



22-24  
marzo  
2023

SOCIETAT  
CATALANA DE  
TRASPLANTAMENT



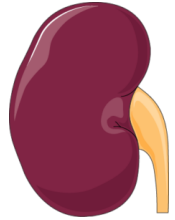
## ***Compatibilidad alélica o molecular para la asignación de órganos***

Dra Maria Meneghini MD PhD

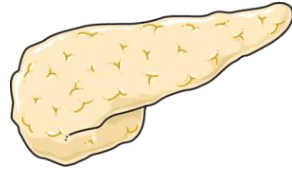
Servei de Nefrologia, Unitat de Trasplantament Renal.  
H. U. Vall d'Hebron

***No conflict of interest to report***

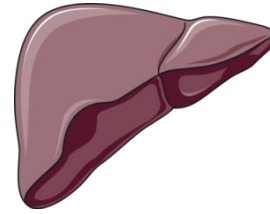
# HLA compatibility in current allocation criteria in Spain (Catalunya)



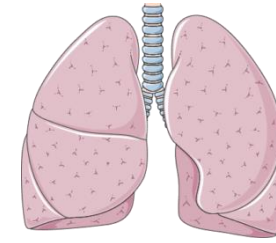
YES



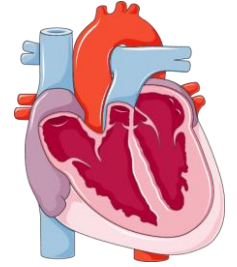
NO



NO



NO



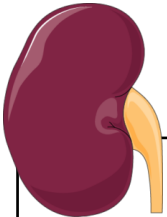
NO



*Number of **antigen/allele HLA mismatches** has shown association with **graft survival***

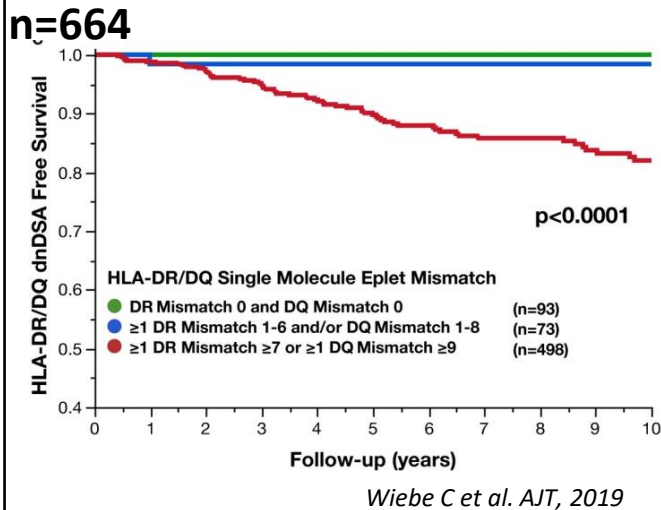
# Molecular HLA compatibility and relevant clinical outcomes in allotransplantation

# Outcome: de novo DSA

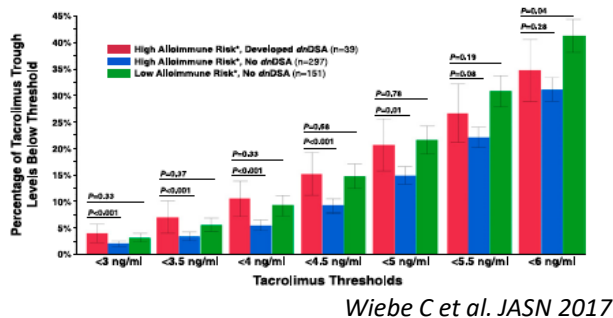


## EPLET MISMATCH

**HLAMatchmaker**  
An Algorithm for Epitopes

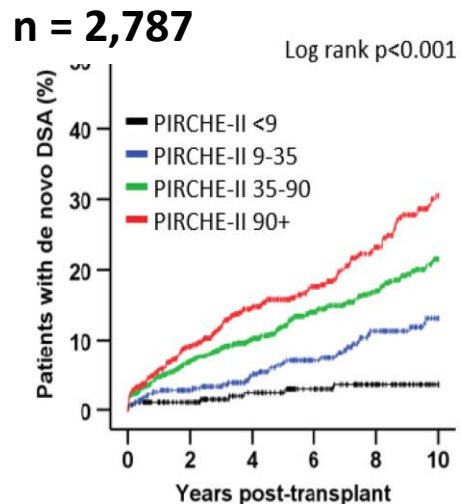


n=596



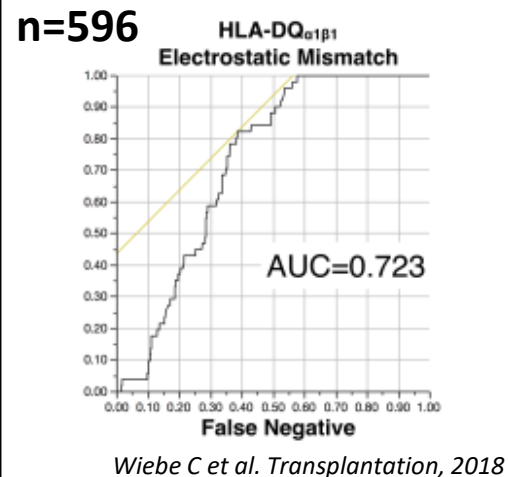
## PIRCHE-II

**PIRCHE**

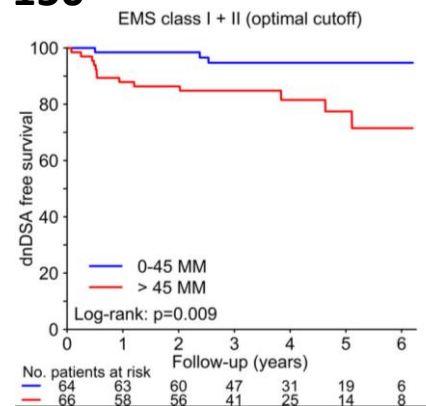


Lachmann N et al. AJT, 2017

## HMS/EMS



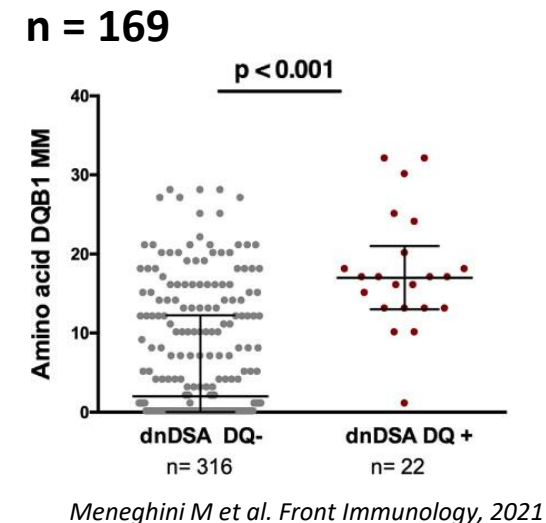
n=150



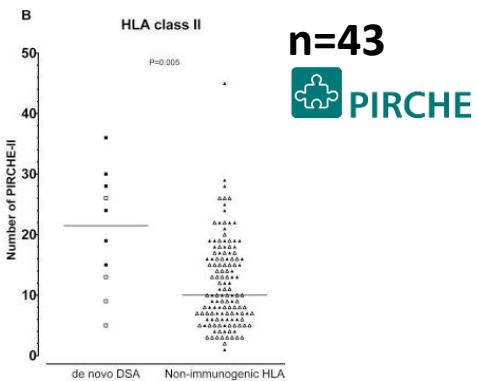
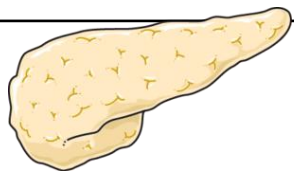
Delion A et al. Clinical Transplantation, 2019

## Amino acid MM

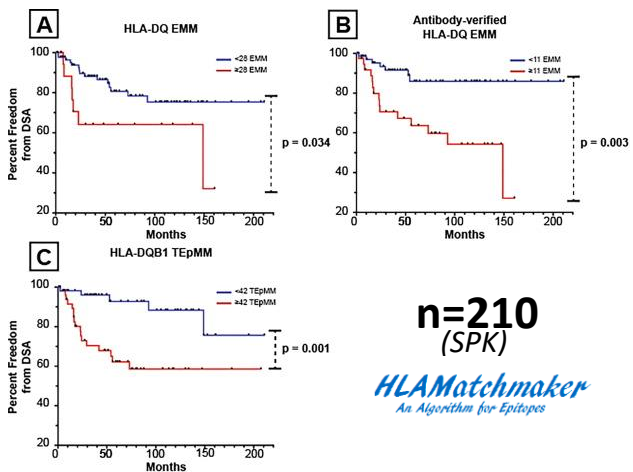
**HLA-EMMA**  
Epitope Mismatch Algorithm



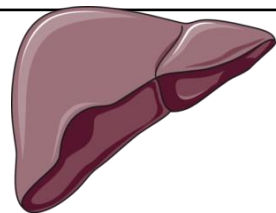
# Outcome: de novo DSA



Chaigne B. *t al. Cell Transplant. 2016*



Ladowski JM. *Et al. Hum Immunol, 2021*



n=190

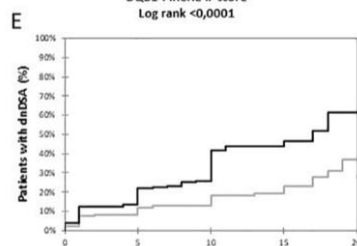
HLAMatchmaker  
An Algorithm for Epitopes

HLA-EMMA  
Epitope Mismatch Algorithm

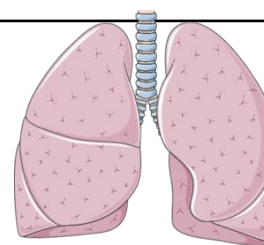
	No Class II DSA <sup>s</sup>	Class II DSA <sup>s</sup>	p-value*
LA allele mismatch	6 (1-8)	7 (5-8)	<b>0.004</b>
HLAMatchmaker			
DRDQ	16 (0-41)	21 (3-33)	<b>0.044</b>
Verified eplet	6 (0-19)	8 (2-15)	<b>0.037</b>
Non-verified eplets	10 (0-24)	13 (1-23)	0.068
HLAMatchmaker DR			
Verified eplet	4 (0-12)	5 (2-8)	0.145
Non-verified eplets	6 (0-16)	8 (1-15)	0.498
HLAMatchmaker DQ			
Verified eplet	1 (0-10)	3 (0-9)	0.202
Non-verified eplets	2 (0-14)	6 (0-12)	0.124
HLA-EMMA DRDQ	25 (0-66)	38 (15-57)	<b>0.004</b>
Solvent accessibility	18 (0-53)	29 (12-45)	<b>0.010</b>
HLA-EMMA DR	15 (0-43)	18 (4-45)	0.216
Solvent accessibility	13 (0-35)	15 (3-39)	0.280
HLA-EMMA DQ	9 (0-43)	25 (0-43)	<b>0.002</b>
Solvent accessibility	6 (0-34)	19 (0-37)	<b>0.004</b>
PIRCHE-II score	86 (16-242)	110 (45-224)	<b>0.031</b>

Vionnet J. *et al. J Hepatology, 2021*

n=407



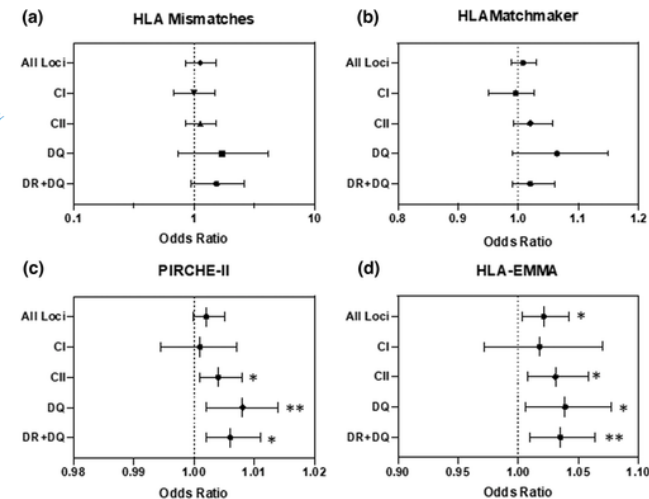
Hamada S. *et al. Transplant Immunology, 2020*



n=73

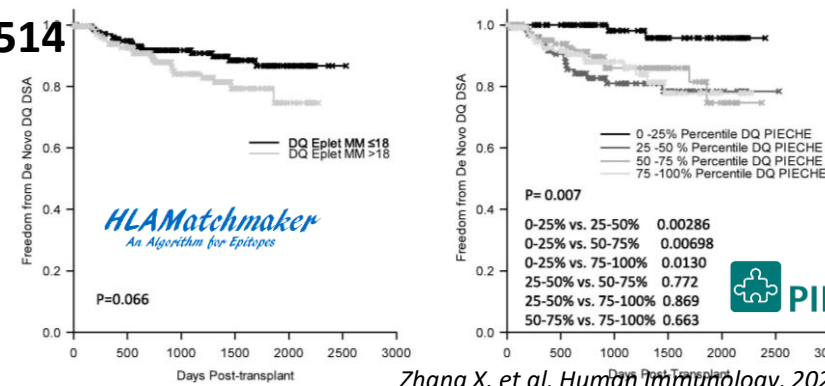
HLAMatchmaker  
An Algorithm for Epitopes

HLA-EMMA  
Epitope Mismatch Algorithm



Bedford A. *et al. Int J Immunogenet. 2022*

n = 514



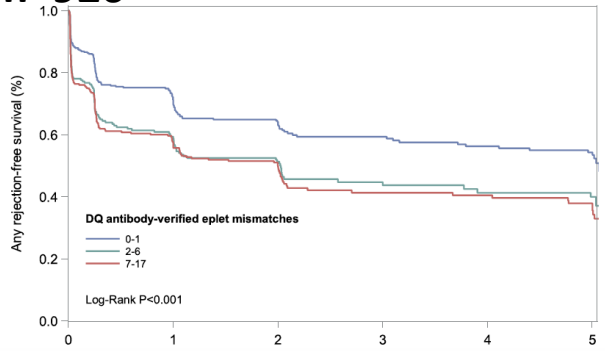
Zhang X. *et al. Human Immunology, 2020*

# Outcome: acute and chronic rejection

## EPLET MISMATCH

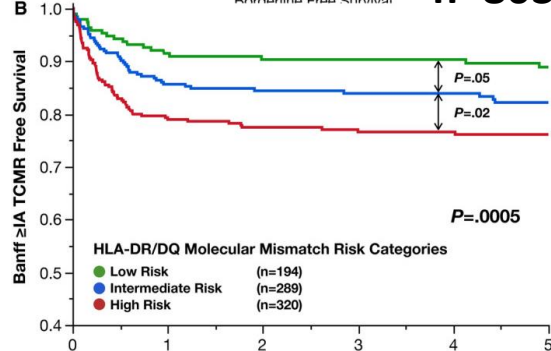
*HLAMatchmaker*  
An Algorithm for Epitopes

n=926



*Senev A. et al. JASN, 2020*

B Borderline Free Survival n=803



*Wiebe C. et al. Am J Transplant. 2020*

n=156

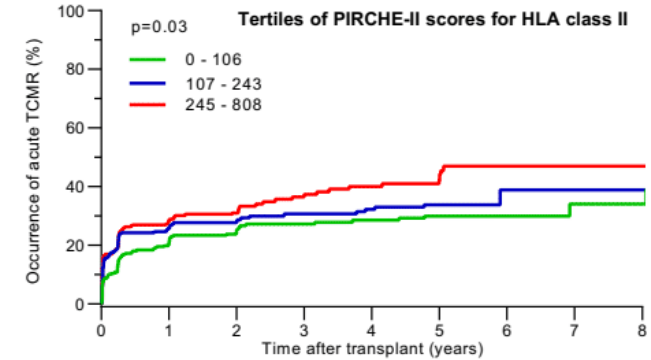
Main exposure	OR [95% CI]	p-Value
<b>HLA-DRB1</b>		
Eplet mismatch categories (tertiles)		
<8	Referent	
8-13	5.70 [1.92, 16.94]	0.002
>13	4.89 [1.53, 15.62]	0.007
Threshold of eplet mismatch (median)		
<9	Referent	
≥9	2.95 [1.23, 7.12]	0.016
Per eplet mismatch	1.07 [1.01, 1.14]	0.034
<b>HLA-DRB3/4/5</b>		
Eplet mismatch categories (tertiles)		
<2	Referent	
2-6	2.79 [1.13, 6.90]	0.027
>6	3.35 [1.09, 10.30]	0.035
Threshold of eplet mismatch (median)		
<3	Referent	
≥3	6.03 [2.08, 17.47]	0.001
Per eplet mismatch	1.09 [0.98, 1.22]	0.124

*Sapir-Pichhadze R. et al. AJT, 2015*

## PIRCHE-II



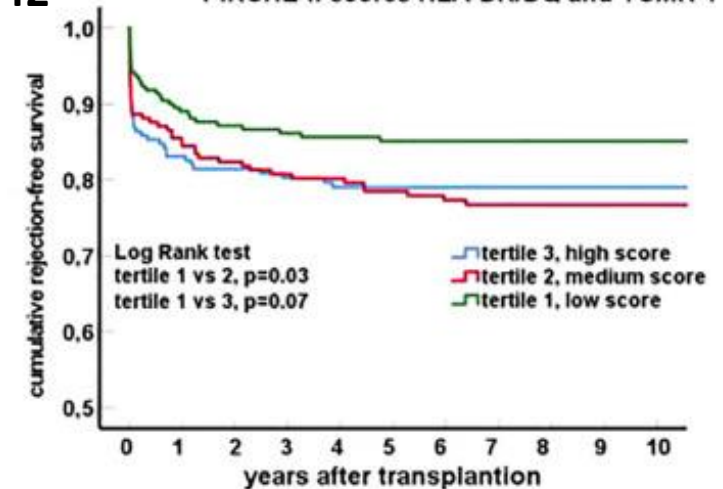
n=893



*Senev A. et al. AJKD, 2022*

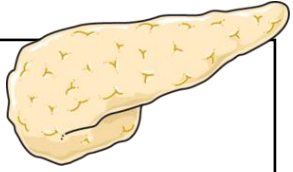
n=642

## PIRCHE-II scores HLA-DR/DQ and TCMR-1

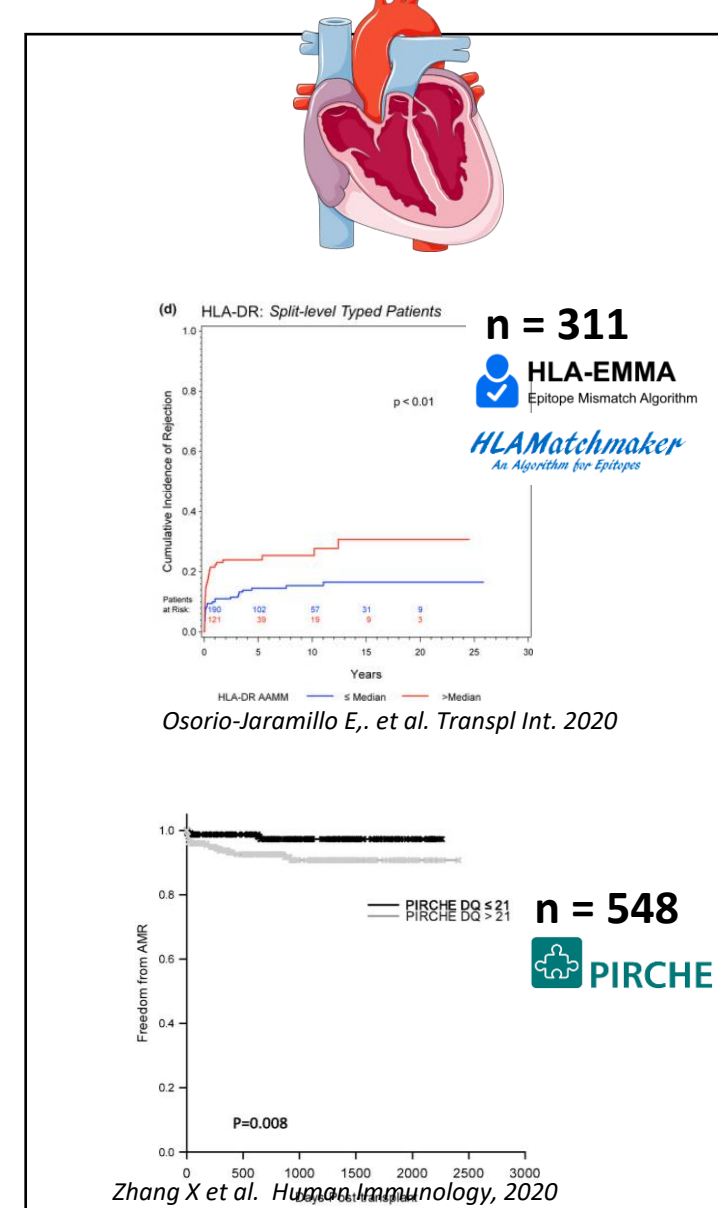
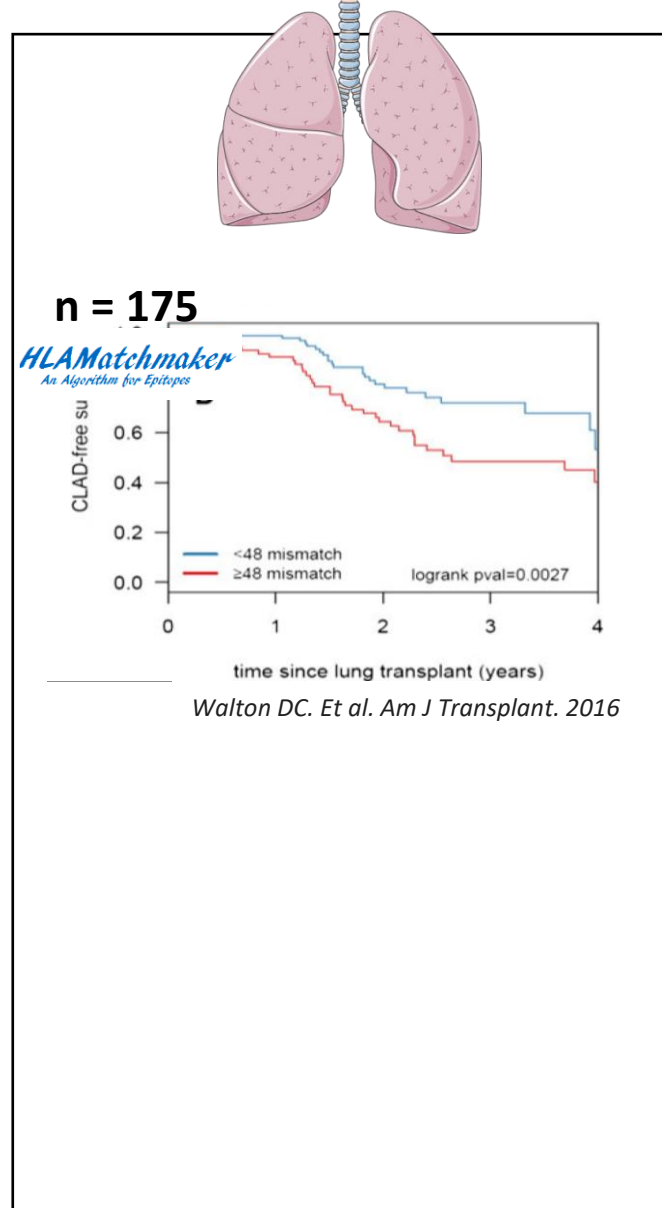
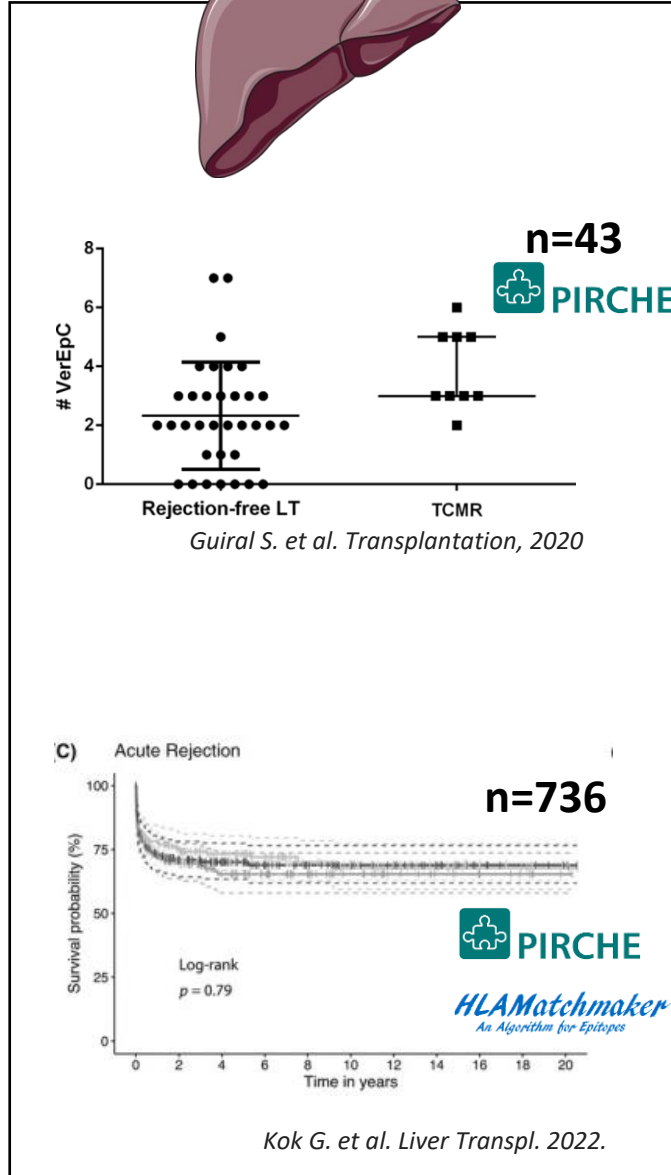


*Betjes MGH. et al. Front Immunol. 2022*

# Outcome: acute and chronic rejection

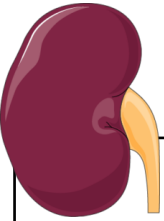


?





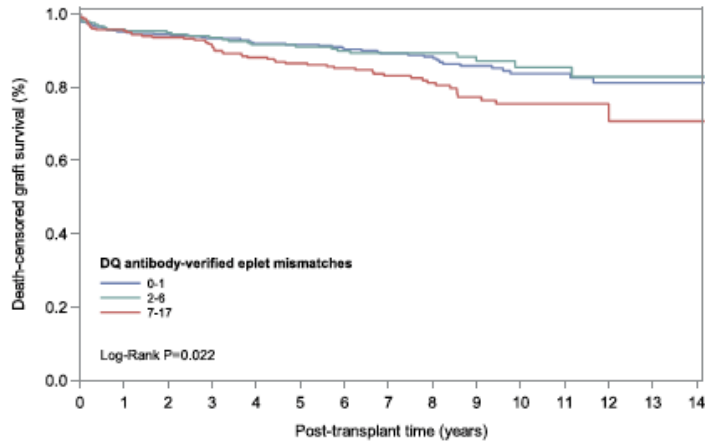
# Outcome: graft loss



## EPLET MISMATCH

*HLAMatchmaker*  
An Algorithm for Epitopes

n=926



*Senev A. et al. JASN, 2020*

n=118,382

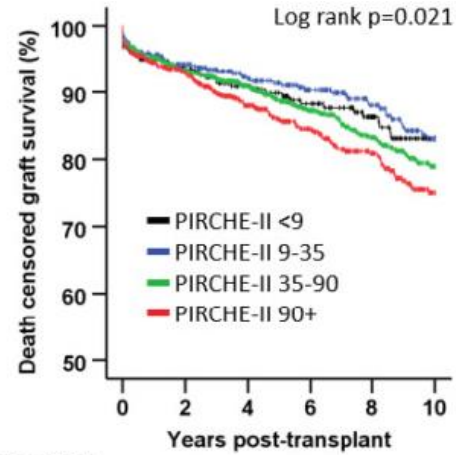
HLA locus and class	Per single AbVer MM HR <sup>v</sup> (95% CI)	Per single Overall MM HR <sup>v</sup> (95% CI)	Per 10 AbVer MM HR (95% CI)	Per 10 Overall MM HR (95% CI)
Class I	1.021 (1.018, 1.024)	1.007 (1.006, 1.008)	1.231 (1.195, 1.268)	1.072 (1.062, 1.083)
HLA-DRB1	1.025 (1.022, 1.028)	1.012 (1.010, 1.014)	1.280 (1.243, 1.318)	1.127 (1.105, 1.149)
HLA-DQB1	1.035 (1.029, 1.041)	1.016 (1.013, 1.019)	1.411 (1.331, 1.495)	1.172 (1.138, 1.207)

*Sapir-Pichhadze R. et al. Kidney Int. 2020*

## PIRCHE-II



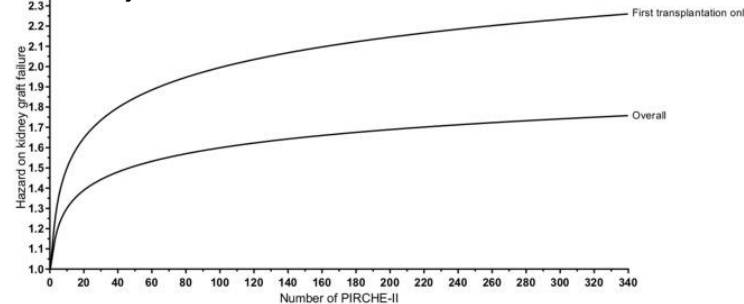
n = 2,787



Number at risk	0	2	4	6	8	10
PIRCHE <9	285	234	190	155	116	77
PIRCHE 9-35	446	370	301	238	179	123
PIRCHE 35-90	1222	1001	787	590	450	299
PIRCHE 90+	834	652	490	363	258	147

*Lachmann N et al. AJT, 2017*

n = 2,918

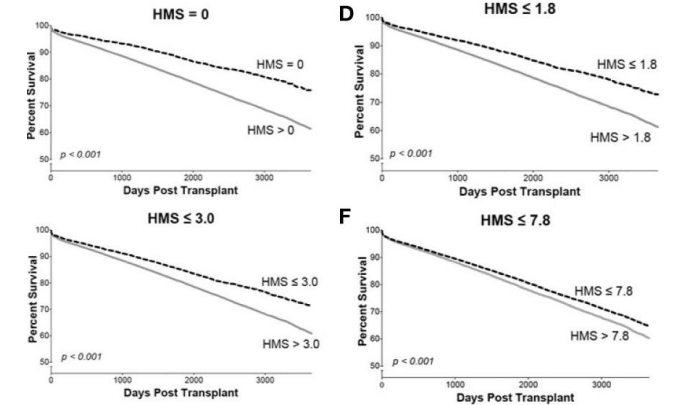


*Geneugelijk K. et al. Front Immunol. 2018*

## HMS/EMS

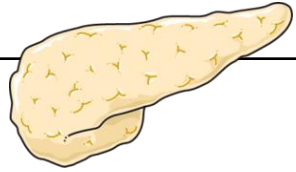


n = 78,865

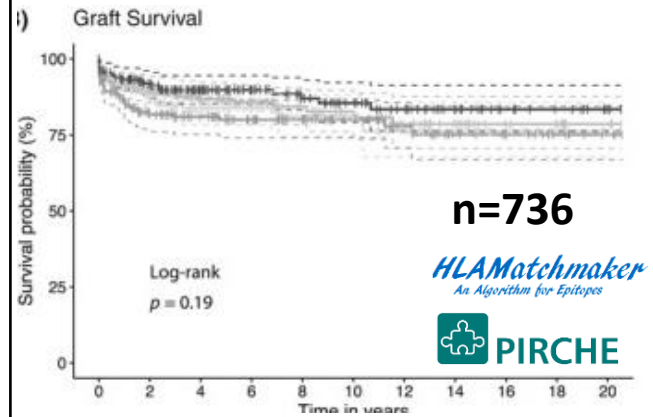
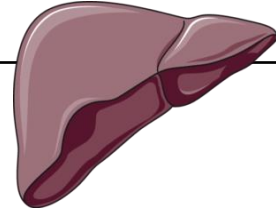


*Bekbolsynov D. et al. Fron Immunol. 2020*

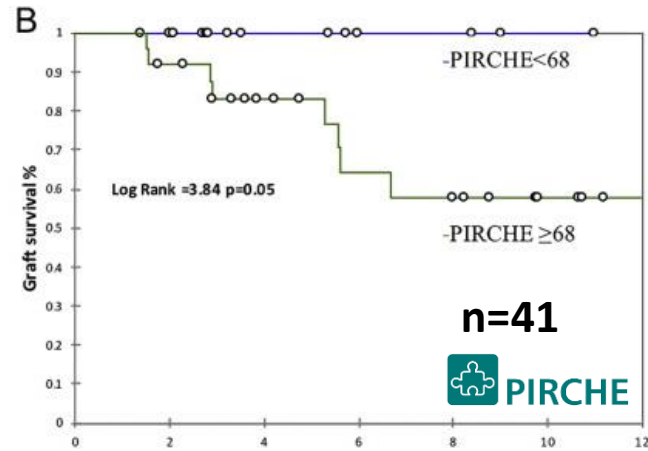
# Outcome: graft loss



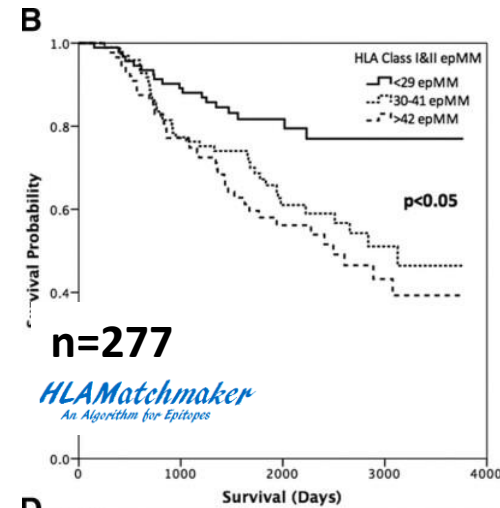
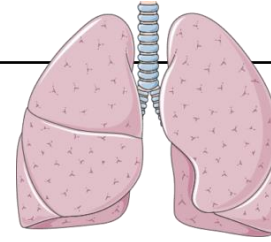
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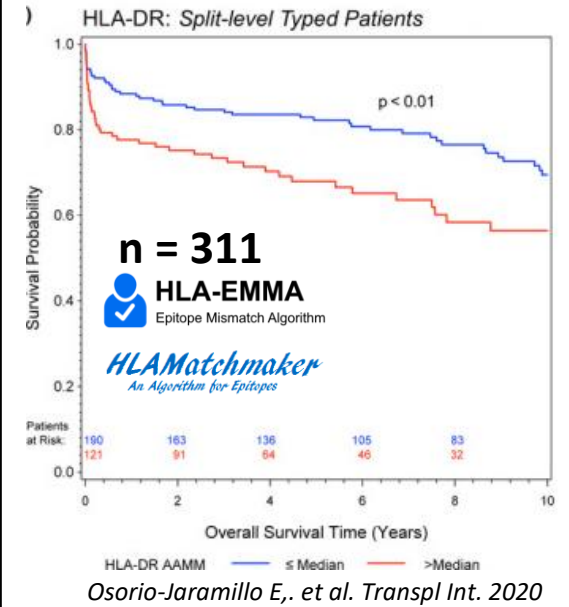
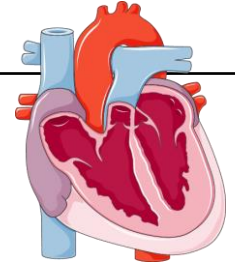
Kok G. et al. Liver Transpl. 2022.



Meszaros M, Transpl Immunol. 2020

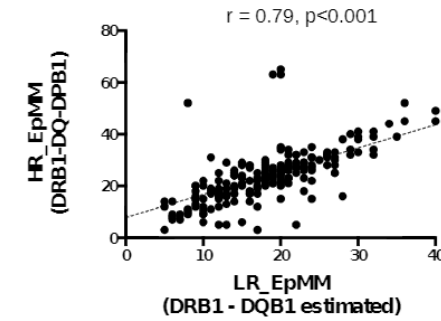
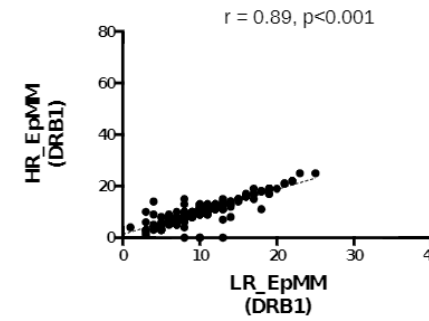
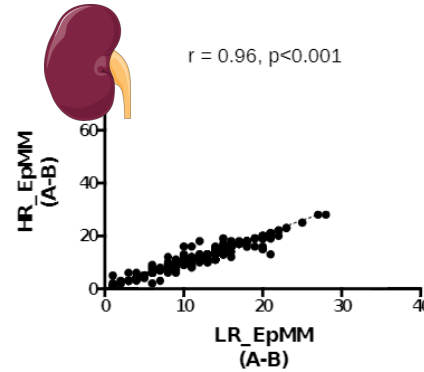


Hiho SJ. et al. Transplant Direct. 2022

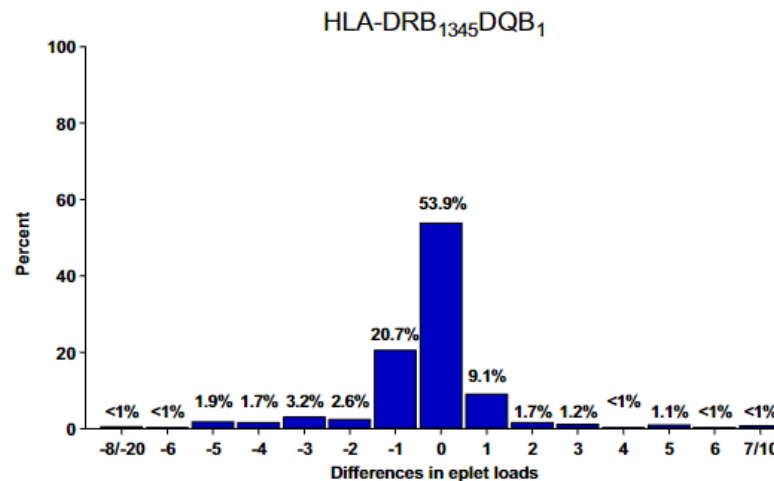
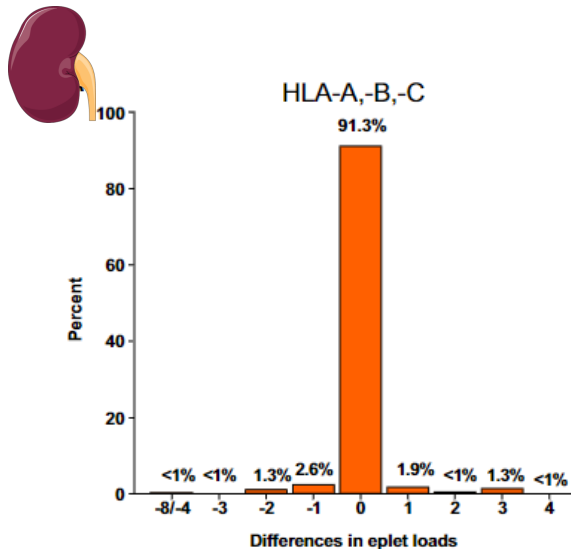


# Reviewing the quality of HLA MM literature (1)


- HLA loci typed (and analysed)
- HLA typing quality



Meneghini M. et al. Front Immunology, 2022



Senev A. et al. Am J Transplant. 2020



	Overall N = 303	Caucasian n = 124	Non-Caucasian n = 179	Odds ratio	95% confidence interval	
# New eplets	n	%	n	%	n	%
0	191	63.0%	88	71.0%	103	57.5%
1	44	14.5%	14	11.3%	30	16.8%
2	24	7.9%	10	8.1%	14	7.8%
3	17	5.6%	4	3.2%	13	7.3%
4	6	2.0%	1	0.8%	5	2.8%
≥5	21	6.9%	7	5.6%	14	7.8%
0 New eplets						
Class I	252	81.2%	112	90.3%	140	78.2%
Class II	222	73.3%	96	77.4%	126	70.4%
				0.6	(0.3-0.9)	.018
				0.4	(0.2-0.8)	.007
				0.7	(0.4-1.2)	.175

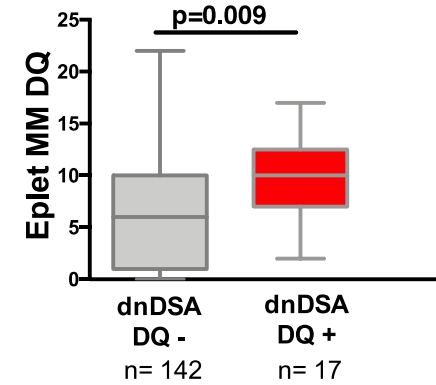
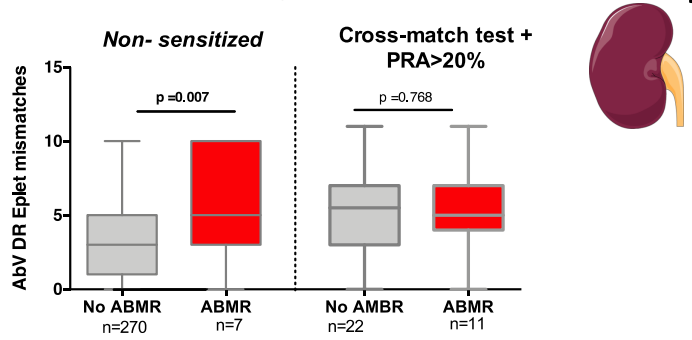
Engen R. et al. American J Transplant. 2021

# Reviewing the quality of HLA MM literature (2)



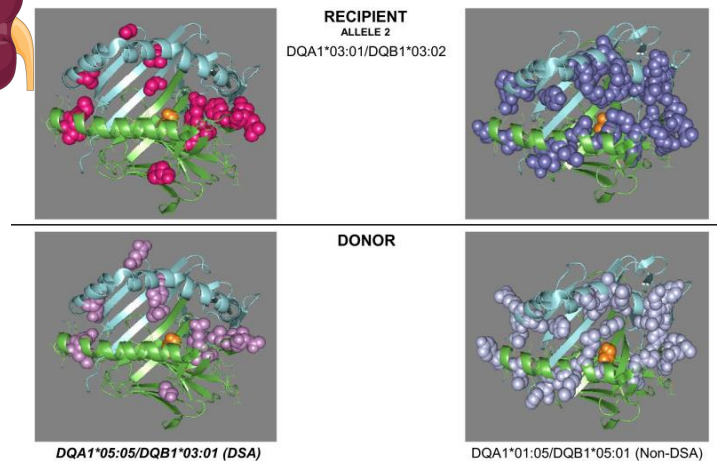
- Inclusion of 0 HLA MM patients

- Inclusion/exclusion of patients with preformed DSA



Meneghini M. Unpublished data.

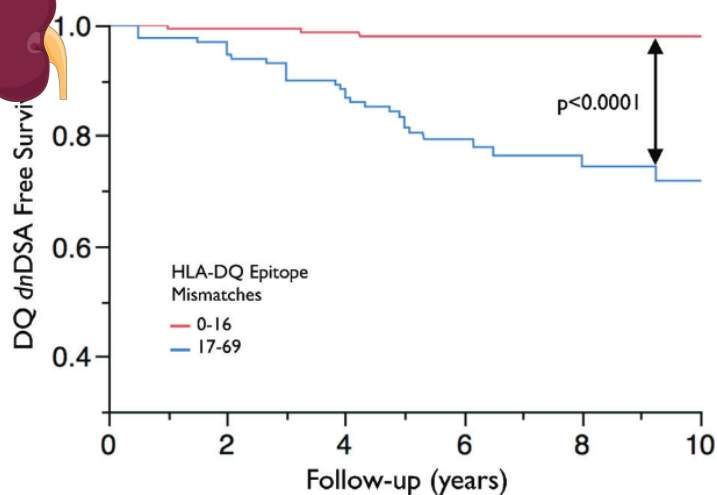
- Also patients with very low mismatched Eplet can experience adverse outcomes: immunogenicity of the MM, not only quantity



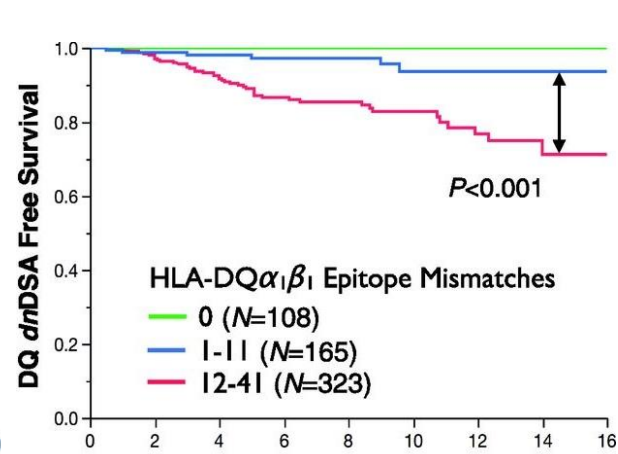
Tambur A. et al. Am J Transplant. 2019

# How to implement molecular HLA MM in clinical practice?

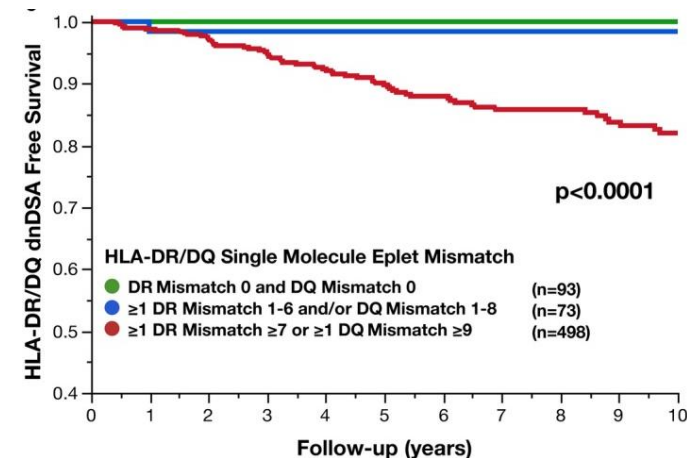
- Which algorithm?
- Single molecule or “global mismatch” load, which loci?
- Antibody verified or not? (*Bezstarosti S. et al. Front Immunol. 2022*)
- Different versions of each algorithm and different cut offs



Wiebe C. et al. *Am J Transplantation*, 2013



Wiebe C. et al. *JASN*, 2017

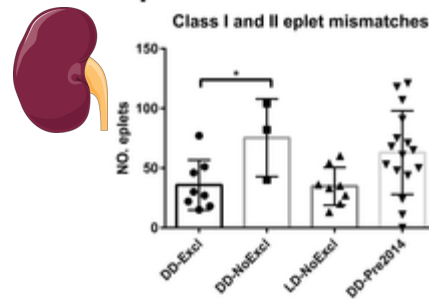


Wiebe C. et al. *Am J Transplantation*, 2019

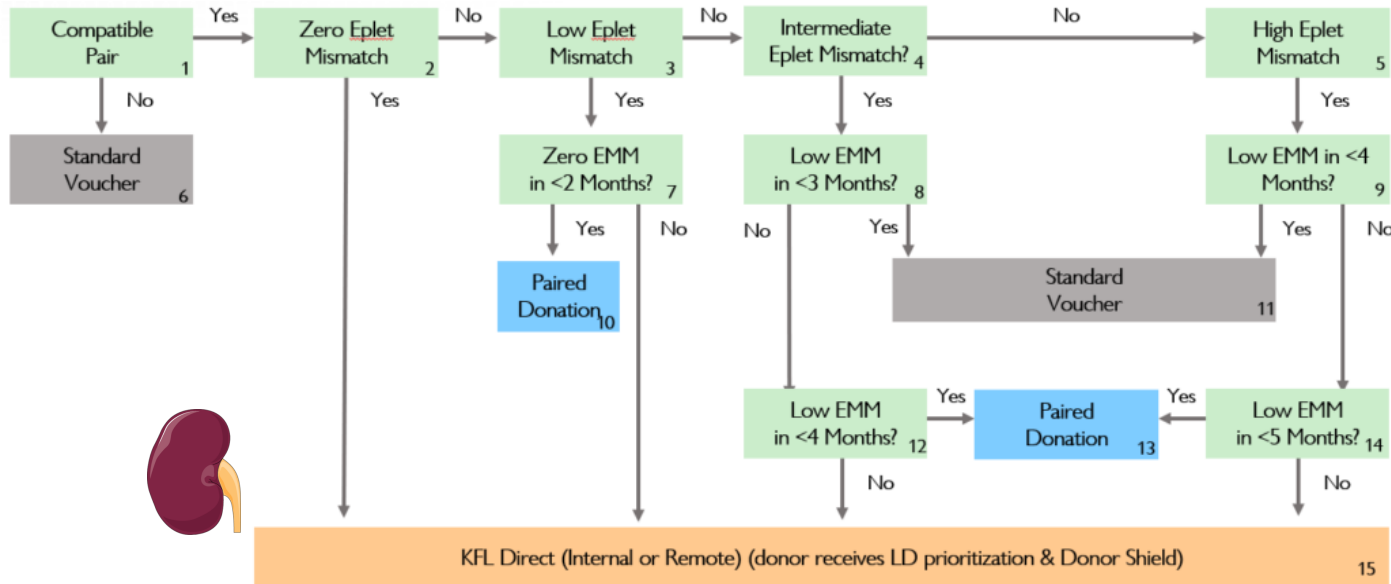
# Prospective use of molecular HLA MM: Allocation

Kausman J. et al *Pediatr. Transplant.* 2016 Prospective organ allocation based on "acceptable eplet load":  
n=35

- at 12 months similar outcomes
- trend toward lower de novo DSA
- high % of predicted donor exclusion
- acceptable waiting time

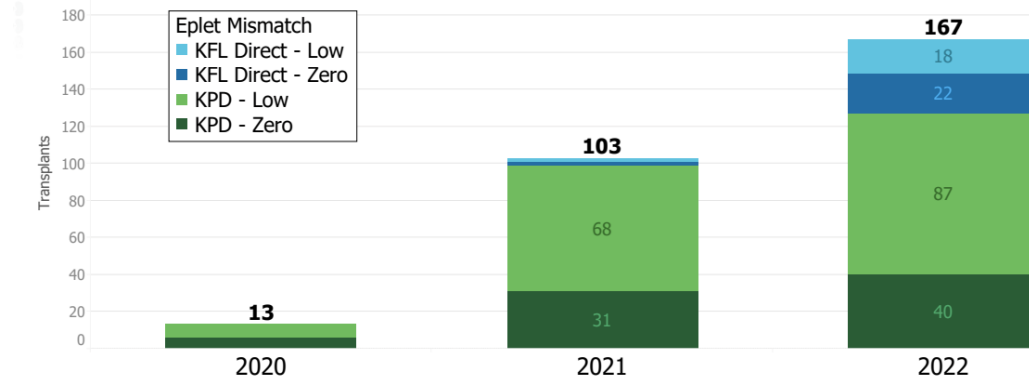


## Kidney for Life program (Living donor KT)



## Kidney for Life Low Eplet Mismatch Transplants

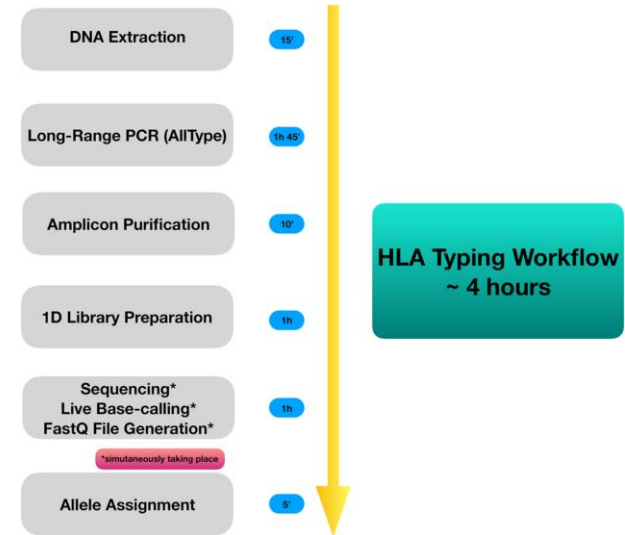
Compatible and Incompatible Pairs per Year





# How to improve HLA compatibility in SOT (Kidney)

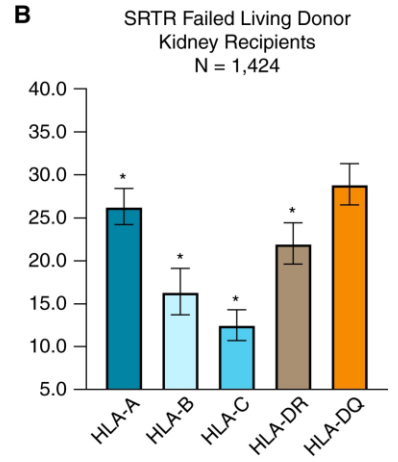
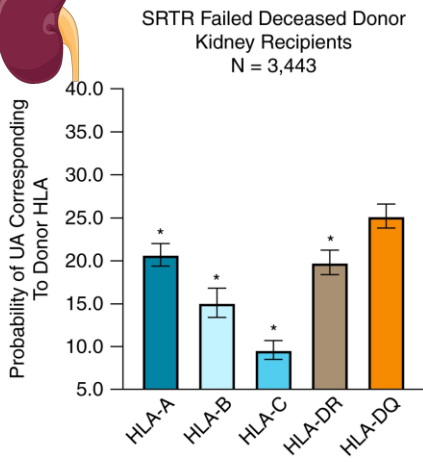
- Improve completeness (quality) of D/R HLA typing
  - Consider matching at HLA-DQ
- NOW**
- Dissect acceptable-permissible mismatches
- FUTURE**



De Santis D. et al. HLA. 2020

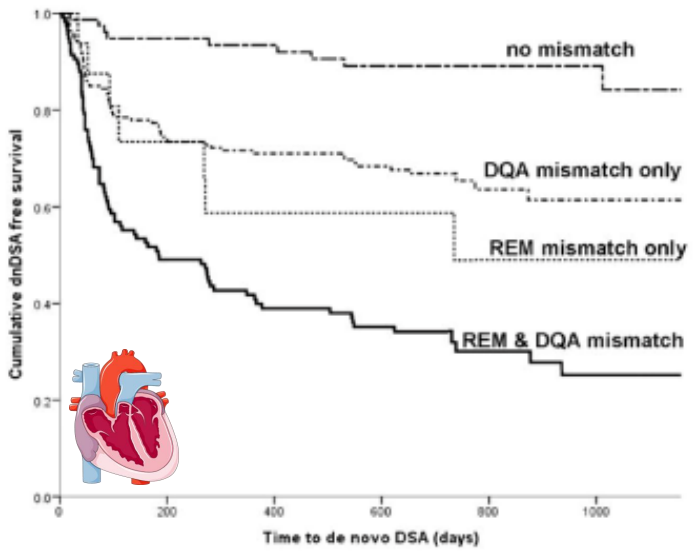


The 18<sup>th</sup> International HLA & Immunogenetics Workshop



\*Probability difference as compared to HLA-DQ, p<0.05

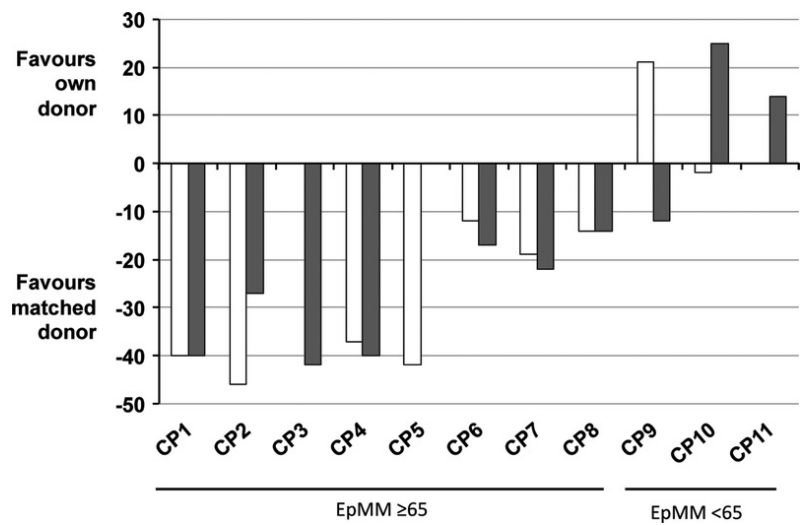
Isaacson D. et al. JASN, 2022



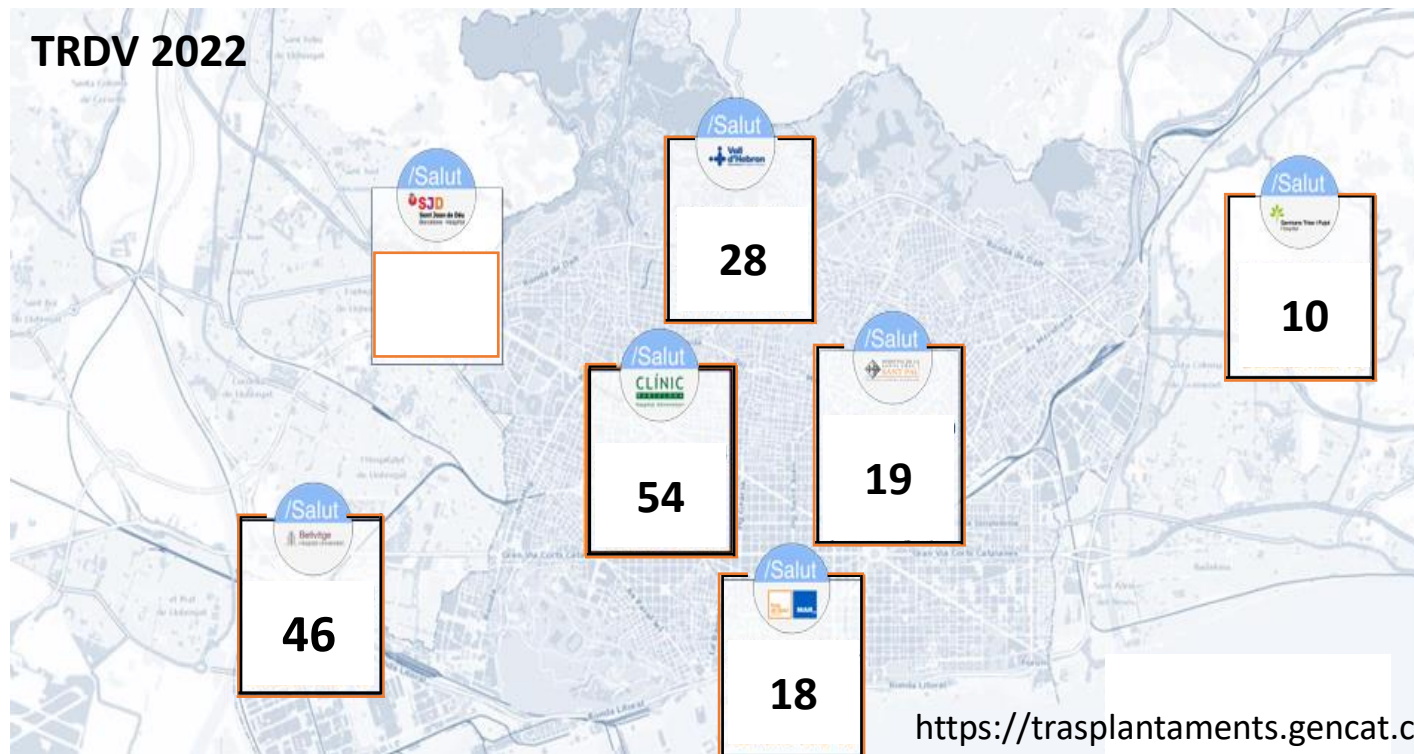
McCaughan J. et al. AJT, 2018

# Specificities of the Catalan reality

Living donor compatible paired exchange to improve compatibility?



Ferrari P. Transplantation, 2017



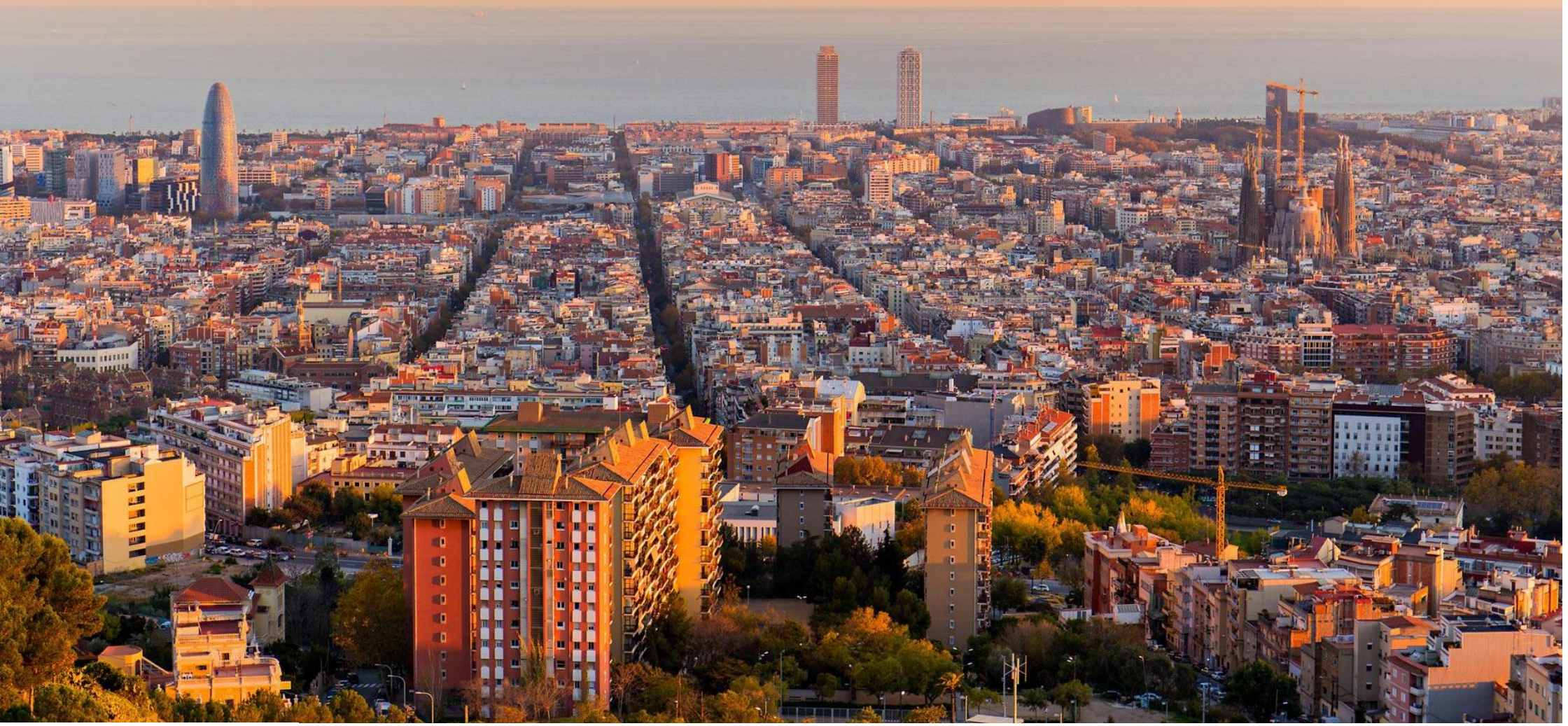


# Conclusions

- In retrospective studies, high molecular HLA mismatch has been associated to adverse outcomes in different types of SOT
- Limitations of those studies must be taken into account: n of patients, different quality of HLA typing and variability of algorithms and cut-offs applied
- In KT, prospective data will be generated to support the use of allocation of LDKT based on improved Eplet compatibility
- HLA compatibility can be improved by higher completeness and quality of HLA typing and paired donation to increase allele-level compatibility. Molecular mismatch algorithms might be used on top of antigen compatibility to improve outcomes
- Further data are needed to establish immunogenicity of different HLA epitopes, and those could be assessed in future for more fair allocation



*Moltes gracies!*







# Experiences in prospective use of molecular HLA MM

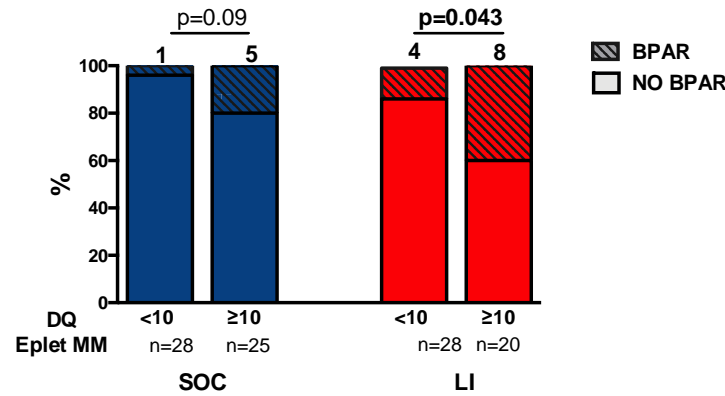
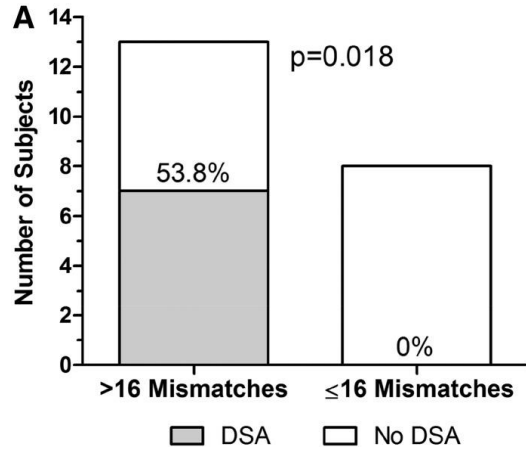
## Treatment individualization

Post hoc analyses of the impact of HLA molecular MM after IS minimization:

Cortar?

### TAC WITHDRAWAL (CTOT-09)

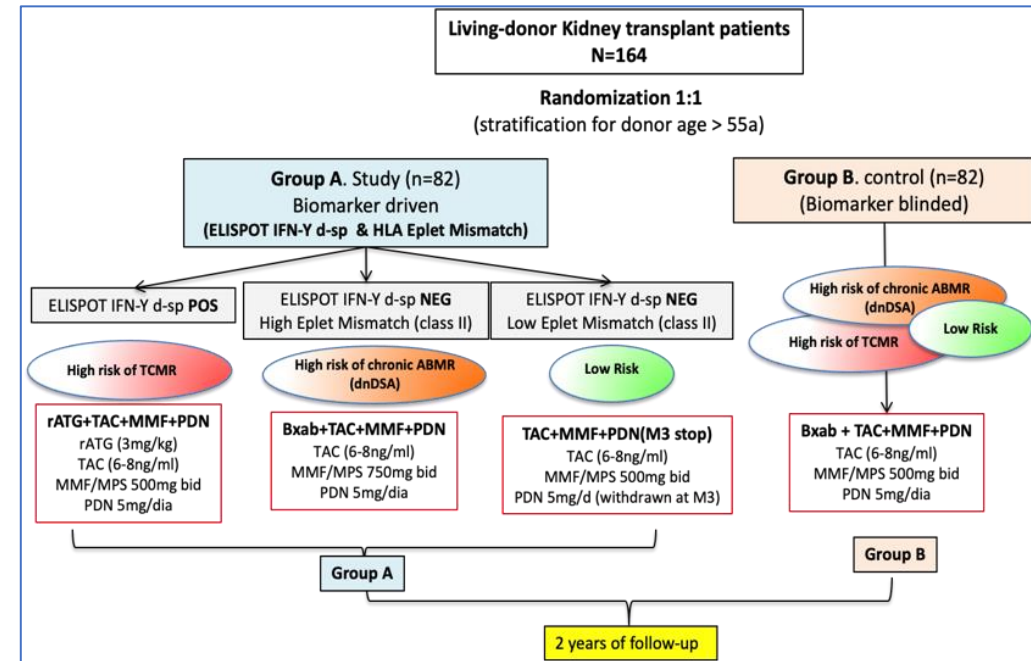
### TAC MONOTHERAPY (CELLIMIN)



Hricik D. et al. Am. J Transplant, 2015

Bestard O. et al. Am J Transplant. 2021

### The BioImmune Trial (NCT03465397)



### CTOT: Biomarker guided CNi substitution in kidney transplantation

Project Number  
5U01AI063594-19

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