AST AMERICAN SOCIETY OF TRANSPLANTATION

HLA Molecular Mismatch Assessment

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CEOT CUTTING EDGE of **TRANSPLANTATION**

TRANSPLANT SUMMIT 2019

NO SIZE FITS ALL: *Uncovering the Potential of Personalized Transplantation*

FEBRUARY 21–23, 2019 • ARIZONA BILTMORE • PHOENIX, AZ

Relevant Financial Relationship Disclosure Statement

Peter Nickerson, University of Manitoba, Winnipeg, Canada

Consultant for Vitaeris Inc. and Astellas Pharma

Honoraria from One Lambda/Thermo Fisher Inc.

AND

My presentation <u>does not</u> include discussion of off-label or investigational use of drugs

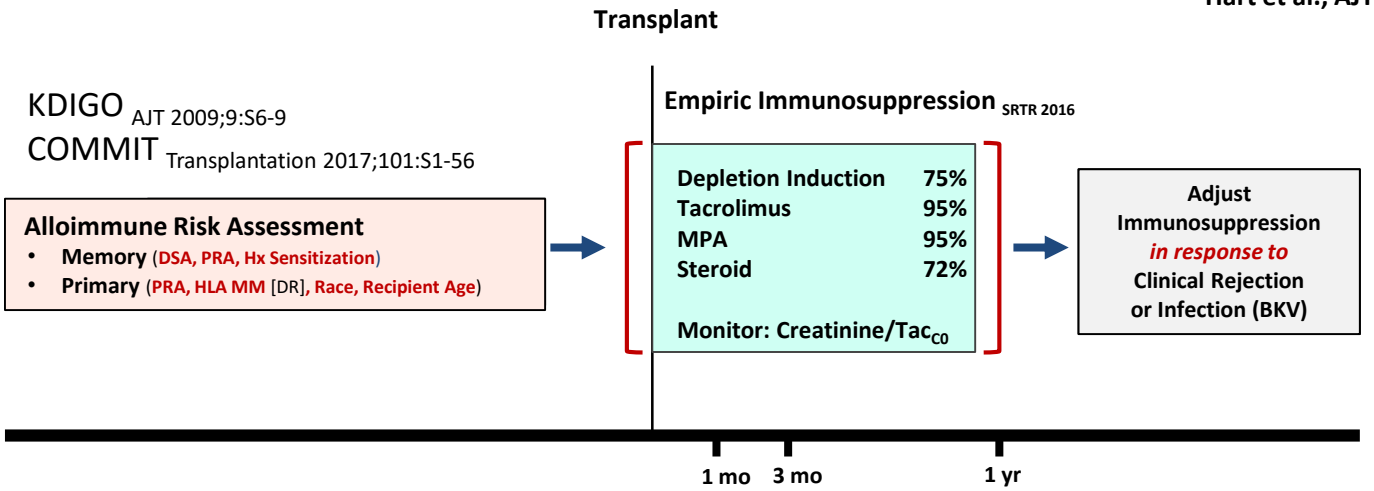
Learning Objectives

- To understand the difference between whole antigen versus molecular HLA mismatch assessment.
- To understand the computational methods available for conducting HLA molecular mismatch assessment.
- To review the literature supporting HLA molecular mismatch as a prognostic biomarker for primary alloimmunity (TCMR, DSA and ABMR) in kidney transplantation.
- To review the evidence supporting HLA molecular mismatch as a predictive biomarker for CNI minimization in kidney transplantation.

United States

Immunosuppression "Standard of Care" in Kidney Transplantation

Hart et al., AJT (2018) S18-113



Variance in Immunosuppression

Induction:	60% Center Practice	11% Risk Profile
Maintenance:	30% Center Practice	5% Risk Profile

Transplant International 2018;31:198-211

Am J Transplant 2016;16:2453-2462

HLA IDENTICAL TRANSPLANTATION PROLONGS GRAFT SURVIVAL

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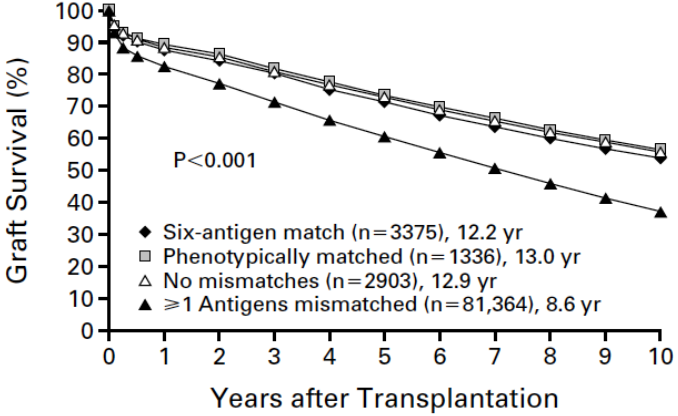
Murray et al., Surg. Forum (1955) 4:432-436

Takemoto et al., NEJM (2000) 343:1078-84



8.5% are 0 MM

93.5% are ≥1MM

"We must now prepare for the second phase in which more sophisticated measures of HLA compatibility should be developed for more accurate prediction ("prognostication") of outcome"

Mickey, Kreisler, Albert, Tanaka, Terasaki

Tissue Antigens (1971) 1:57

Prognostic Biomarker

A biomarker that indicates an increased (or decreased) likelihood of a future clinical event.

FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. Silver Spring (MD): Food and Drug Administration (US); 2016

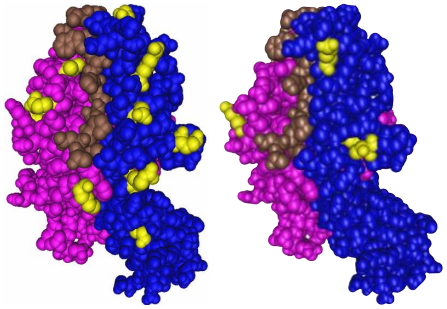
Sensitization in Transplantation: Assessment of Risk (STAR) 2017 Working Group Meeting Report

Pre-Transplant donor-recipient HLA laboratory evaluation						PROGNOSTICATION	
CDC crossmatch	Flow crossmatch	Single Ag Bead	History of sensitization	HLA Molecular MM	HLA identical	Immune Risk Assessment	
DSA positive	DSA positive	DSA positive				Active memory and at risk for hyperacute rejection	MEMORY
Negative	DSA positive	DSA positive				Active memory and at risk for ABMR and TCMR	MEMORY
Negative	Negative	DSA positive				Active memory and at risk for ABMR and TCMR	MEMORY
Negative	Negative	Negative	Pregnancy or prior transplant with repeat MM			At risk for latent memory with a recall B and T cell response	MEMORY
Negative	Negative	Negative	cPRA with unknown repeat MM			Potential risk for latent memory with a recall B and T cell response	MEMORY
Negative	Negative	Negative	No	High		Increased risk for de novo alloimmune response	PRIMARY
Negative	Negative	Negative	No	Low		Baseline risk for de novo alloimmune response	PRIMARY
Negative	Negative	Negative	No	0	Yes	Low risk for de novo alloimmune response	PRIMARY

MM, Mismatch; DSA, donor-specific antibody; ABMR, antibody-mediated rejection; TCMR, T cell–mediated rejection.

Tambur et al., AJT (2018) 18: 1604-1614

Traditional Whole Antigen Mismatch



$DQ\alpha_1\beta_1$ Molecule 1 **$DQ\alpha_1\beta_1$ Molecule 2**

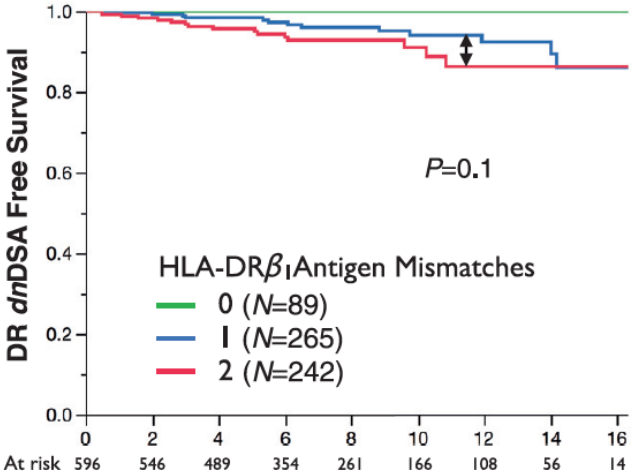
Antigen Mismatch = 2

Risk for Primary Alloimmunity

Current Standard

HLA-DR and DQ Whole Antigen MM are not useful to prognosticate risk for *de novo* DSA

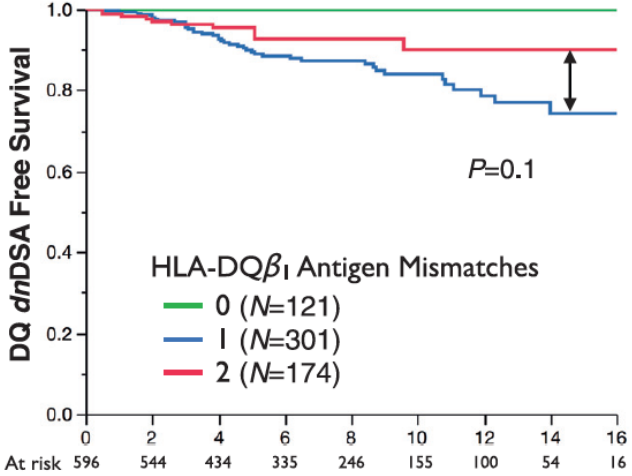
(n=596, ROC analysis)



Years

AUC = 0.58

Sensitivity 65% (0 vs. 1+ MM)



Years

AUC = 0.54

Sensitivity 62% (0 vs. 1+ MM)

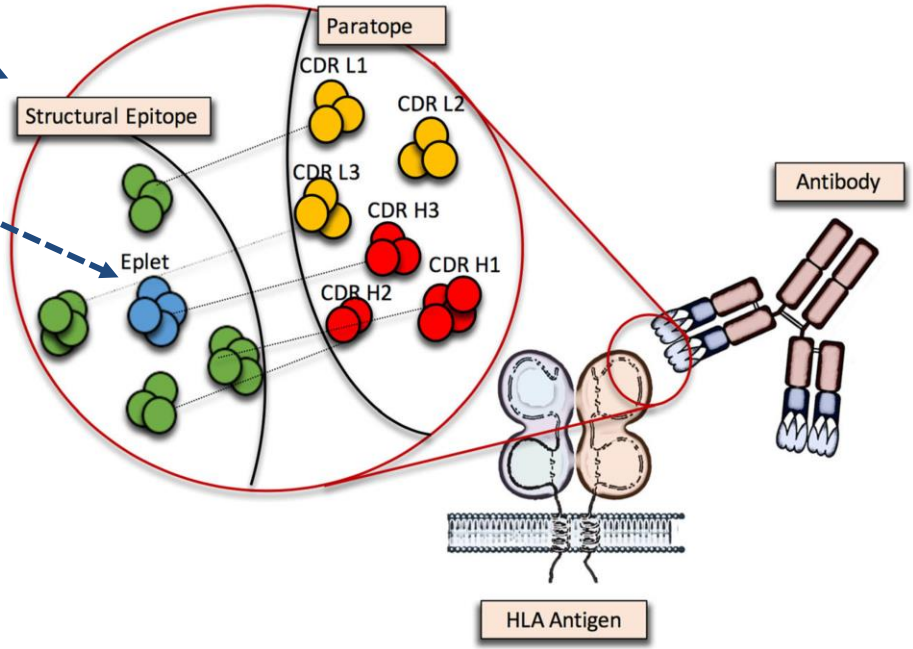
Wiebe et al., JASN (2017) 28:3353-3362

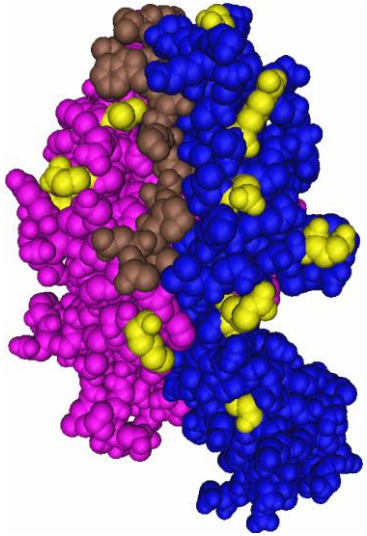
HLA Molecular Mismatch induces BCR Allorecognition

Biological Basis is the Epitope – Paratope Structural Relationship

Antigenicity
Binding Affinity

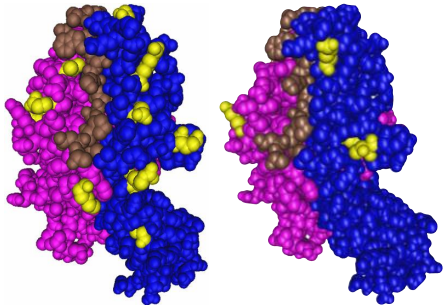
Immunogenicity
Donor Specific Aminoacids





Pediatr Nephrol (2017) 32:1861-69

Traditional Whole Antigen Mismatch



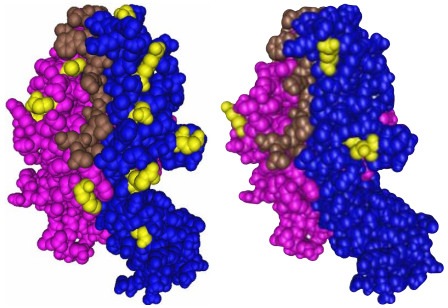
DQα$_1$β$_1$ Molecule 1

DQα$_1$β$_1$ Molecule 2

Antigen Mismatch = 2

Risk for Primary Alloimmunity

HLA Matchmaker Eplet Mismatch Sum



DQα$_1$β$_1$ Molecule 1

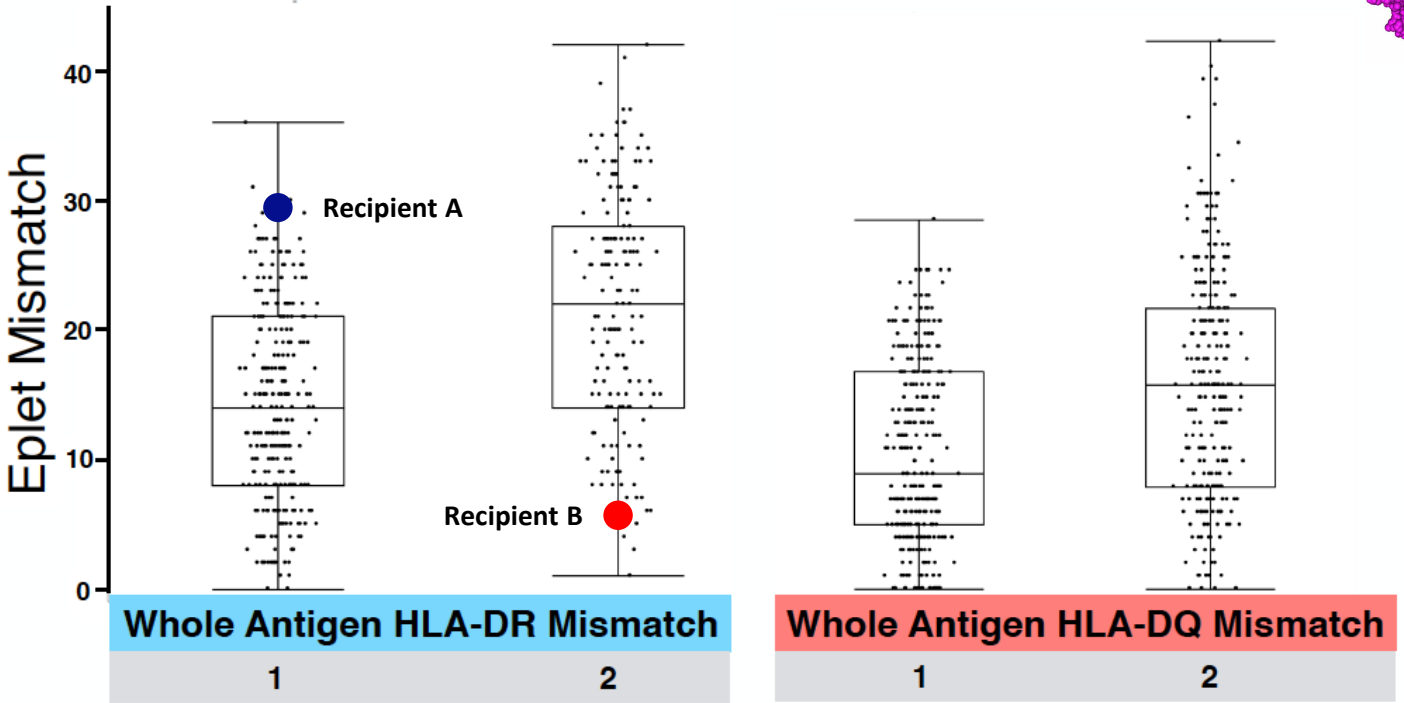
DQα$_1$β$_1$ Molecule 2

Eplet Mismatch Sum = 12

Risk for Primary Alloimmunity

Assessing Donor – Recipient Relatedness

Traditional Whole Antigen HLA MM *versus* HLA Eplet MM



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

Independent Correlates of *de novo* DSA

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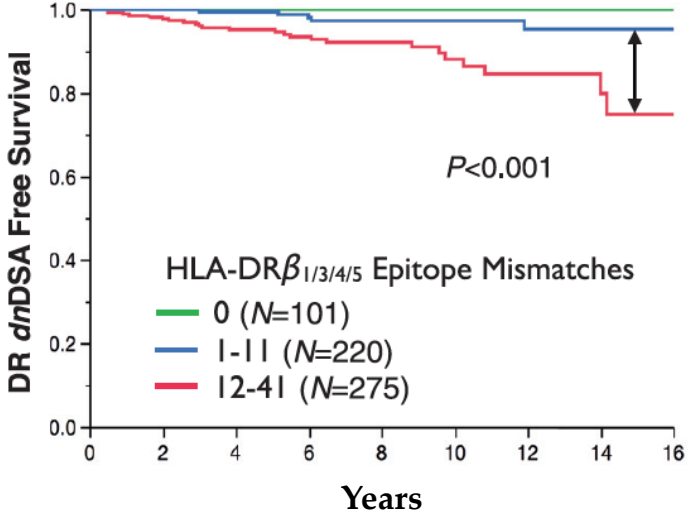
Total Cohort	DR *dn*DSA *n*=596, 29 Events		DQ *dn*DSA *n*=596, 51 Events	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Recipient age at transplant, yr	0.97 (0.95 to 0.99)	0.02	0.97 (0.95 to 0.98)	0.002
Nonadherence	3.07 (1.40 to 6.52)	<0.01	3.11 (1.71 to 5.58)	<0.001
Cyclosporin versus tacrolimus	2.14 (0.93 to 4.70)	0.07	1.97 (1.06 to 3.52)	0.03
HLA-DR$\beta_{1/3/4/5}$ eplet mismatch/ten mismatches	2.79 (1.84 to 4.27)	<0.001		
HLA-DQα_1/β_1 eplet mismatch/ten mismatches			2.00 (1.52 to 2.67)	<0.001

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

HLA Matchmaker (HLA DRDQDP matching v2.0)

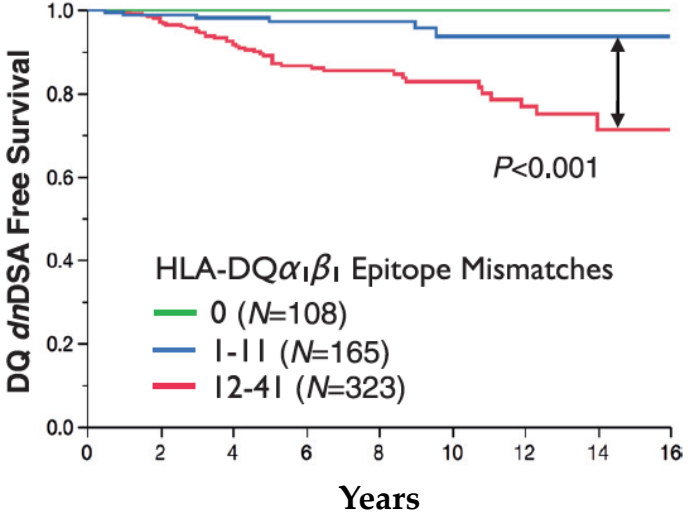
HLA-DR/DQ Molecular MM Eplet thresholds defining high risk for DSA

(n=596, ROC analysis)



AUC = 0.73

Sensitivity 90% (0-11 vs. 12+ Ep MM)

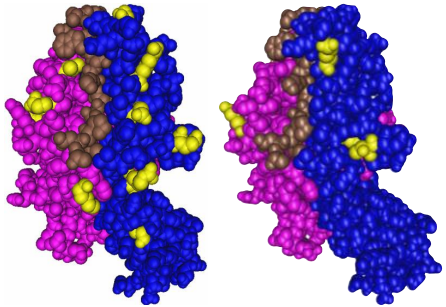


AUC = 0.72

Sensitivity 94% (0-11 vs. 12+ Ep MM)

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

Traditional Whole Antigen Mismatch



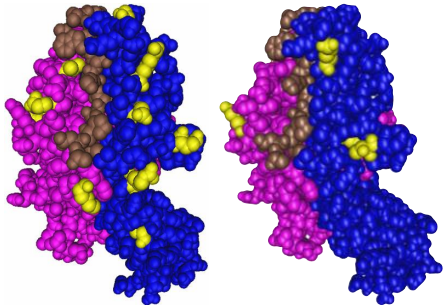
DQα1β1 Molecule 1

DQα1β1 Molecule 2

Antigen Mismatch = 2

Risk for Primary Alloimmunity

HLA Matchmaker Eplet Mismatch Sum



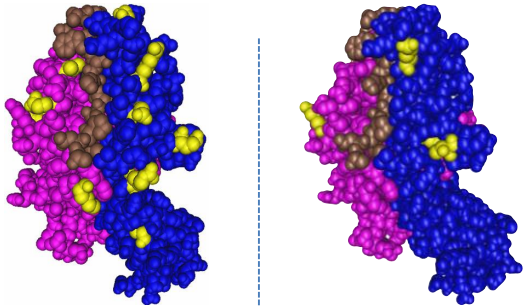
DQα1β1 Molecule 1

DQα1β1 Molecule 2

Eplet Mismatch Sum = 12

Risk for Primary Alloimmunity

Single Molecule Eplet Mismatch



DQα1β1 Molecule 1

Eplet Mismatch = 9

Risk for Primary Alloimmunity

DQα1β1 Molecule 2

Eplet Mismatch = 3

Risk for Primary Alloimmunity

Receiver Operating Characteristic Curves

Single Molecule Eplet Mismatch

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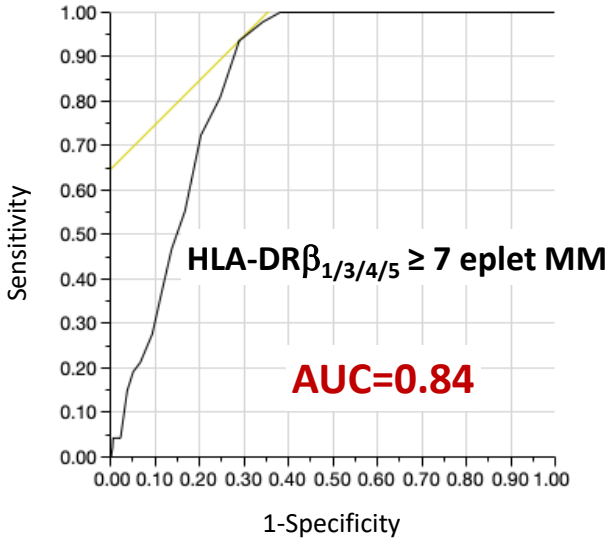
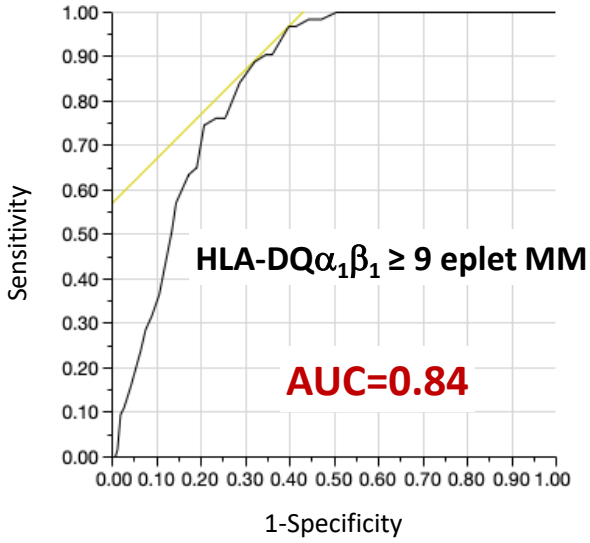
HLA-DR *de novo* DSA



HLA-DQ *de novo* DSA



Wiebe et al., DOI:10.111/ajt.15177

HLA-DR/DQ Molecular Mismatch Score:

A Prognostic Biomarker for Primary Alloimmunity in Kidney Transplantation

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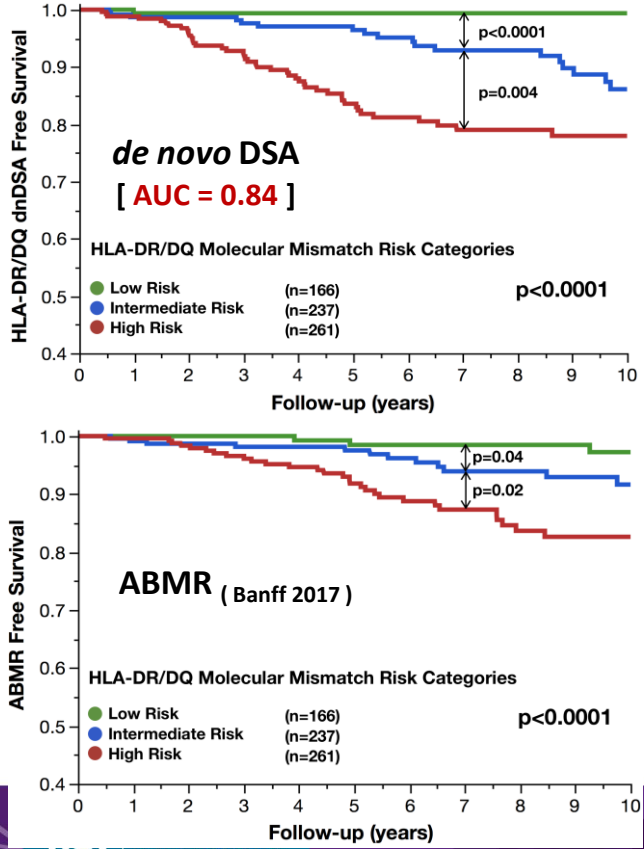
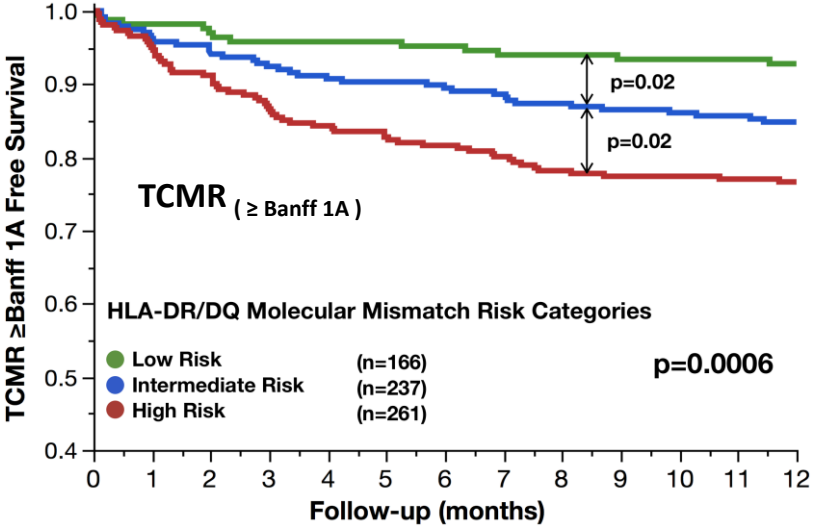


Low Risk (**25%** of transplants)

Intermediate Risk (**35%** of transplants)

High Risk (**40%** of transplants)



Wiebe et al., DOI:10.111/ajt.15177

HLA-DR/DQ Molecular Mismatch Score (Accepted into FDA BQP)

Context of Use:

Prognostic biomarker (determined at the time of transplant in conjunction with baseline HLA Ab testing to rule-out preformed alloimmunity) **categorizing kidney transplant recipients** as **high, intermediate, or low risk** categories for ***de novo* DSA, graft rejection and graft failure**, with categories to be used independently or in pairs for **enrichment** or use of all categories **to stratify risk** in phase 2 and 3 clinical trials

Benefit:

Improve efficiency of clinical trials **versus current standard** of primary alloimmune risk assessment

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Predictive Biomarker

A biomarker that identifies individuals that are more likely to respond after exposure to a particular medical product or environmental agent.

FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. Silver Spring (MD): Food and Drug Administration (US); 2016

Tacrolimus withdrawal in Immune Quiescence (CTOT-09)

Hricik et al., JASN (2015) 26:3114-22

National Institute of Allergy and Infectious Diseases

CTOT

University of Manitoba

Consented/Enrolled Subjects
N=52

Transplanted Subjects
N=47

Randomized Subjects
N=21

Tac, MMF, Pred
N=7

MMF, Pred
N=14

DSMB Stops Trial

No TCMR
1 DSA (DQ)

TCMR (N=3)
DSA (N=2)
DSA and TCMR (N=3)
DR and DQ (N=2)
DQ only (N=3)

"Low Risk" Primary Kidney Transplant

- Living Donor – no Brain Death, minimal IRI
- No DSA, PRA <30%
- 81% Caucasian, 4.8% African American

Rx: Thymo, Tacrolimus, MMF, Prednisone

"Immune Quiescence"

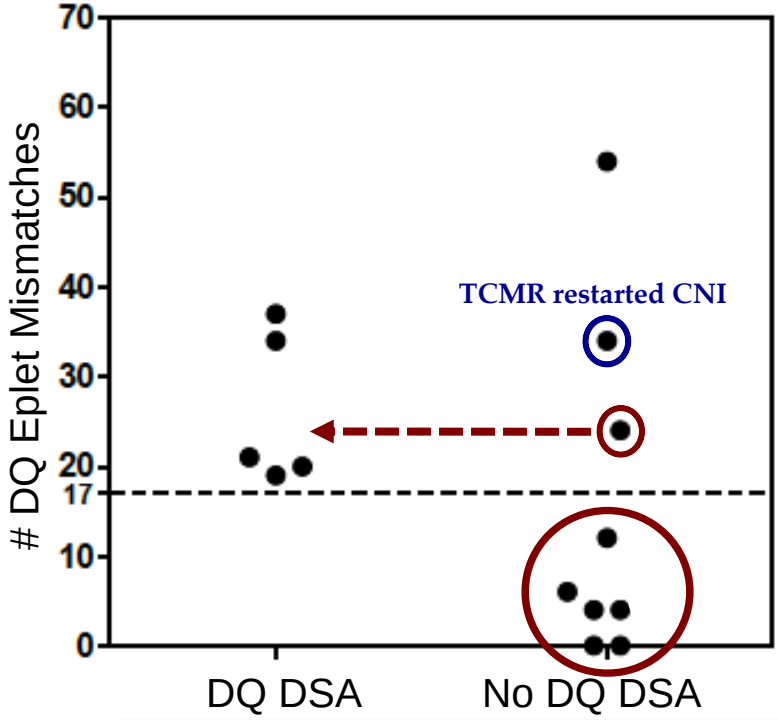
- 0 to 6 mo course: No Acute Rejection
- 6 mo Protocol Biopsy: Normal Histology
- 6 mo Antibody Screen: No DSA

Tacrolimus Tapered over 3 months

Low Risk ≠ Low Risk to Minimize
Quiescence ≠ Low Risk to Minimize
Post-transplant Biomarkers can Define Adequacy of Immunosuppression
Post-transplant Biomarkers cannot Predict Safety to Minimize

HLA-DR/DQ Molecular Mismatch Score:

A Predictive Biomarker for Immunosuppressive Minimization (CTOT-09 RCT)



De novo DQ DSA associated with high Eplet MM load (≥ 17)

5/8 in Tac withdrawal

(P=0.0310)

6/8 in longer follow-up

(P=0.0096)

Patients do tolerate no CNI without developing de novo DSA

Hricik et al., JASN (2015) 26:3114-22

HLA-DR/DQ Molecular Mismatch Score:

A Predictive Biomarker for Immunosuppressive Minimization (Manitoba Cohort)

Wiebe et al. JASN (2017) 28: 3353–62

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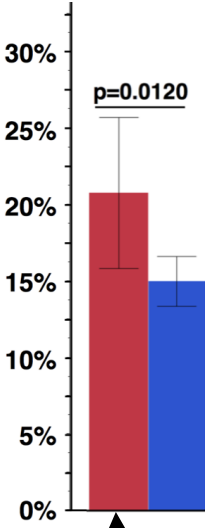
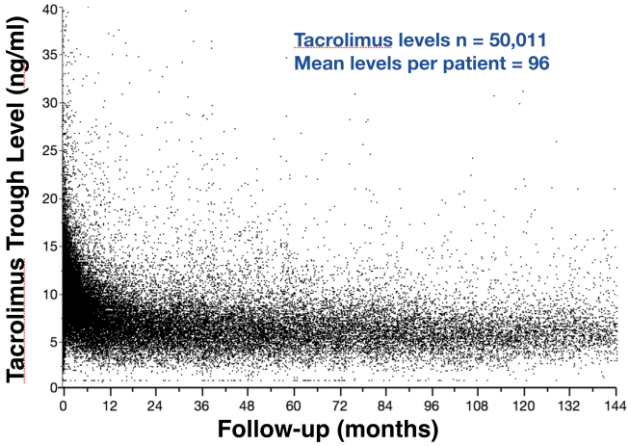
% Tacrolimus Trough Levels < 5ng/ml





No dnDSA

dnDSA

High Alloimmune Risk

(HLA-DR or DQ Eplet MM >11)

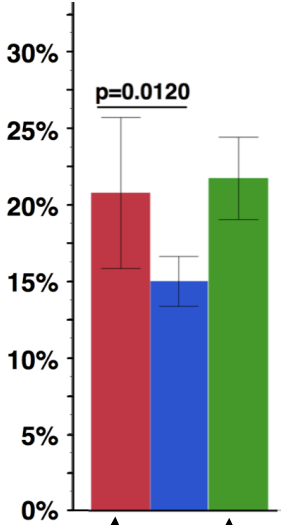
HLA-DR/DQ Molecular Mismatch Score:

A Predictive Biomarker for Immunosuppressive Minimization (Manitoba Cohort)

Wiebe et al. JASN (2017) 28: 3353–62

University of Manitoba

% Tacrolimus Trough Levels < 5ng/ml



A Low Risk HLA DR/DQ Molecular Mismatch modulates the Tacrolimus C_0 required to prevent dnDSA

No dnDSA

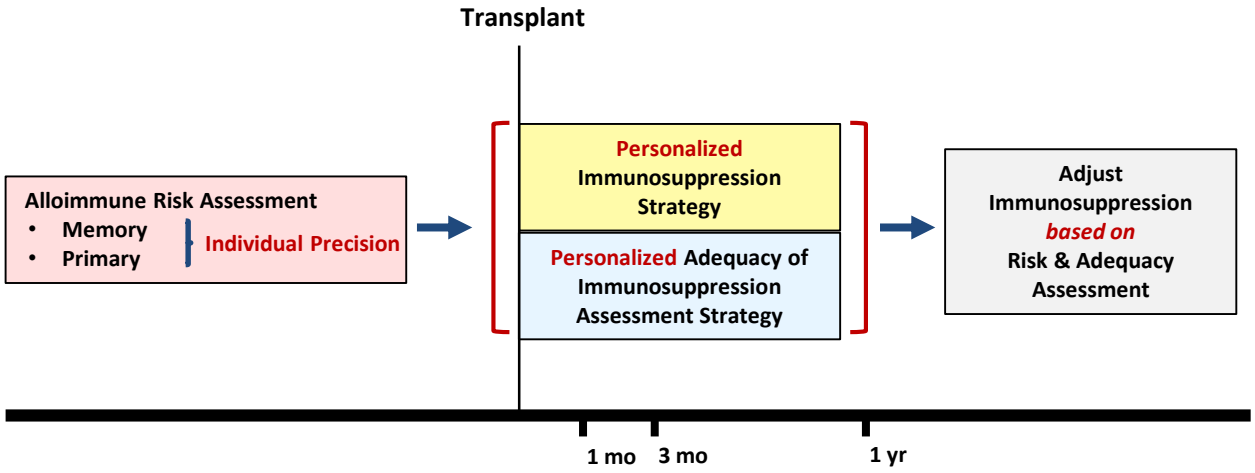
No dnDSA

dnDSA

Low Alloimmune Risk
(HLA-DR and DQ Eplet MM ≤11)

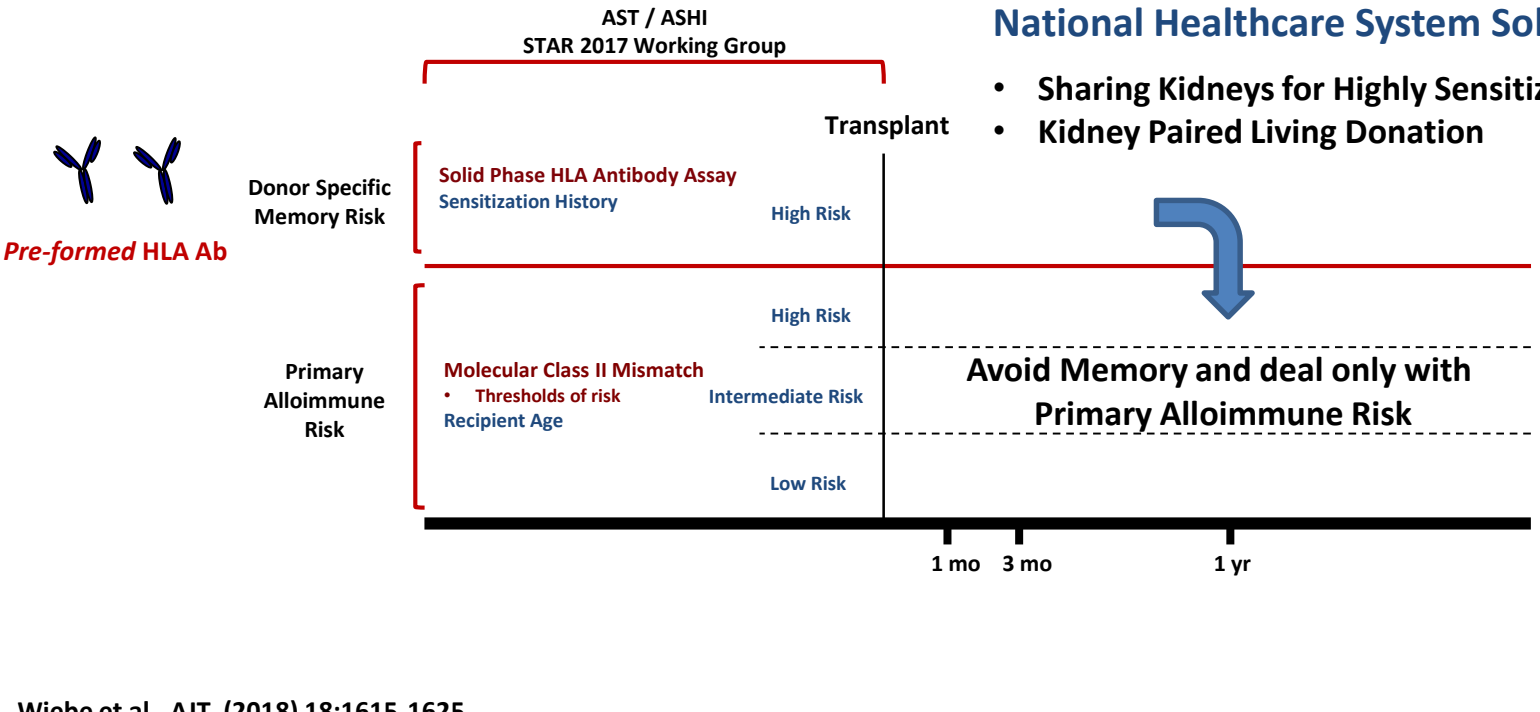
High Alloimmune Risk
(HLA-DR or DQ Eplet MM >11)

Transitioning from Empiric to Precision Medicine



Wiebe et al., AJT (2018) 18:1615-1625

Transitioning from Empiric to Precision Medicine

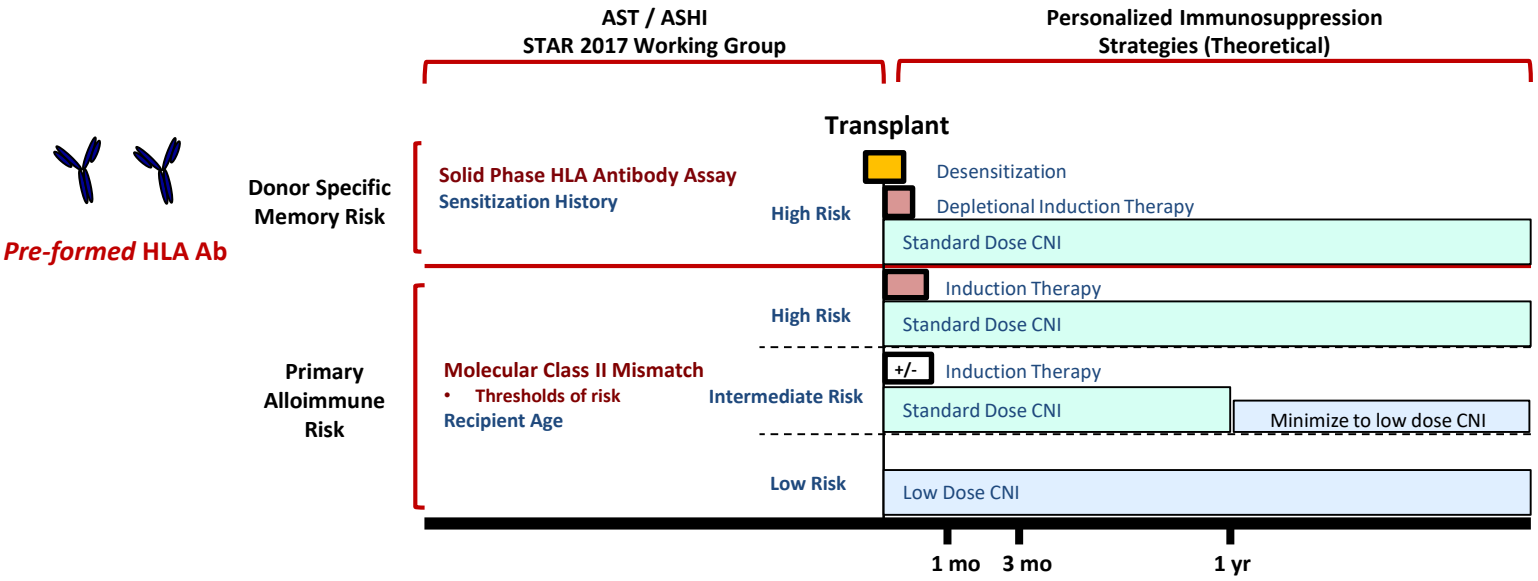


National Healthcare System Solutions

- Sharing Kidneys for Highly Sensitized Patients
- Kidney Paired Living Donation

Wiebe et al., AJT (2018) 18:1615-1625

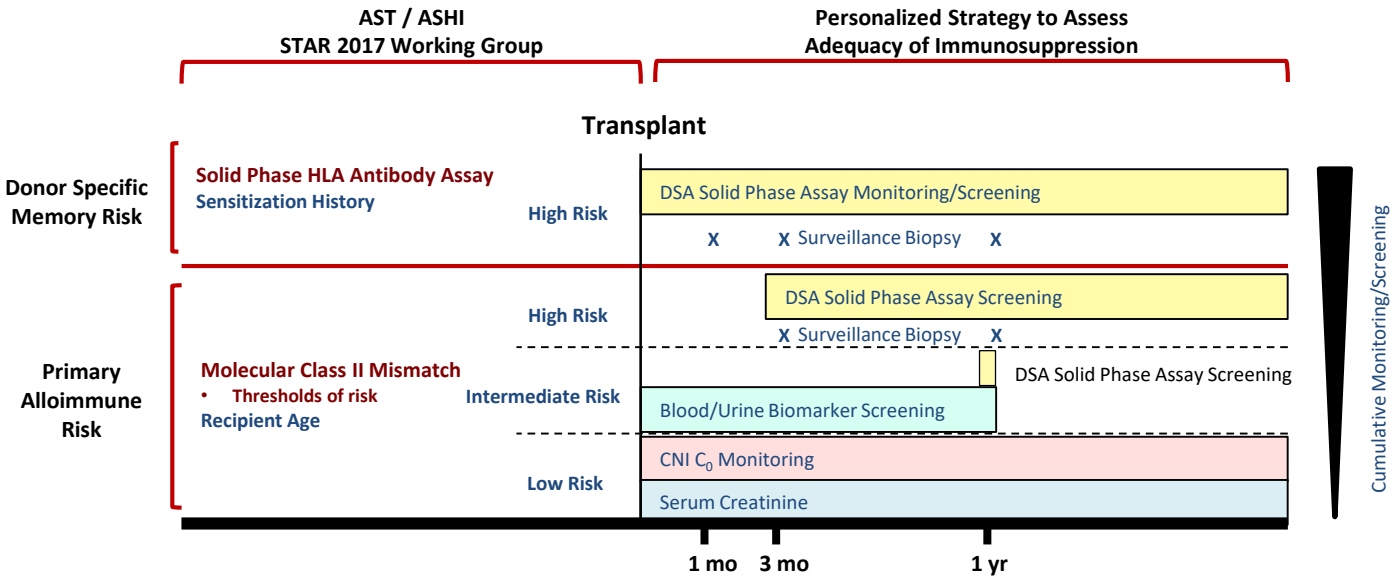
Transitioning from Empiric to Precision Medicine



Clinical Trials required to Test the Hypothesis

Wiebe et al., AJT (2018) 18:1615-1625

Transitioning from Empiric to Precision Medicine



Clinical Trials required to Test the Hypothesis

Wiebe et al., AJT (2018) 18:1615-1625

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Department of Pathology

Ian Gibson

University of Cambridge

Vasilis Kosmoliaptsis

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