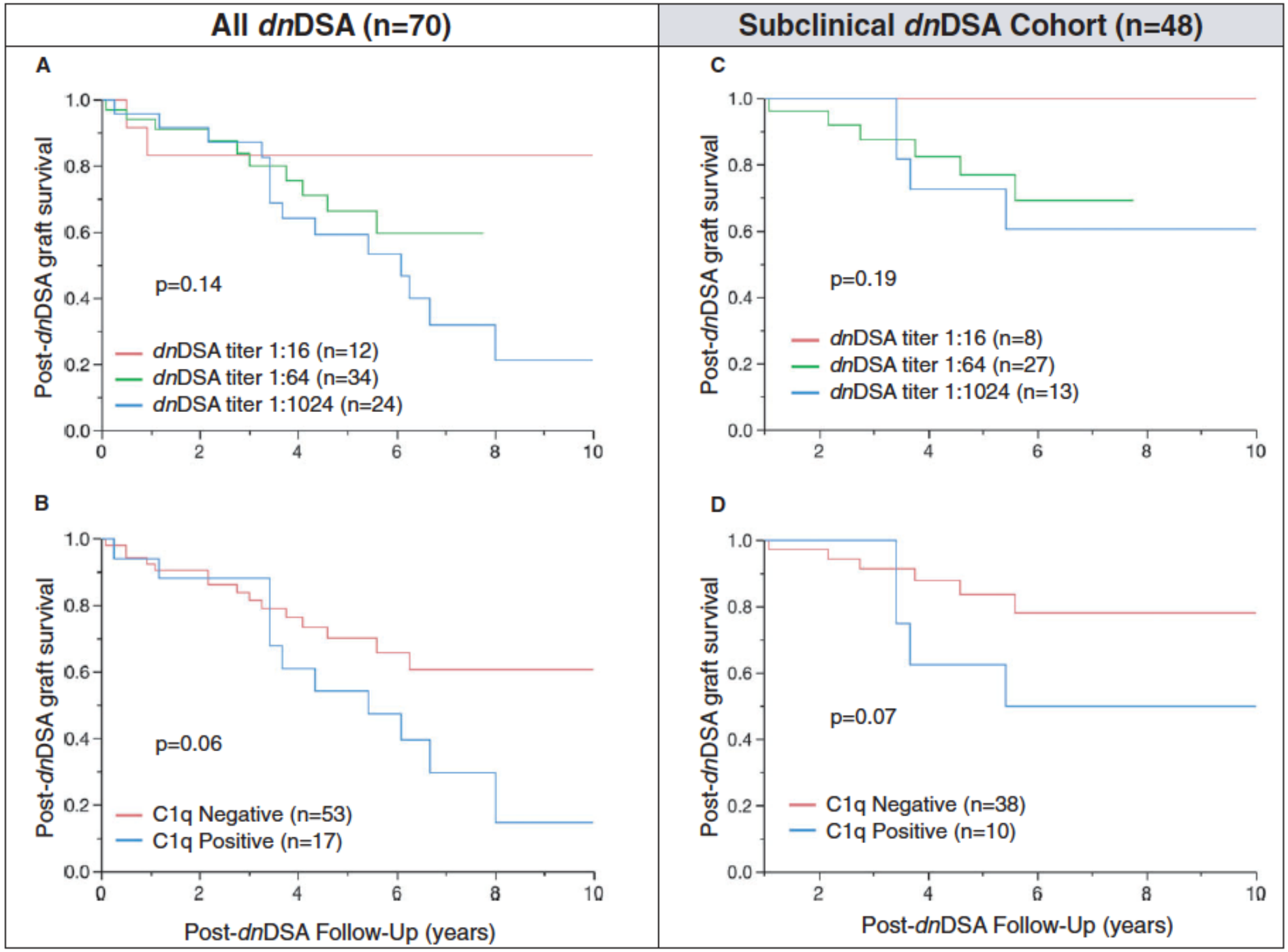
For clinical dnDSA the slope does not reflect the **step-wise eGFR decline** of **-6.38 ± 7.71 ml/min/1.73m^2** seen at the onset of clinical dnDSA

For each 1.0 ml/min/1.73m^2 decrease in eGFR at 3 years post-subclinical dnDSA onset, the risk of graft loss increased (HR 1.06 [1.03-1.09], p<0.0001)

Wiebe et al., AJT (2015) 15: 2921-2930

Clinical/Serologic Predictors for Graft Loss at DSA onset

Consecutive Adult and Pediatric Kidney Transplants (n=508, 1999 to 2012)



Wiebe et al., AJT (2017) 17: 703-711

Clinical/Serologic Predictors for Graft Loss at DSA onset

Consecutive Adult and Pediatric Kidney Transplants (n=508, 1999 to 2012)

Multivariate Model (n=70, 27 events)*		Hazard Ratio	p value
A)	C1q positive *dn*DSA	1.06 (0.5-2.4)	0.88
	Non-Adherence	4.22 (1.4-14.4)	<0.01
	Clinical vs. Subclinical Phenotype	2.38 (1.0-6.9)	0.05
B)	*dn*DSA Titer ≥1:64	1.41 (0.4-9.4)	0.65
	Non-Adherence	3.97 (1.2-14.0)	<0.01
	Clinical vs. Subclinical Phenotype	2.51 (1.0-6.9)	0.04
C)	*dn*DSA Titer ≥1:1024	0.57 (0.2-1.4)	0.23
	Non-Adherence	5.17 (1.6-18.0)	<0.01
	Clinical vs. Subclinical Phenotype	3.04 (1.2-8.6)	0.02

Wiebe et al., AJT (2017) 17: 703-711

At onset of de novo DSA, 76% meet ABMR criteria (Banff 2013)

Banff Grade	0	1	2	3
g	55%	32%	13%	0%
i	28%	24%	24%	24%
t	39%	32%	11%	18%
v	94%	3%	0%	3%
ptc	24%	10%	45%	21%
C4d	52% C4d positive			
cg	87%	8%	5%	0%
ci	29%	37%	19%	5%
ct	11%	53%	26%	10%
cv	40%	47%	13%	0%

TCMR (Banff 2007) common (91% with ABMR)

- **32% Borderline**
- **29% ≥ Grade 1**

Only 18% have no TCMR or ABMR

Transplant glomerulopathy uncommon

IFTA common

Wiebe et al., AJT (2015) 15: 2921-2930

Biopsy Predictors for Graft Loss at DSA onset

Consecutive Adult and Pediatric Kidney Transplants (n=508, 1999 to 2012)

76% ABMR$_{(Banff\ 2013)}$ at biopsy for *de novo* DSA

			Univariate		Multivariate	
B. Banff Histologic Predictors‡ (n=38)						
g	(55%, 32%, 13%, 0%)		1.53 (0.8-2.9)	0.2015	-	
i	(28%, 24%, 24%, 24%)		1.77 (1.2-2.9)	0.0083	-	
t	(39%, 32%, 11%, 18%)	**Tubulitis**	2.73 (1.6-5.0)	0.0002	3.01 (1.7-5.6)*	<0.0001
v	(94%, 3%, 0%, 3%)		0.95 (0.1-2.1)	0.9240	-	
ptc	(24%, 10%, 45%, 21%)		1.11 (0.7-0.9)	0.6663	-	
C4d	(52% C4d positive)		1.33 (0.4-4.4)	0.6203	-	
cg	(87%, 8%, 5%, 0%)	**CG**	2.14 (1.0-4.1)	0.0575	3.01 (1.2-7.1)*	0.0221
ci	(29%, 37%, 19%, 5%)		1.38 (0.8-2.5)	0.2735	-	
ct	(11%, 53%, 26%, 10%)		1.36 (0.8-2.4)	0.2840	-	
cv	(40%, 47%, 13%, 0%)		1.11 (0.6-2.1)	0.7434	-	

Banff cg score increases 1 grade per 3 years of post *de novo* DSA follow-up

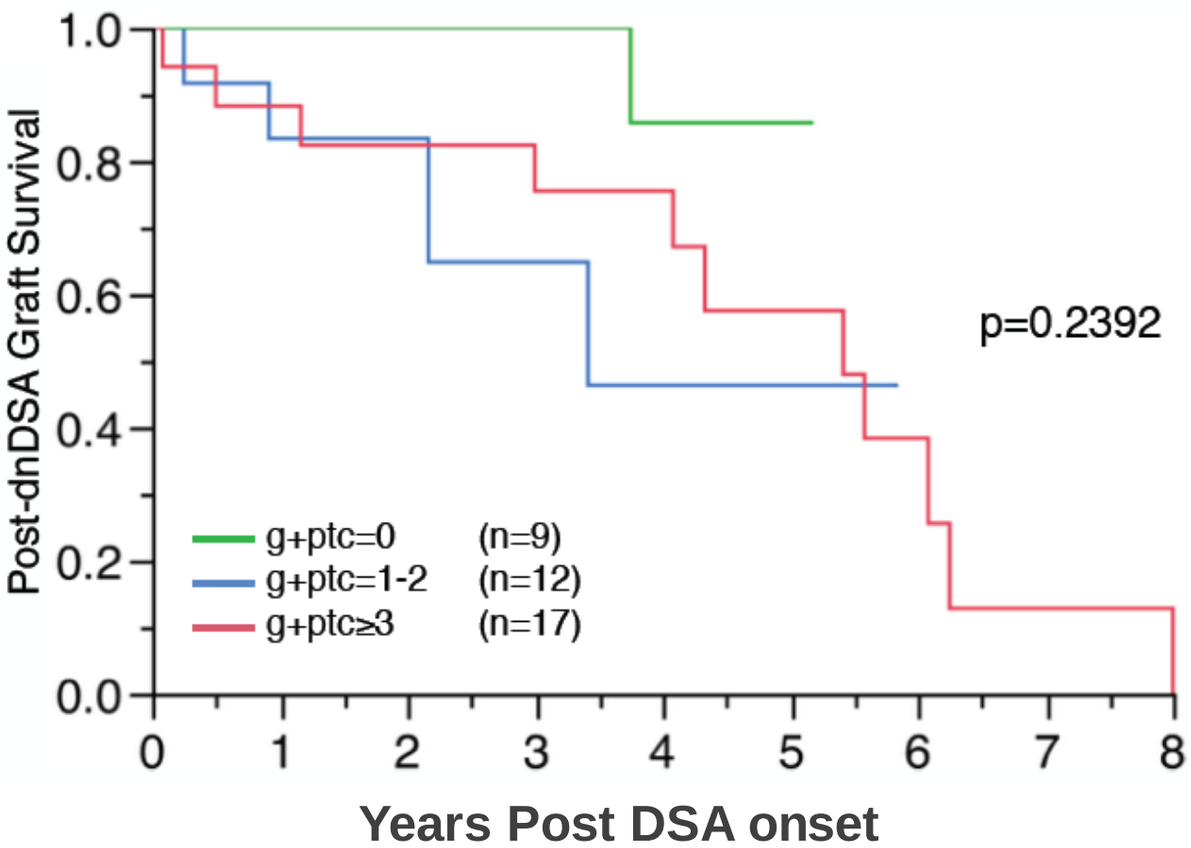
(R^2 = 0.36, p=0.0018)

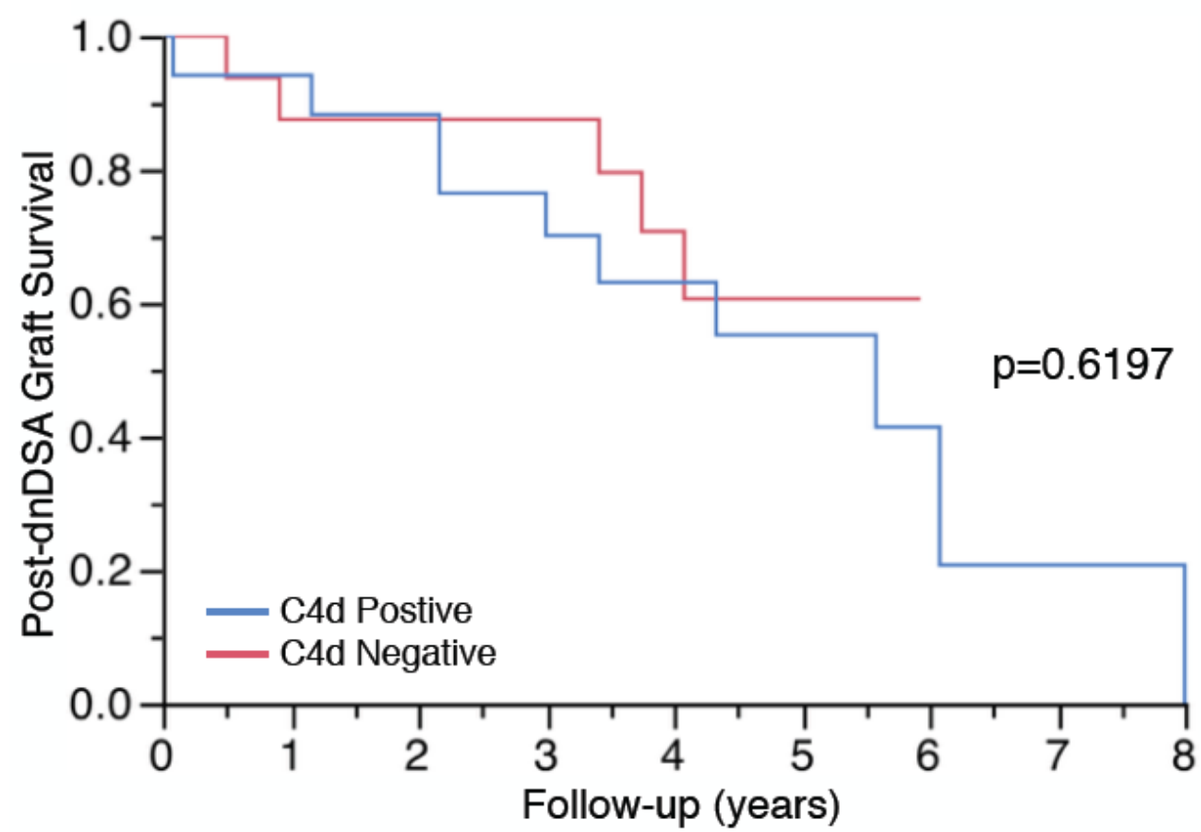
Wiebe et al., AJT (2015) 15: 2921-2930

Biopsy Predictors for Graft Loss at DSA onset

Consecutive Adult and Pediatric Kidney Transplants (n=508, 1999 to 2012)

Microvascular inflammation grade & C4d⁺ does not correlate with graft loss





Wiebe et al., AJT 2015; 15: 2921-2930

De novo DSA related Subclinical ABMR

Can we shut off the process?

⇧Tac / MMF + Pulse Steroid + IVIG (2g/kg)/mo x 3

DSA	Banff Acute							Banff Chronic			
	G	I	T	V	PTC	C4d		G	I	T	V
DR12 DQ4,7	0	2	2	0	**2**	**Pos**		0	0	1	1
DQ4 (Case)	**1**	1	1	0	**2**	**Pos**		0	1	0	0
DQ9	0	0	0	**3**	0	Neg		0	0	0	1
DQ7	0	1	1	0	**2**	**Pos**		0	0	1	0

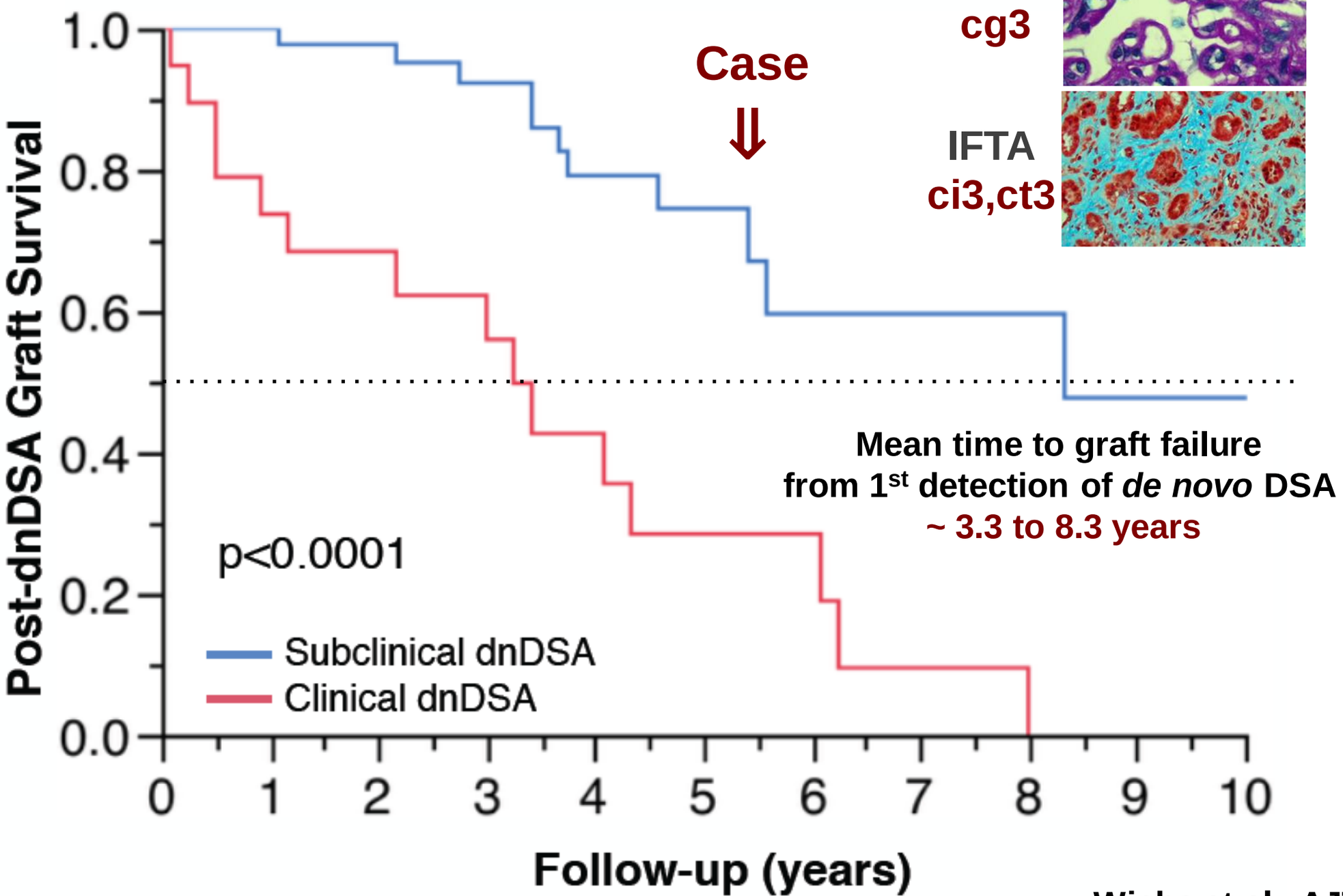
6 mo

Optimizing Tac/MMF, Pulse Steroids and IVIG appears to be insufficient

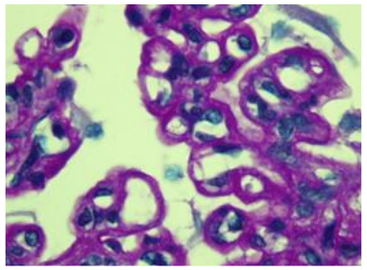
Wiebe et al. AJT (2012) 12:1157-1167

Time to Graft Loss from de novo DSA Onset

Consecutive Adult and Pediatric Kidney Transplants (n=508, 1999 to 2012)



TG
cg3



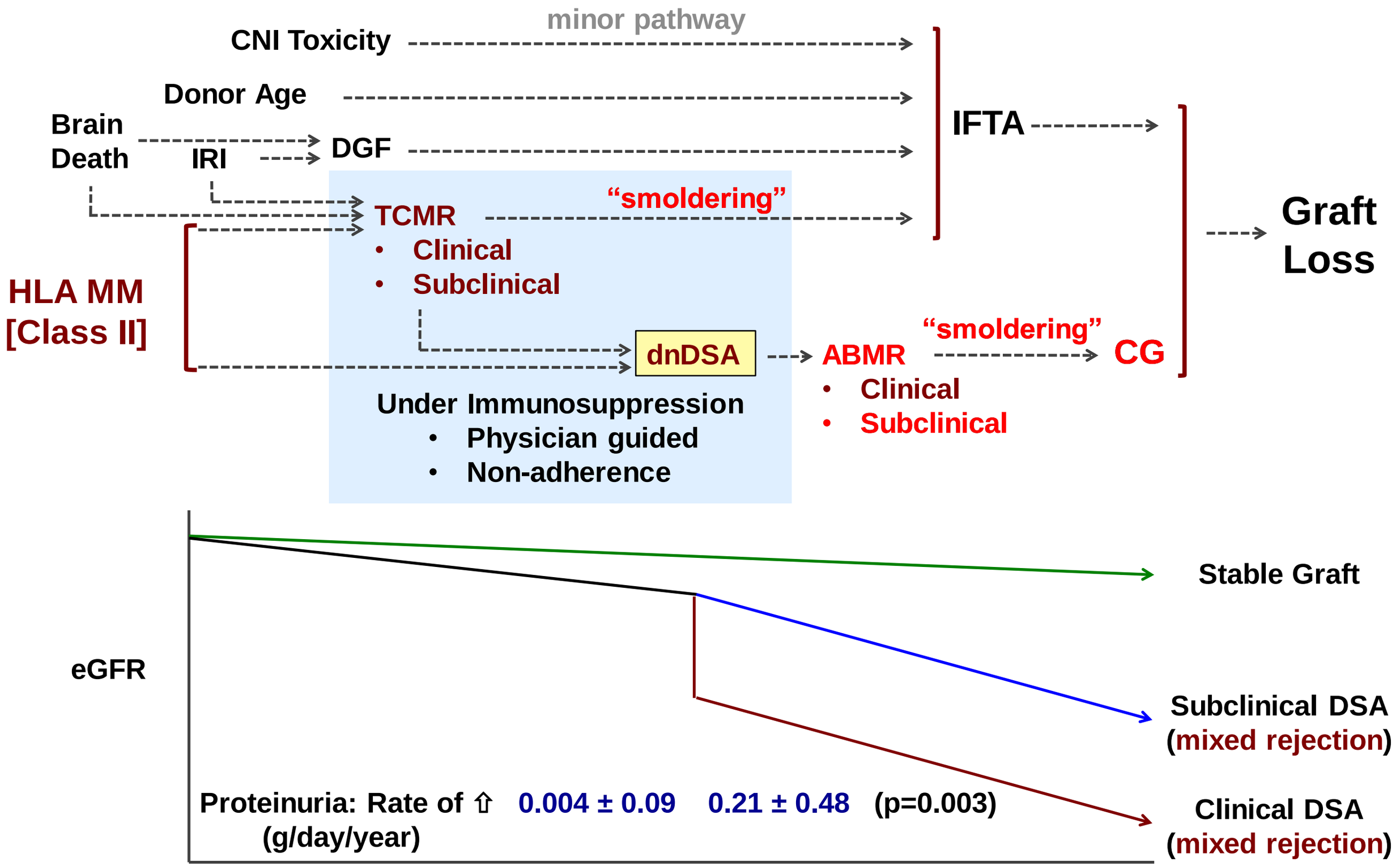
∝ de novo DSA

IFTA
ci3,ct3

∝ early $TCMR_{0\text{-}12mo}$
∝ non-adherence

Wiebe et al., AJT (2015) 15: 2921-2930

Model of Alloimmune Mediated Graft Loss



Wiebe et al., AJT (2015) 15: 2921-2930

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