Monitoring of Kidney Function and its Temporal Association with Antibody Induced Damage

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Relevant Financial Relationship Disclosure Statement

Chris Wiebe, University of Manitoba, Winnipeg, Canada

Nothing to disclose

AND

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

Reported incidence of *de novo* DSA varies significantly

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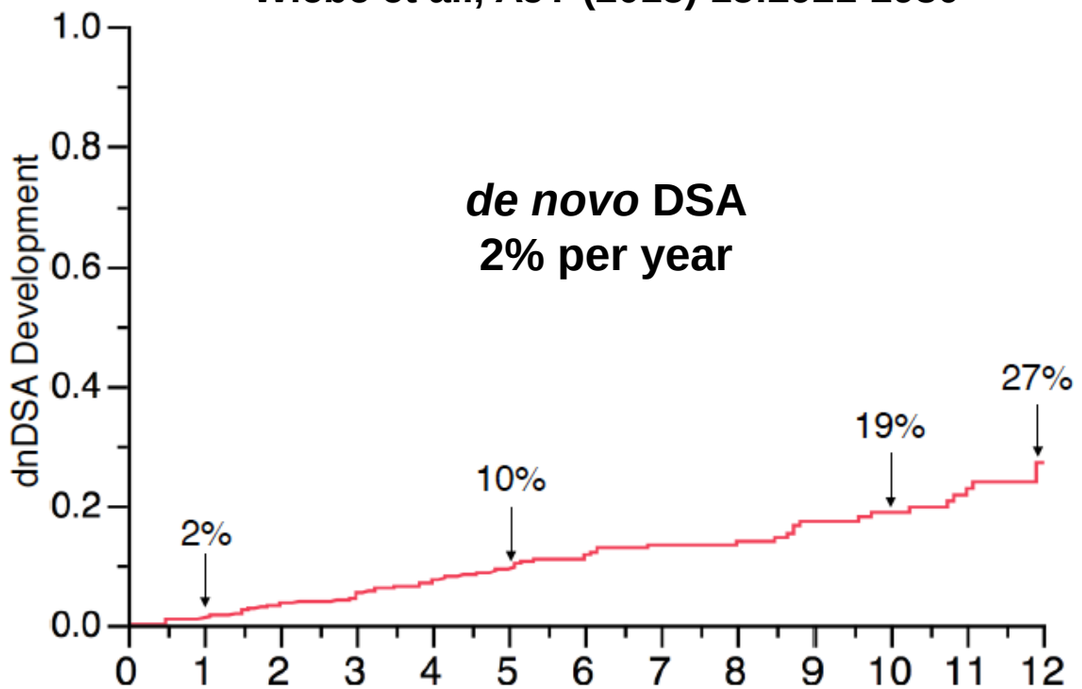
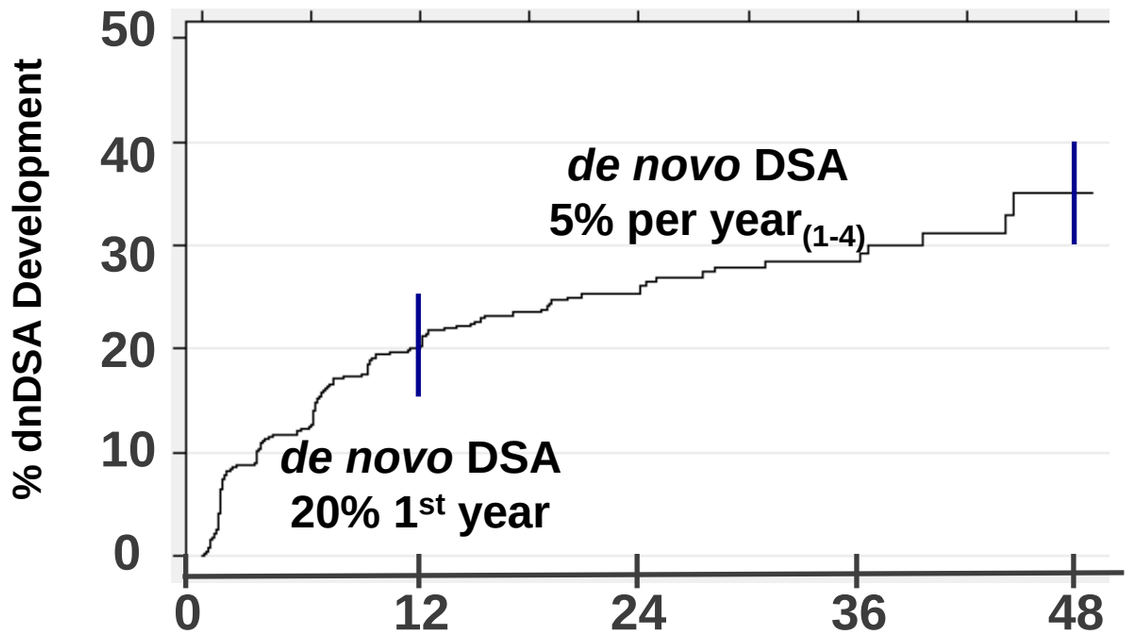
Wiebe et al., AJT (2015) 15:2921-2930



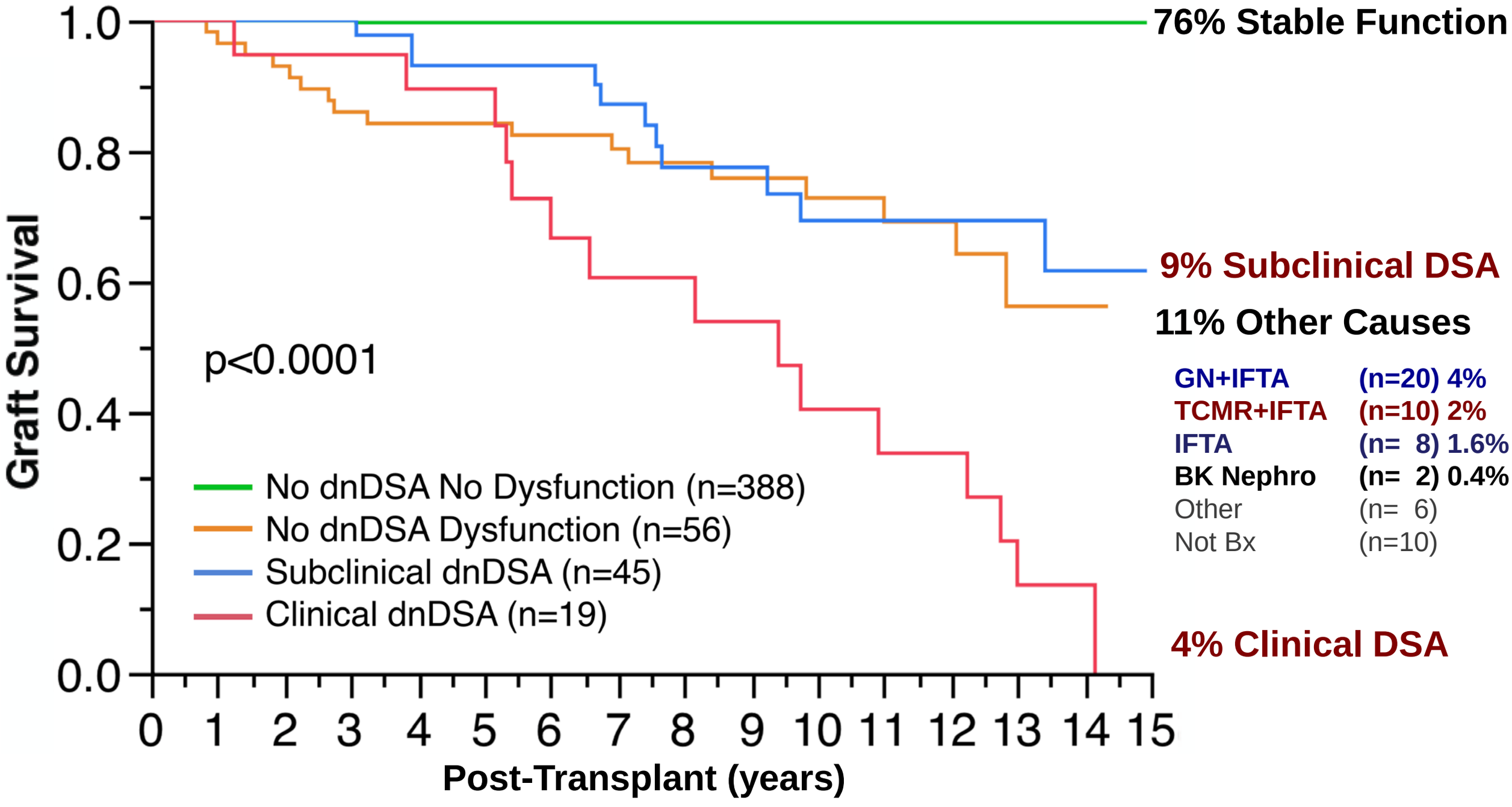
DeVos et al., Transplantation (2014) 97:534-540



Ref.	1st Tx		"*de novo*" DSA	
			1st Yr	>1st Yr
Cooper	n.a.		27.0%	0% yr 2
DeVos	93%		20.0%	5.0%/yr
Heilman	91%		17.6%	n.a.
Everly	100%		11.0%	2.3%/yr
Wiebe	95%		2.0%	2.0%/yr

Etiology of Late Allograft Dysfunction and Loss

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



76% Stable Function

9% Subclinical DSA

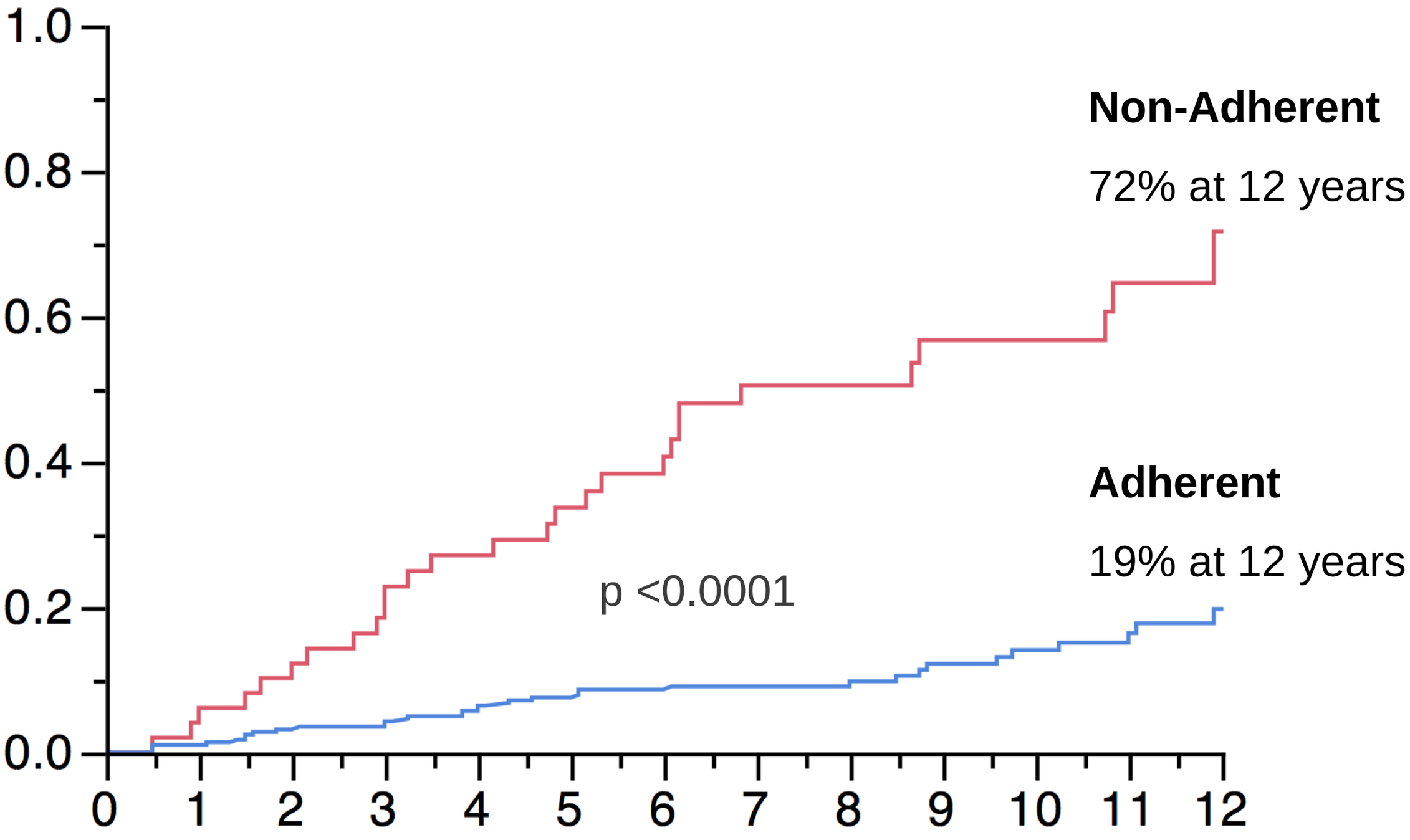
11% Other Causes

GN+IFTA	**(n=20) 4%**
TCMR+IFTA	**(n=10) 2%**
IFTA	**(n= 8) 1.6%**
BK Nephro	**(n= 2) 0.4%**
Other	(n= 6)
Not Bx	(n=10)

4% Clinical DSA

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

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



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

De Novo DSA and Graft Dysfunction

Estimated eGFR Rate of Decline (ml/min/1.73m²/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	

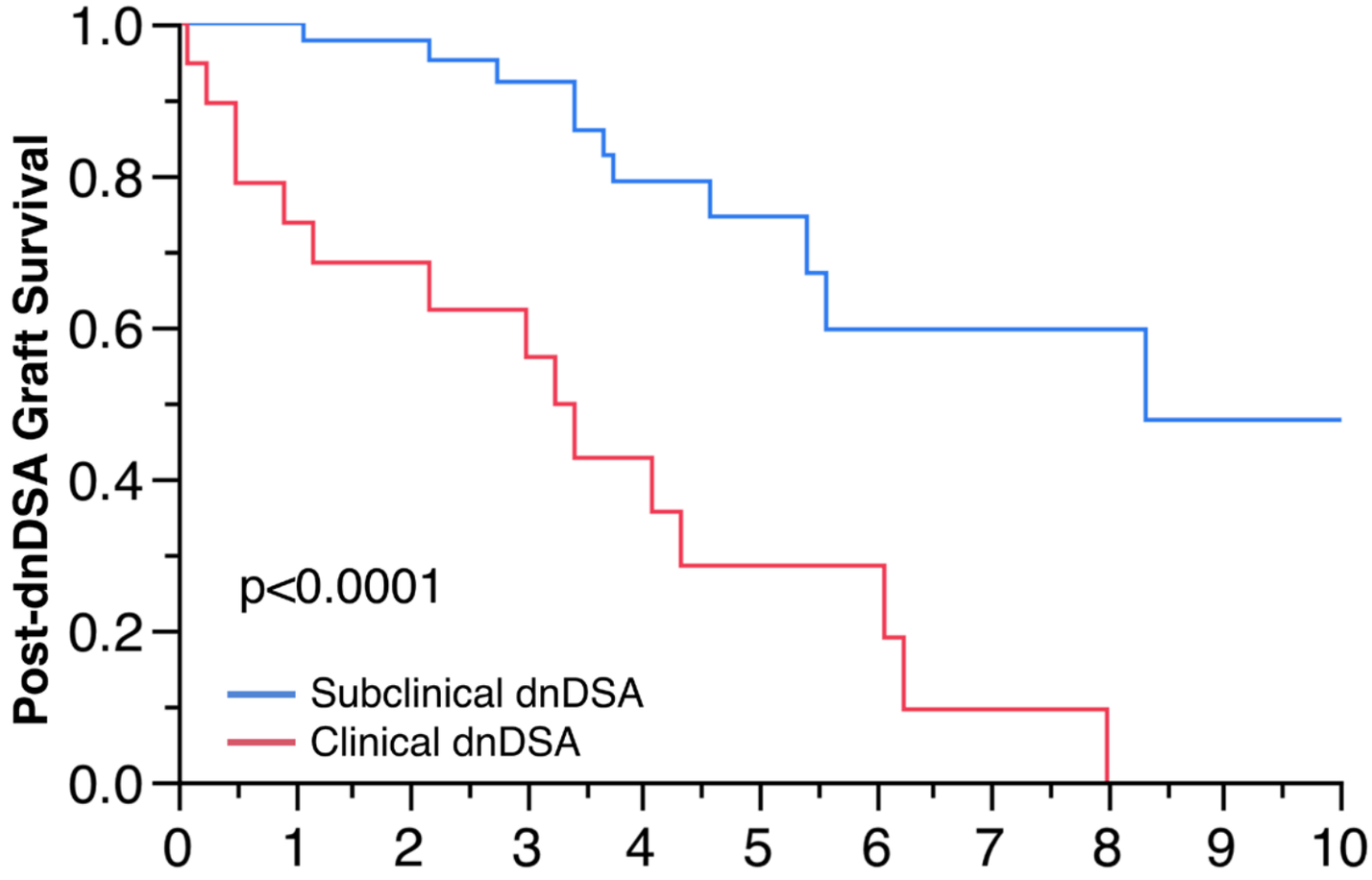
Rowe et al. J. Genontology (1976)

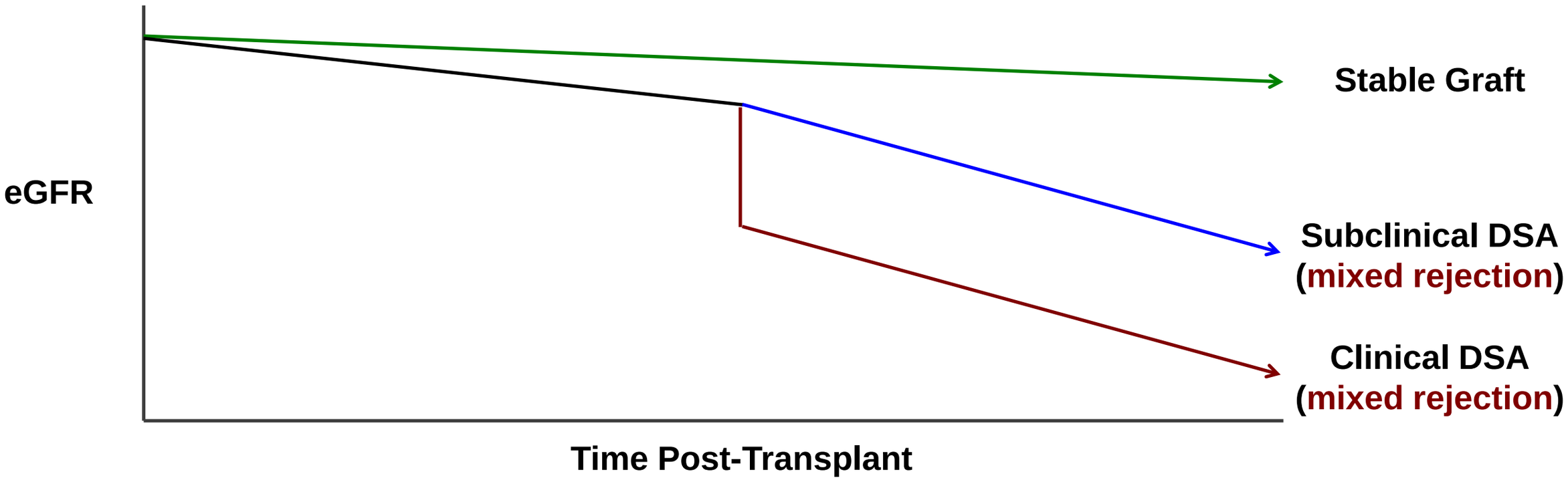
Healthy Men (n=293)

Age (Years)	**eGFR decline (ml/min/1.73m²/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 *dn*DSA the slope does not reflect the **step-wise eGFR decline** of **-6.38 ± 7.71 ml/min/1.73m²** seen at the onset of clinical *dn*DSA

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



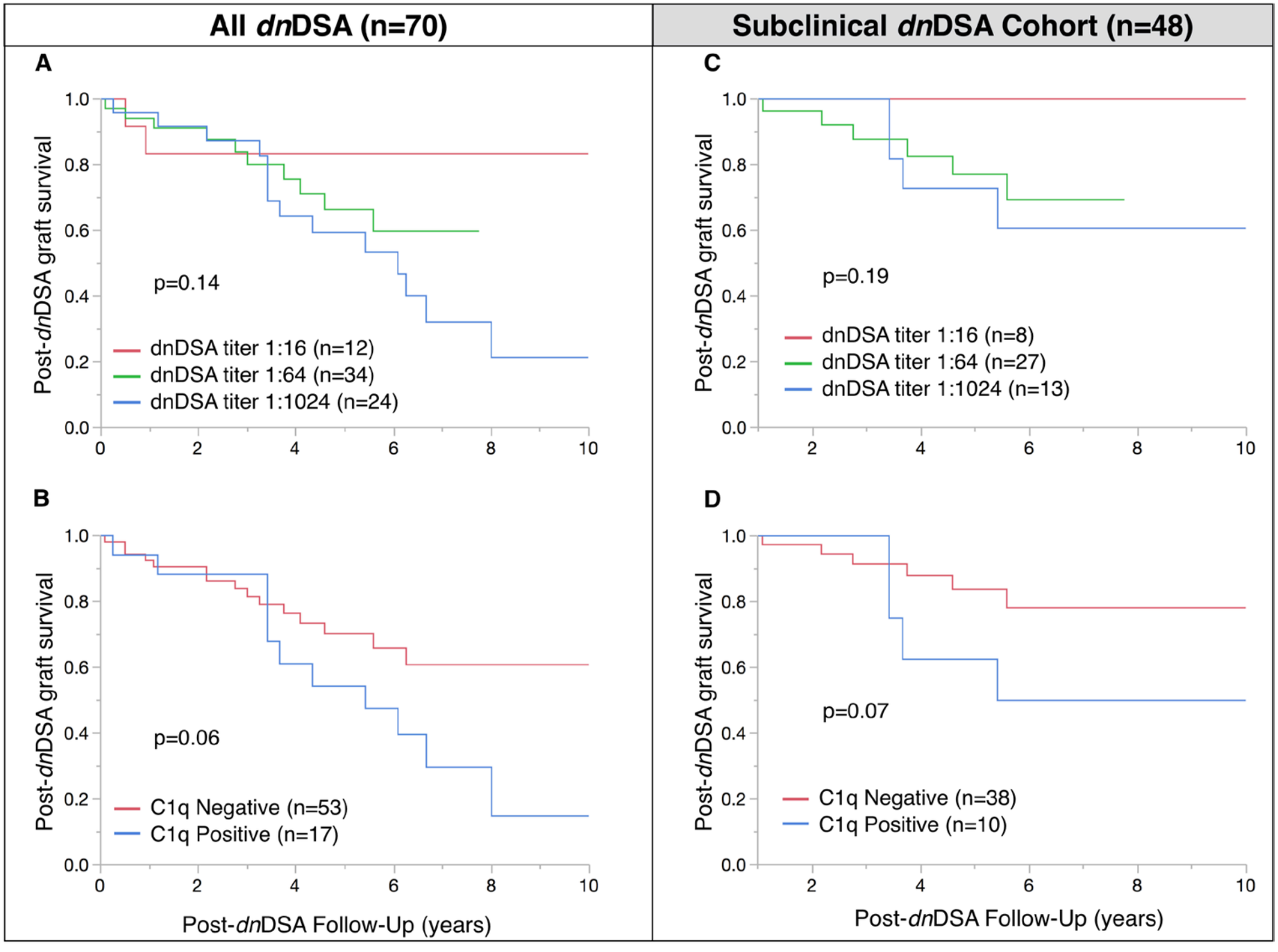


Wiebe et al., AJT (2015) 15: 2921-2930

Clinical/Serologic Predictors for Graft Loss at DSA onset

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

Figure 2. Post-*dn*DSA Graft Survival by *dn*DSA Titer or C1q Status*



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

Clinical Endpoint: Graft Survival

De novo DSA clinical trial with 5 yr graft survival as endpoint

(sample size for power 80%, a 0.05, drop-out 10%)

A. Death Censored 5 year Graft Survival

dnDSA Group	Median 5 year Graft Survival	Risk Reduction in Graft Loss		
		25%	35%	50%
All dnDSA	60%	601	306	150
Clinical dnDSA	28%	243	108	79
Subclinical dnDSA	75%	1591	590	377

Caveat

- **90% of clinical _de novo_ DSA patients are non-adherent**

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

Surrogate Endpoint: eGFR

In CKD trials, FDA will consider eGFR as an ESRD surrogate endpoint:

- Doubling of serum creatinine (57% decline in eGFR), or
- A 40% decline in eGFR over 2 years, assuming a baseline of 50 ml/min

Thompson et al., AJKD (2014) 64:836

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

Subclinical *de novo* DSA clinical trial with eGFR as surrogate endpoint

Study Duration	Mean eGFR Decline (ml/min/ 1.73m^2)	Risk Reduction in eGFR Decline	
		50%	70%
2 years	7.83±15.6	550 (23%)	282 (31%)
3 years	10.8±20.3	490 (27%)	251 (35%)

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

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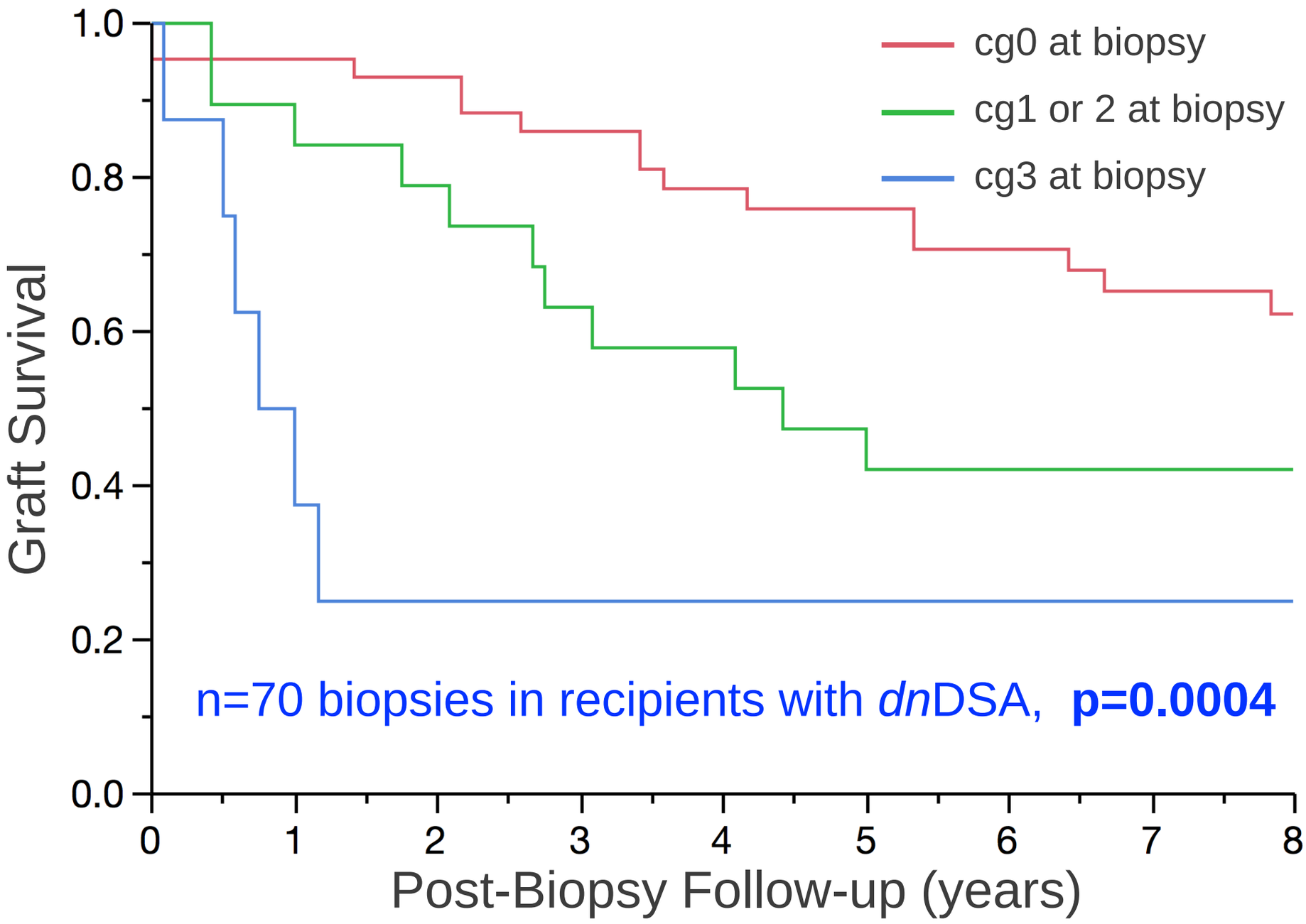
Multivariate Predictors of Banff Chronic Scores

*dn*DSA (n=371 biopsies) and Recipients without *dn*DSA (n=720 biopsies)

Banff Score n (% with score)		Cellular Rejection ≤ 12 months OR per rejection	*dn*DSA Development OR of yes vs. no	Time Post-Transplant OR per year (95%CI)	Non-Adherence OR of yes vs. no
cg≥1	89 (8%)	1.16 (0.8-1.6)	**4.42 (2.5-8.1)*** **	**1.32 (1.2-1.4)*** **	1.64 (0.9-2.9)
cg≥2	30 (3%)	0.70 (0.3-1.3)	**10.36 (3.6-37.8)*** **	**1.37 (1.3-1.5)*** **	1.24 (0.5-2.9)
cg=3	13 (1%)	0.82 (0.3-2.1)	**18.50 (3.2-350.9)*** **	**1.44 (1.3-1.7)*** **	0.90 (0.2-3.3)
ci≥1	558 (51%)	**1.55 (1.3-1.9)*** **	1.00 (0.7-1.4)	**1.40 (1.2-1.5)*** **	**1.40 (1.3-1.5)****
ci≥2	177 (16%)	**1.73 (1.4-2.1)*** **	1.28 (0.8-1.9)	**1.27 (1.2-1.3)*** **	**2.04 (1.3-3.1)*** **
ci=3	39 (4%)	**1.30 (0.9-1.9)**	0.63 (0.3-1.4)	**1.30 (1.2-1.4)*** **	**3.36 (1.5-7.6)****
ct≥1	671 (62%)	**1.30 (1.1-1.6)****	0.70 (0.5-1.0)	**1.83 (1.6-2.1)*** **	**1.52 (1.0-2.2)***
ct≥2	168 (15%)	**1.58 (1.3-2.0)*** **	1.10 (0.7-1.7)	**1.32 (1.2-1.4)*** **	**2.28 (1.4-3.6)*** **
ct=3	53 (5%)	1.31 (0.9-1.8)	0.99 (0.5-2.0)	**1.29 (1.2-1.4)*** **	**4.19 (2.1-8.6)*** **

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

For Recipients with *dn*DSA cg Score Correlates with Graft Survival



Unpublished data

Surrogate Endpoint: Banff CG Score

Rationale for CG

- Correlates strongly with *de novo* DSA
- Infrequent at the onset of *de novo* DSA (87% cg0)
- Increases in grade after the onset in *de novo* DSA (**1 grade /3 yrs**)
- Is a prognostic biomarker of graft loss

Caveat

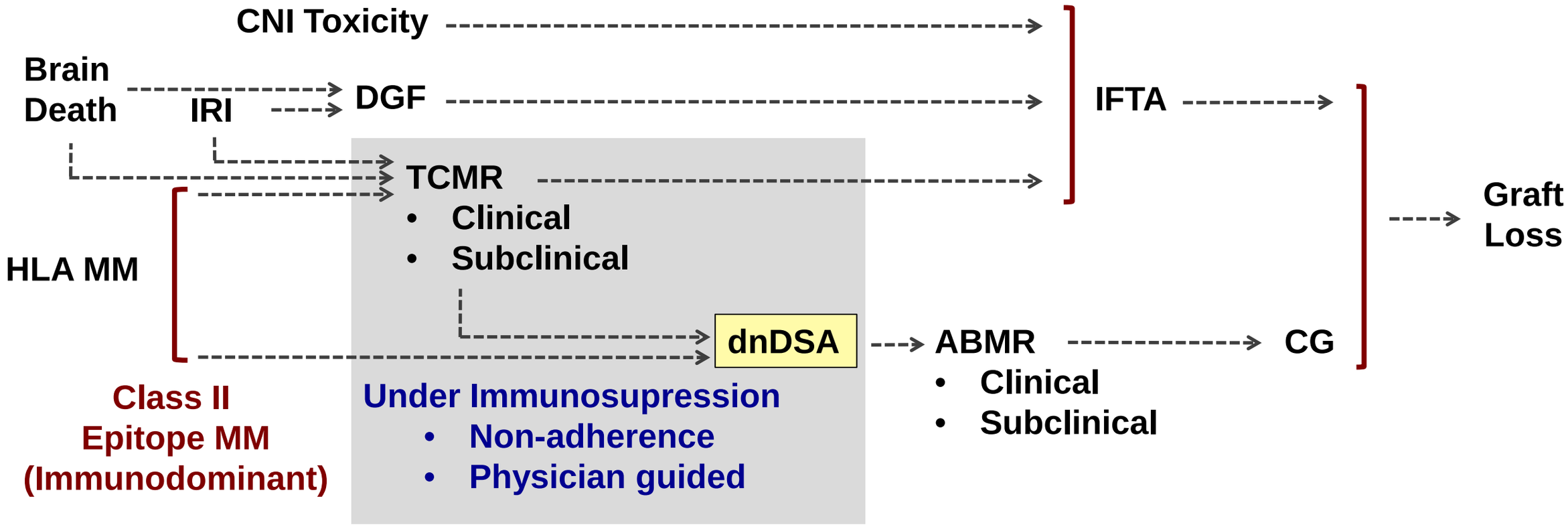
- Validation that preventing the development and/or progression in response to treatment correlates with improved graft survival is required

Key Consideration

- **Electron Microscopy** many be a useful tool to detect changes with more sensitivity (earlier) than Light Microscopy

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

Clinical Trial Design for *de novo* DSA patients



- **Enrichment strategies to increase endpoint frequency**
  - **Prognostic Biomarkers – DSA titer, MNA, tubulitis, Banff CG score**
- **Endpoints**
  - **Clinical – Graft loss**
  - **Surrogate – ∆ eGFR, ∆ Banff CG score**

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MHRC
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Fostering New Knowledge for Improved Health