THE UNIVERSITY OF BRITISH COLUMBIA

Implementation of Precision Medicine in Kidney Transplantation

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BC Kidney Day
November 10, 2023

Learning Objectives

- Overview of burden of kidney disease in Canada
- To describe the current challenges in kidney transplantation
- To describe the approach of applying precision medicine to improve outcomes in transplantation
- To describe willing to across as a solution for highly sensitized patients

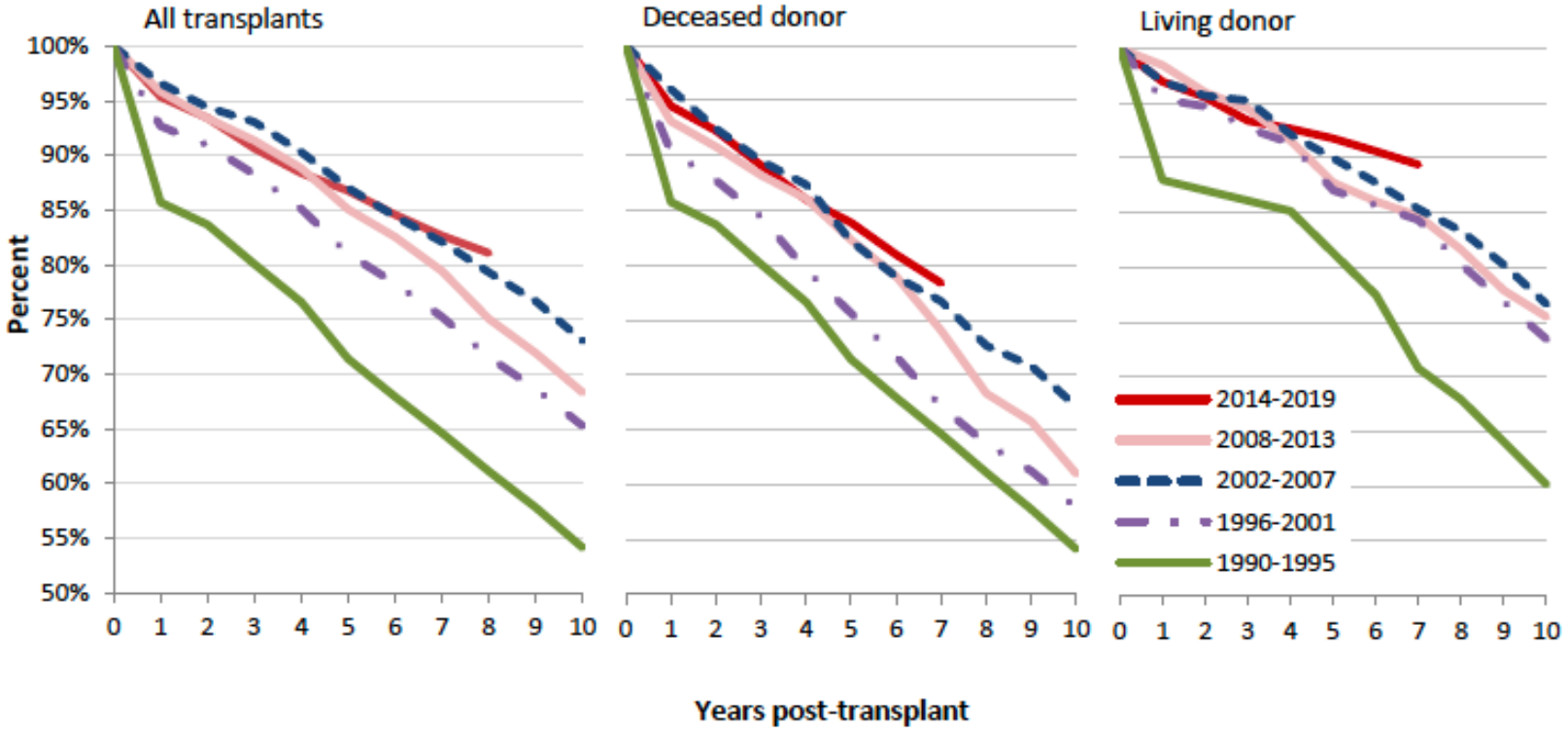
Background: Burden of Kidney Disease

- CKD affects 1 in 10 Canadians[1] , with 48,000 Canadians with ESRD[2]
- Unadjusted 5-year mortality rate of 55%[2]
- Health care cost of $2.5 billion annually[1]

- Kidney transplantation provides both mortality[3] and quality of life benefits[4]
- Transplant saves $250,000/patient over 5 years compared to hemodialysis[5]
- 52% of ESRD patients in BC are treated with a kidney transplant (Canada: 43%)

1. Manns B, et al. The Financial Impact of Advanced Kidney Disease on Canada Pension Plan and Private Disability Insurance Costs. *Can J Kidney Health Dis.* 2017;4: 2054358117703986.
2. *Canadian Organ Replacement Register, 2008 to 2017: End-Stage Kidney Disease and Kidney Transplants.*
3. Merion RM, et al. Deceased-donor characteristics and the survival benefit of kidney transplantation. *JAMA.* 2005;294(21): 2726-2733.
4. Ortiz F, et al. Health-related quality of life after kidney transplantation: who benefits the most? *Transpl Int.* 2014;27(11): 1143-1151.
5. Rabeau Y. The Economics of Kidney Failure. *The Kidney Foundation of Canada – Quebec Branch.* 2012.

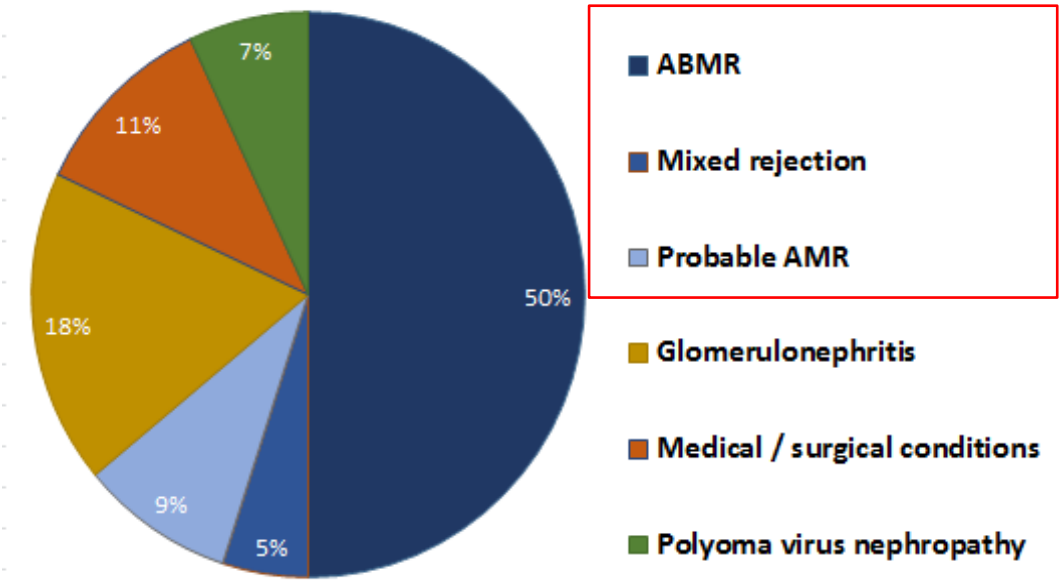
Background: Stagnant long-term kidney transplant outcomes



Rejection is a leading cause of premature graft loss

American Journal of Transplantation

Sellares et al, 2011



Dual Challenges in Transplantation

Infection (UTI, Resp, CMV, BK)
Malignancy (PTLD, SCC)
Med toxicities (GI, leukopenia)

Rejection

Dual challenges in transplantation: Mr. A

- 40M, Type 1 DM, T8 paraplegia
- May 2020: pre-emptive LD Tx
  - Induction: Basiliximab (weak)
  - Acute rejection POD#10
  - Pyelonephritis (recurrent)
  - Graft failed < 2 yrs
- Mar 2023: deceased donor Tx
- Induction: ATG (strong)
- CMV viremia >100,000
- Febrile neutropenia (Neut 0.1)

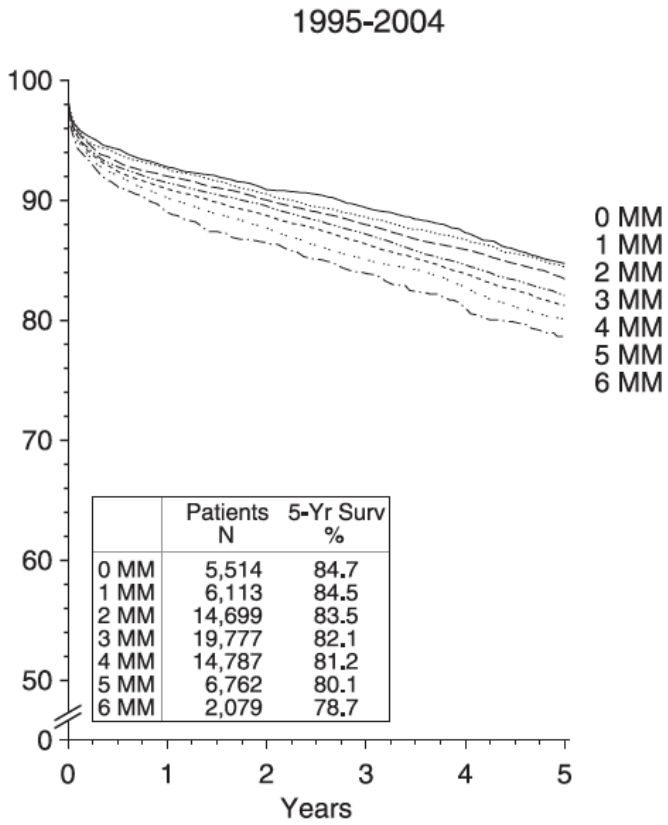
Precision Medicine CanPREVENT AMR: Applying precision medicine technologies in Canada to prevent antibody-mediated rejection and premature kidney transplant loss

$9.7 MILLION AWARDED TO KIDNEY TRANSPLANTATION RESEARCH

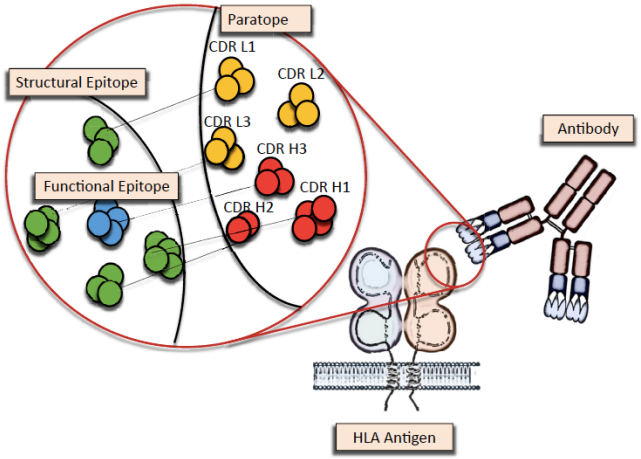
GCTC
GENOME CANADA
TRANSPLANT CONSORTIUM

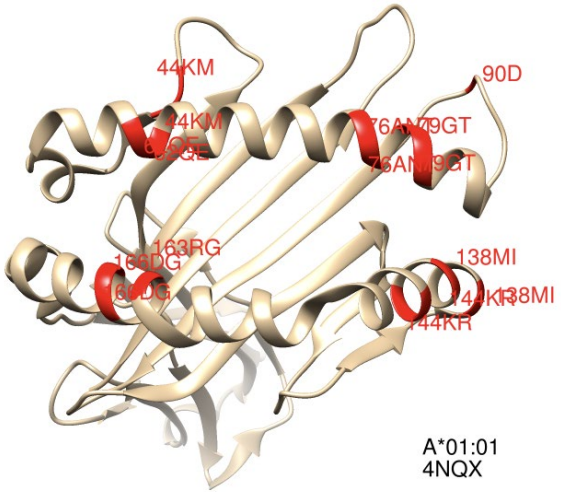
GenomeCanada

Precise matching of donors and recipients

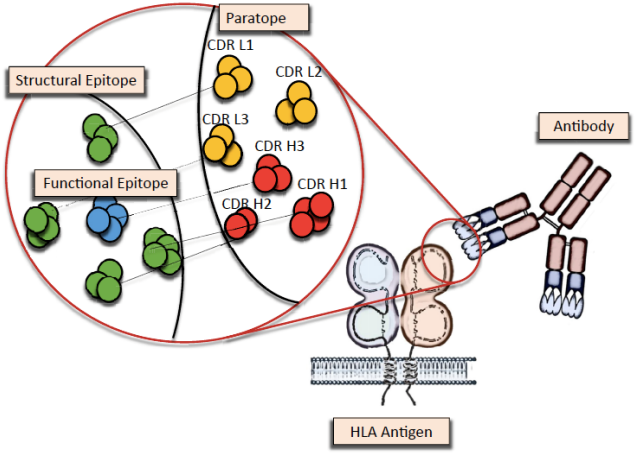


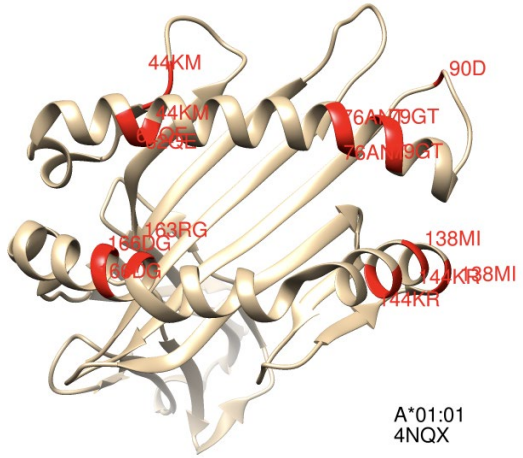
Opelz, Transplantation 2007





Recipient B*7		
Donor 1	B*8	1 mismatch
Donor 2	B*35	1 mismatch
Donor 3	B*44	1 mismatch





		80	90
Recipient B*7		AQTDRESLRN	LRGYYNQSEA
Donor 1	B*8	T---------	----------
Donor 2	B*35	T--Y------	----------
Donor 3	B*44	T--Y--N--T	ALR-------

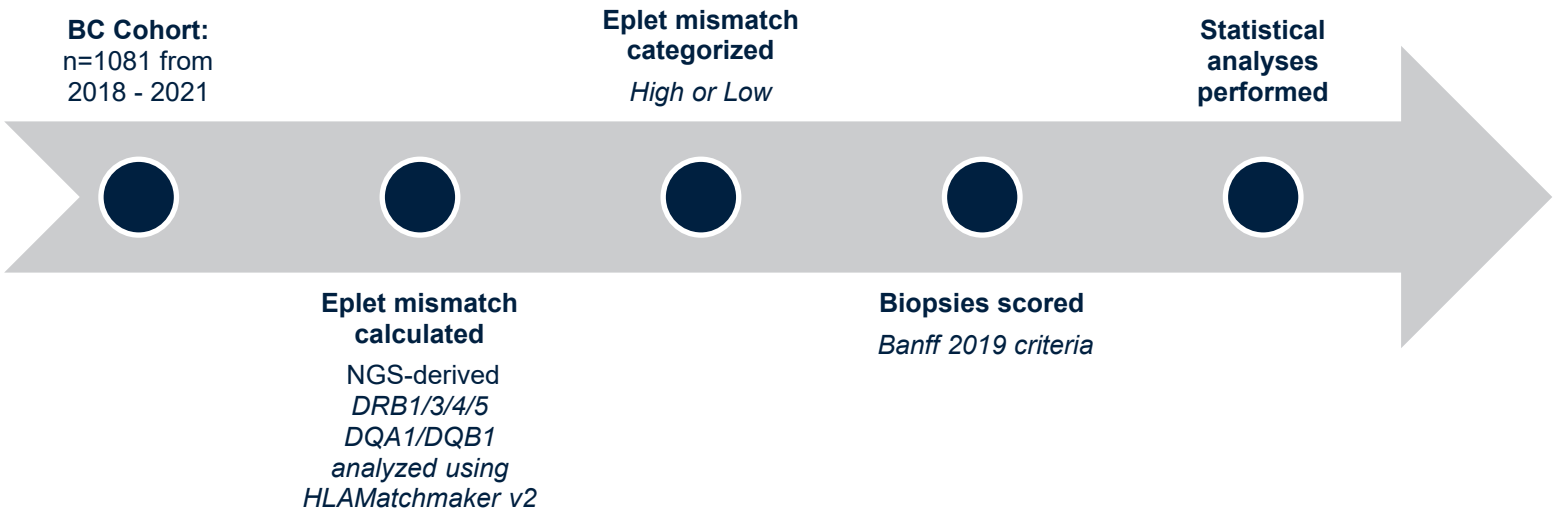
Impact of induction on acute rejection in kidney transplant recipients with eplet mismatches

Jenny Tran*, Yoojin Choi*, Mei Lin Bissonnette, Cindy Luo, Doris Chang, Casara Hong, Laura Bywater, Karen Sherwood, Paul Keown, Matthew Kadatz, James Lan

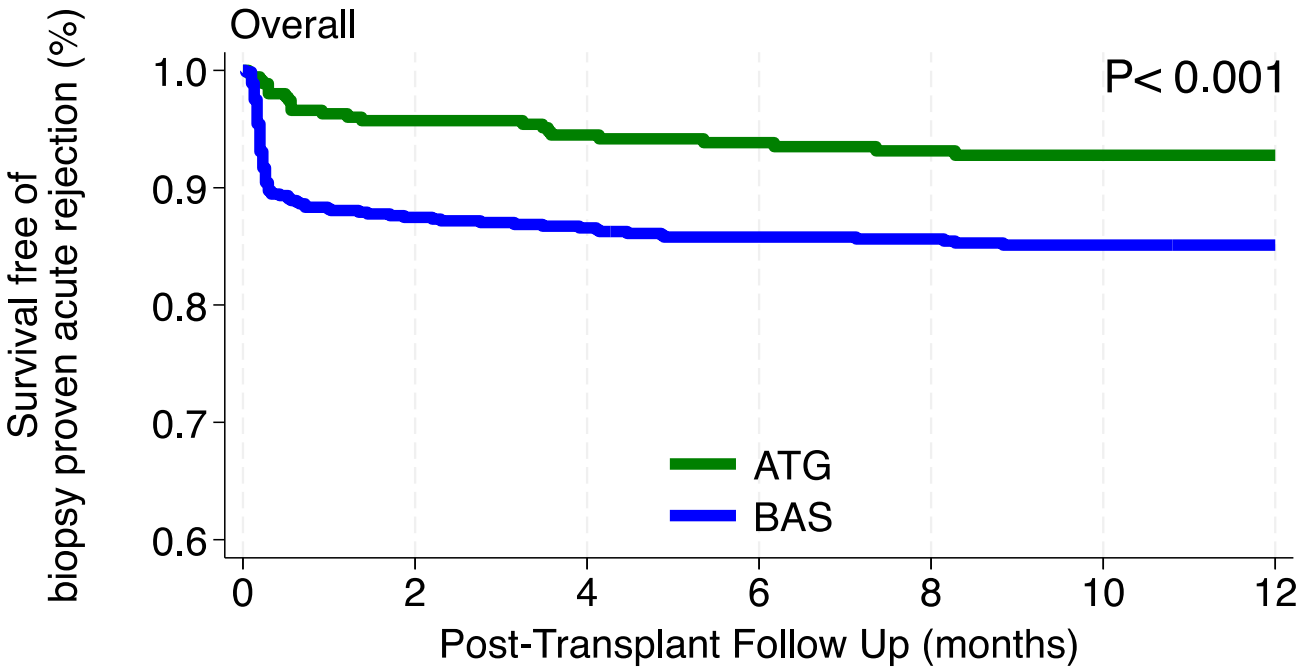
American Society of Histocompatibility and Immunogenetics, 2023
Canadian Society of Transplantation, 2023

* **High:** ≥7 at DR, ≥9 at DQ, or a combination of ≥7 DR or ≥9 DQ

Methods

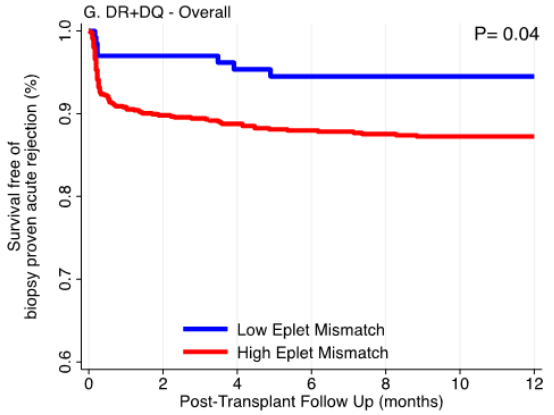


PROMIS data validated by Cindy, Casara & Laura; PROMIS biopsy data extracted by Yoojin & Jenny; Eplet mismatch calculated by Jenny; Biopsies scored by MeiLin; Statistical analyses performed by Doris & Matt; Study supervised by James

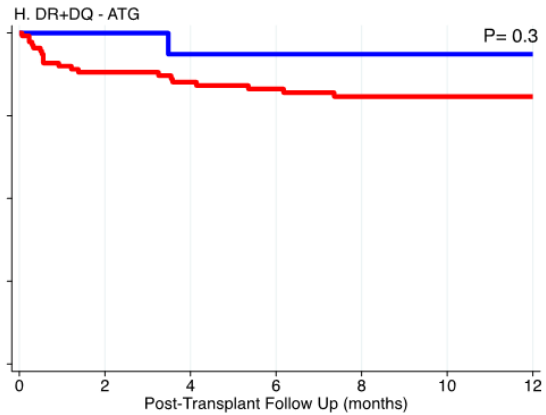

Overall
P< 0.001
Survival free of biopsy proven acute rejection (%)
1.0
0.9
0.8
0.7
0.6
ATG
BAS
0
2
4
6
8
10
12
Post-Transplant Follow Up (months)
Number at risk
ATG: 356 322 304 281 252 241 0
BAS: 725 597 561 527 504 483 0

High eplet mismatch identifies patients at increased risk of acute rejection

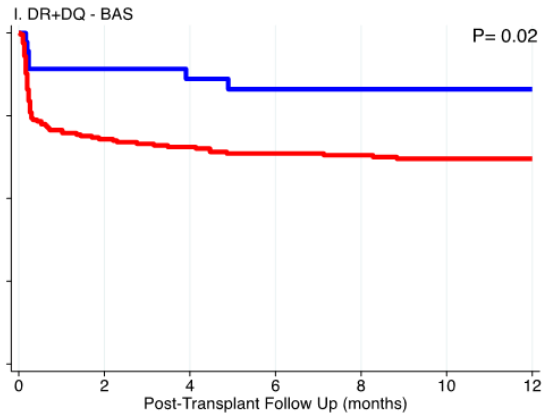
DR+DQ: Total



DR+DQ: ATG



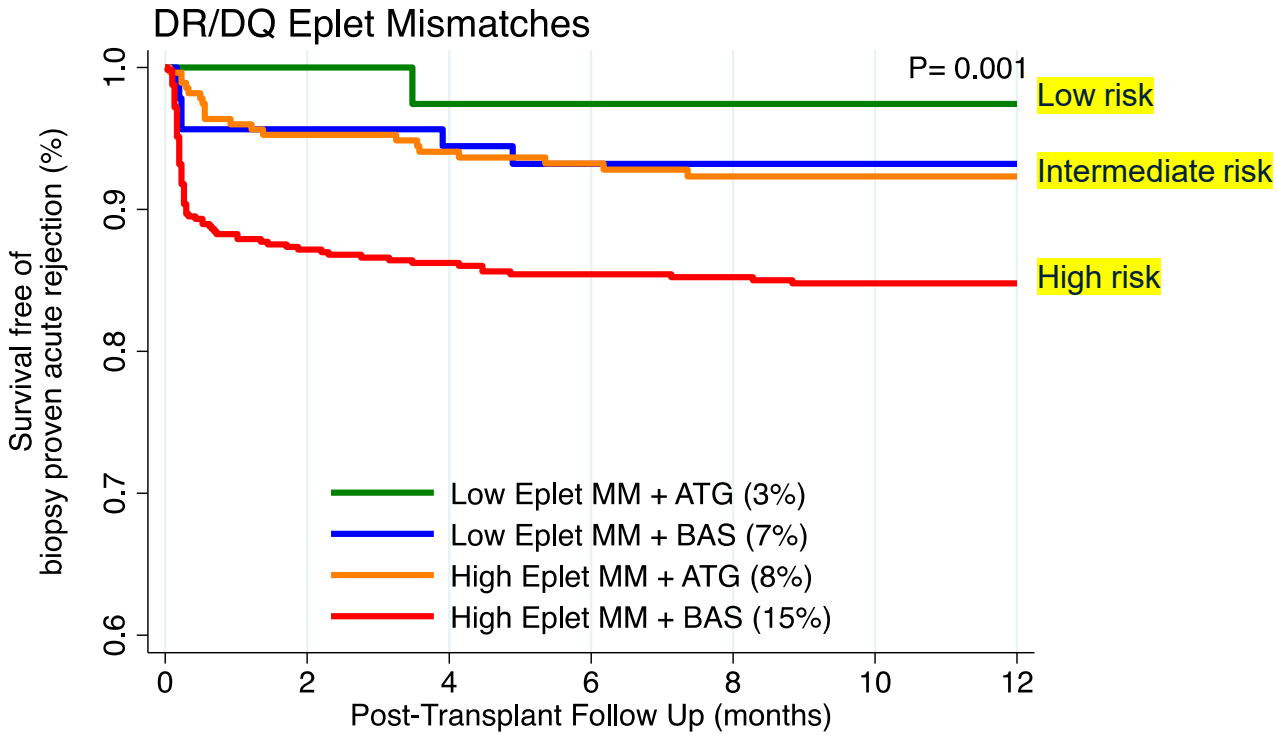
DR+DQ: BAS



MV Regression for Acute Rejection

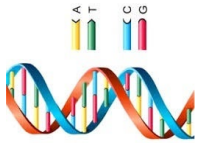
	Class II Eplet Mismatch
	HR (95% CI)
HLA MM	
Low	Reference
High	**2.93 (1.36 – 6.29)**
Induction	
ATG	Reference
BAS	1.72 (1.06 – 2.81)
Recipient Age	
< 40	Reference
41 – 60	0.48 (0.31 – 0.74)
≥ 61	0.25 (0.14 – 0.45)
Donor Type	
Living Donor	Reference
Deceased Donor	0.94 (0.62 – 1.44)
Donor Age	
< 40	Reference
41 – 60	1.99 (1.28 – 3.09)
≥ 61	1.83 (0.96 – 3.48)

Combining eplet mismatch with induction type stratifies patients into 3 acute rejection risk categories



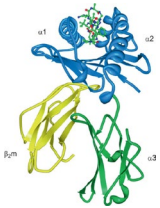
Is “precision medicine” a buzz term or can we actually implement it?

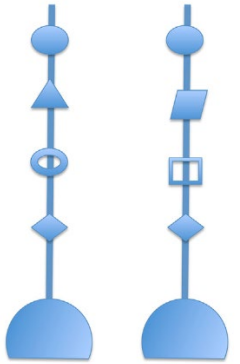
Rapid high resolution typing in deceased donor transplant



HLA-A*02:01

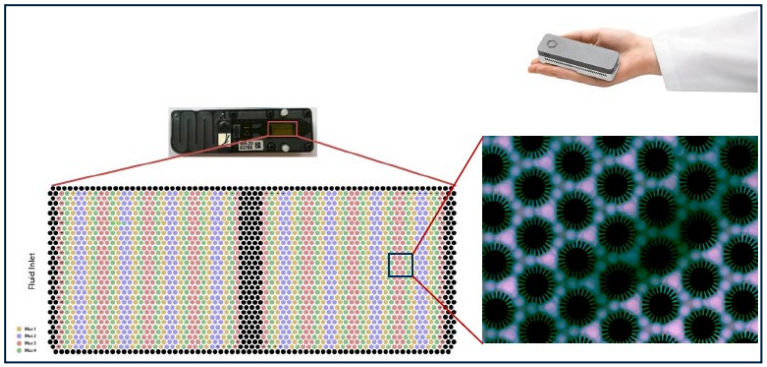
HLA matchmaker

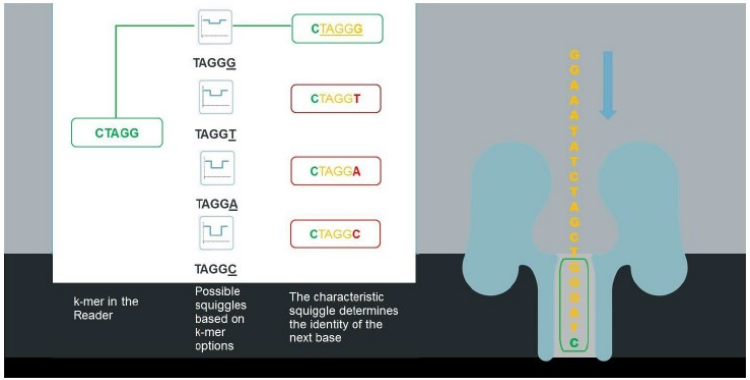




HLA antigen 1 HLA antigen 2

Oxford Nanopore for rapid deceased donor high resolution typing





Dr. Karen Sherwood

- 512*4=2048 pores
- 450 bases/pore/sec
- Long reads (avg > 10K bp)
- Easy and rapid workflow

	Miseq	Nanopore
Library prep	10-12 hr	1.5 hr
Sequencing time	40 hr	1 hr

Rapid high resolution typing in deceased donor transplant

Total turn-around time 5 hr 30 minutes

- DNA extraction: 20 minutes
- Set-up: 15 minutes
- PCR time: 135 minutes
- Library prep time: 80 minutes
- Sequencing time: 60 minutes
- HLA analysis: 15 minutes
- Epitope mapping: 5 minutes
- Final report

Applying precision medicine to organ allocation

1954-2022

Rejection

Infection
Malignancy
Med toxicities

2023 - Future: improved HLA matching

What about the highly sensitized patients?

- 40 F, blood group A, ESRD from IgA
- On dialysis since 2010
- No kidney offers despite being in HSP
- History of severe peritonitis → PD no longer possible
- Multiple attempts at fistula creation all failed
- Line access no longer possible → thigh graft
- cPRA = 100% (history 1 pregnancy, 2 blood transfusions)

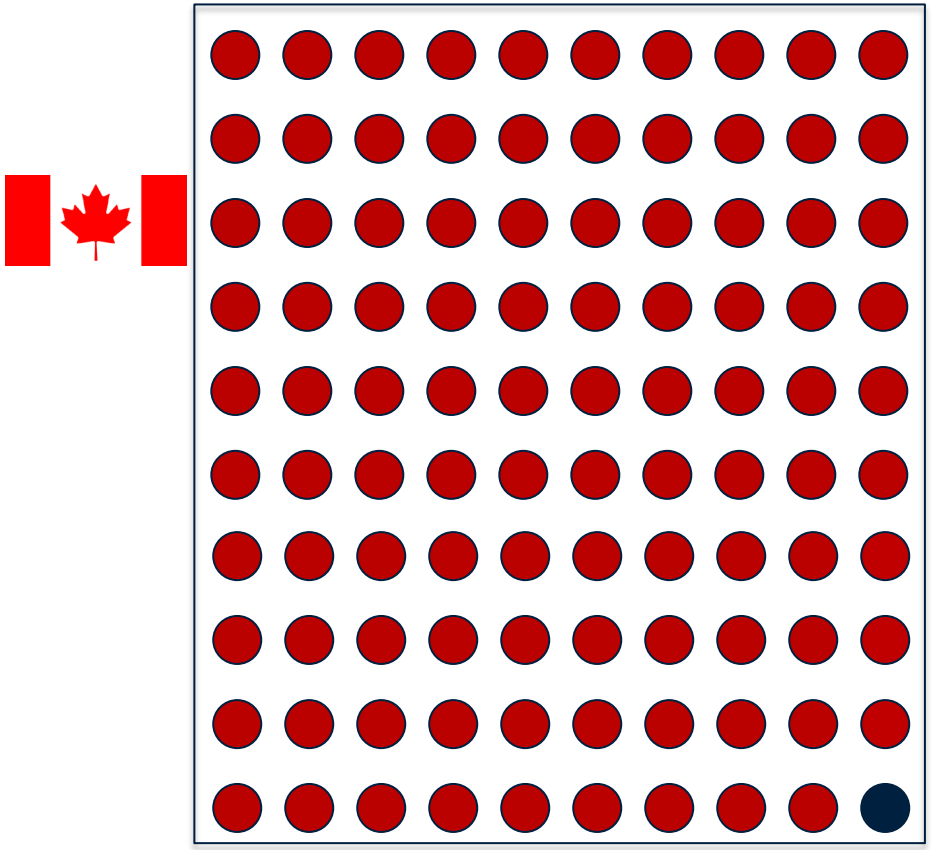
Patient’s HLA antibody profile

Cumulative Specificities for cPRA

Specificities for Calculating cPRA

A:1 3 11 25 26 29 30 31 32 33 34 36 43 66 68 69 74
B:7 8 13 18 35 37 38 39 41 42 44 45 46 47 48 49 50 51 52 53 54 55 57 58 59 60 61 62 63 64 65 67 71 72 73 75 76 77 78 81 82
Cw:9 10 15
DR:4 7 8 9 10 11 12 13 14 15 16 17 18 0103
DRw:51 52
DQ:2 6
DP:1 3 5 6 9 10 11 13 14 15 17 18 19 20

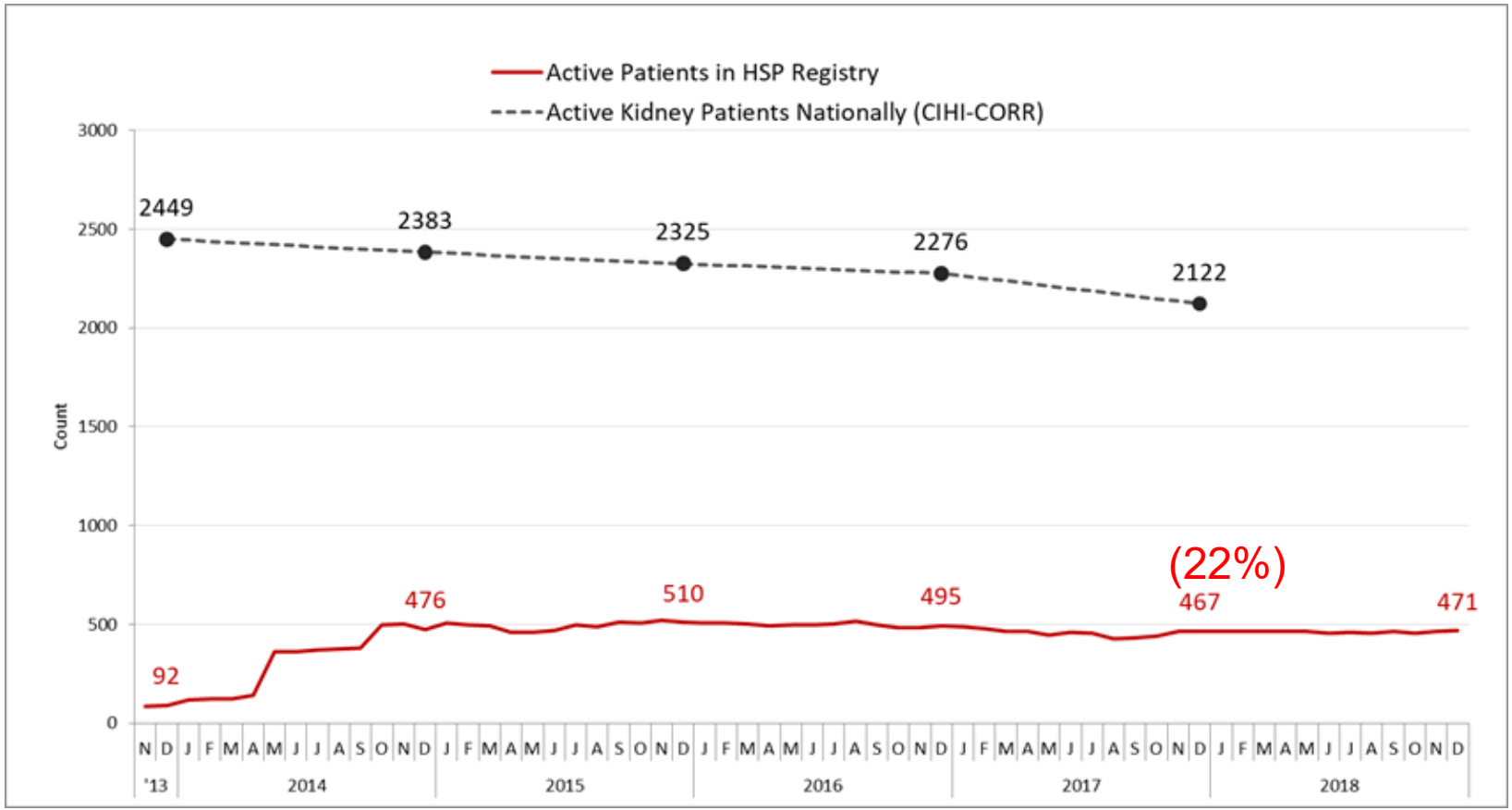
Organ sharing for highly sensitized patients



Patient 3:

cPRA = 99/100

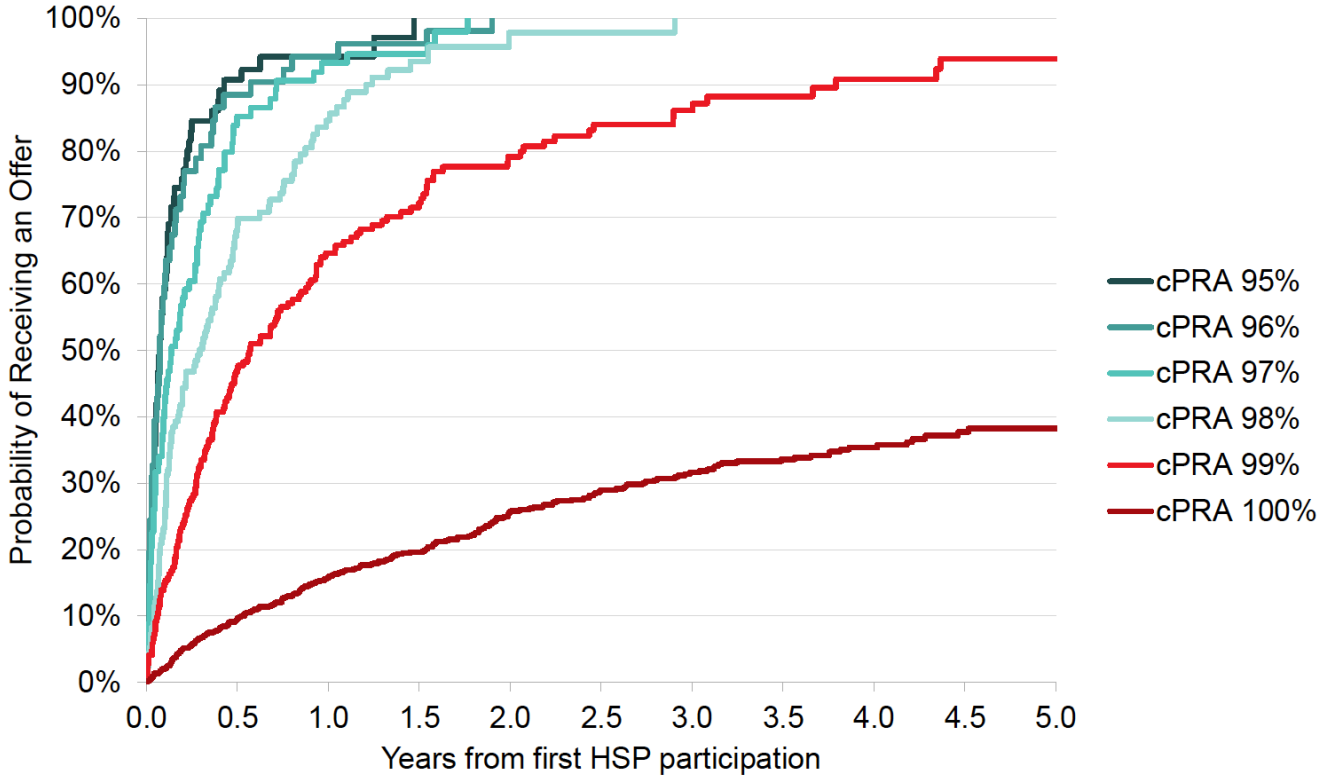
= 99%



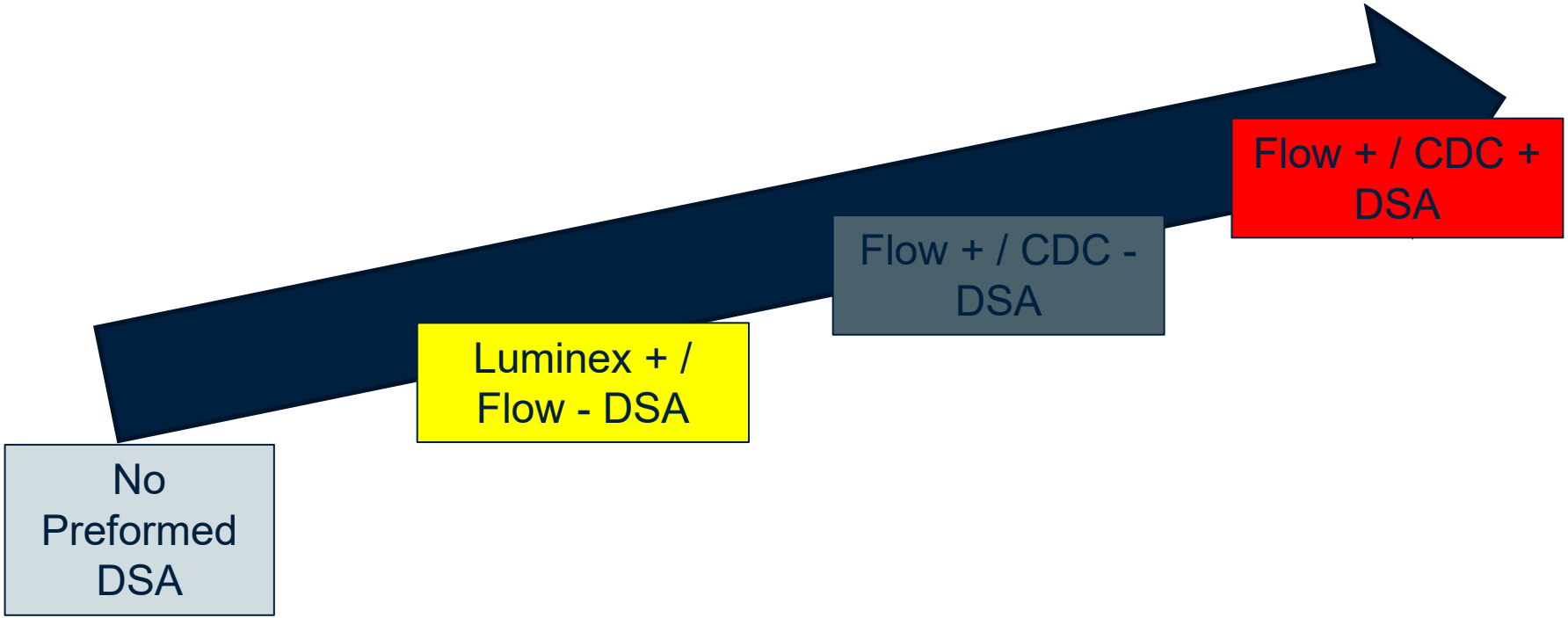
CBS, Feb 28 2019

Offer probability over time by cPRA

Approximate time to 90% probability of receiving offer	
cPRA 95%	5 months
cPRA 96%	7 months
cPRA 97%	9 months
cPRA 98%	14 months
cPRA 99%	46 months



Crossing Preformed DSA: The Science of Risk Assessment

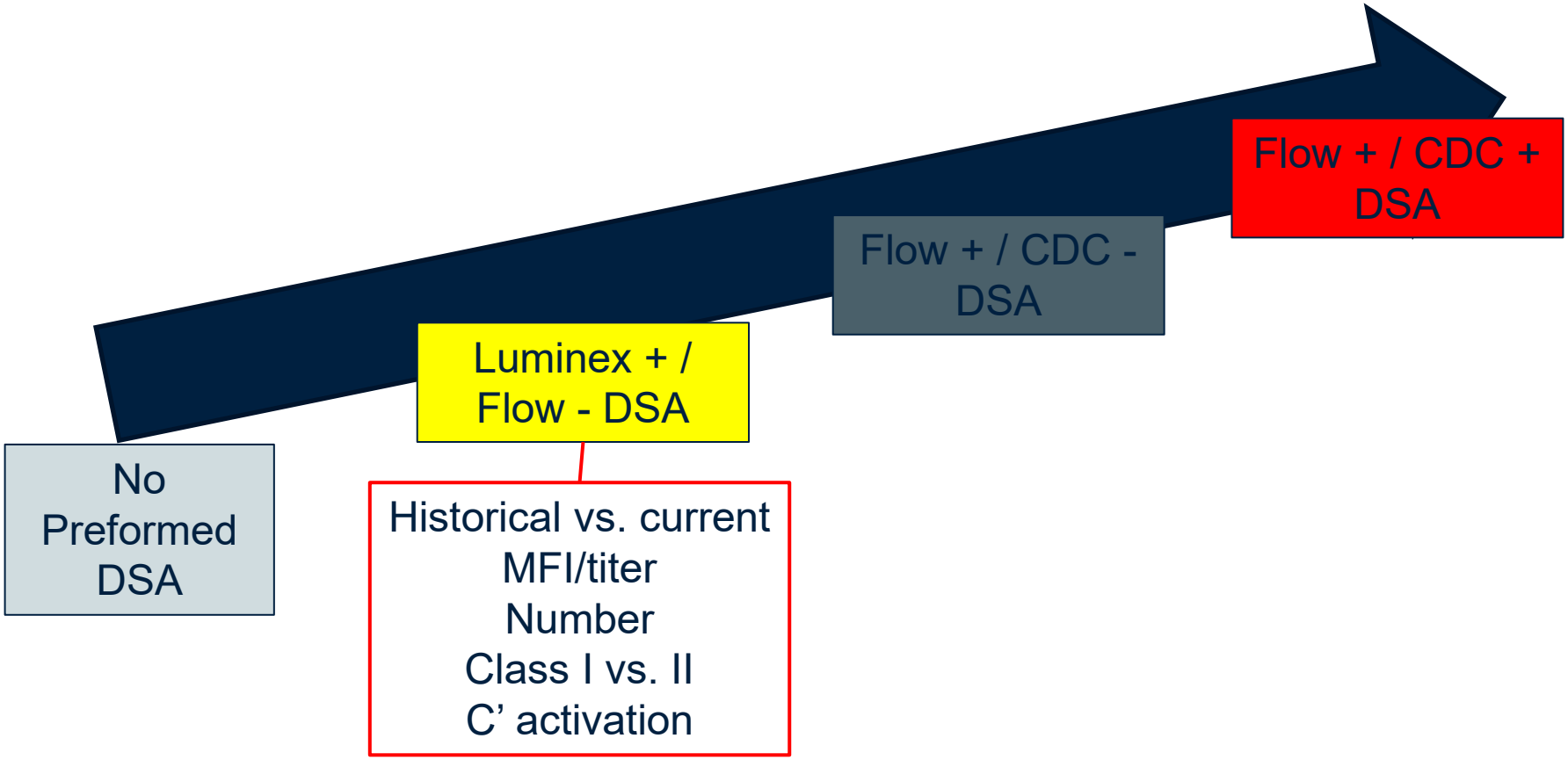


Crossing Preformed DSA: The Imperfect Science of Risk Assessment

Meta-analysis of PLNF transplants	Rejection Risk	Graft Survival
Mohan et al, JASN 2012	AMR: RR=1.98 [1.36–2.89], P<0.001	Graft loss: RR=1.76 [1.13–2.74], P=0.01
Buttigieg et al, NDT 2018	AR (1yr): RR=1.35 [0.90-2.02], P=0.14	Graft loss: RR=1.66 [0.94-2.94], P=0.08

References	Origin/study design	Study groups	Luminex vendor/cut-off	FCXM sampling/cut-off	Desensitization for PLNF group	Induction immunosuppression	Maintenance immunosuppression
Adebiyi *et al.* [13]	USA Retrospective	DSA[a] (−) $n = 498$ PLNF[b] $n = 162$	One Lambda 2-fold above negative control and absolute intensity >500 MFI	Peripheral blood or lymph node T cells ≥330 MFI B cells ≥1000 MFI	Not reported/not performed	No induction in low-risk ATG in high-risk Basiliximab in clinical trials	Mostly tacrolimus, MMF and steroids A minority mTORi instead of MMF
Orandi *et al.* [11]	USA Retrospective	DSA (−) $n = 9669$ PLNF $n = 185$ FCXM (+) $n = 536$ CDCXM (+) $n = 304$	Vendor not reported >1000 MFI	Cut-off and sampling not reported	Not reported/not performed	Not reported	Not reported
Higgins *et al.* [12]	UK Retrospective	DSA (−) $n = 28$ PLNF $n = 23$ FCXM (+) $n = 44$ CDCXM (+) $n = 17$	One Lambda ≥500 MFI	Peripheral blood or spleen RMF 4.0 for first grafts, 2.5 for re-grafts	Double filtration plasmapheresis	Basiliximab	Tacrolimus, MMF and steroids
Verghese *et al.* [14]	USA Retrospective paediatric population	DSA (−) $n = 72$ PLNF $n = 10$	One Lambda Cut-off not reported	Cut-off and sampling not reported	Not reported/not performed	Daclizumab Alemtuzumab	Cyclosporine or tacrolimus, azathioprine or MMF or sirolimus, steroid or steroid-free

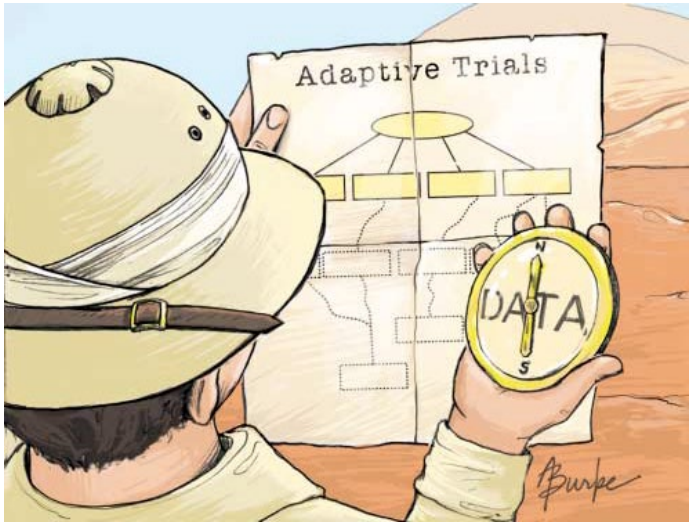
Crossing Preformed DSA: The Science of Risk Assessment



Adaptive Design as a Method to Implement WTC

- Adaptive design = allows for planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial[1]

- Allows the trial to adjust for information that was not available when the trial began



JAMA 2006

[1]FDA: Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry

Standard 3+3 Design

Study Question: *what is the maximum tolerable dose of a new drug*

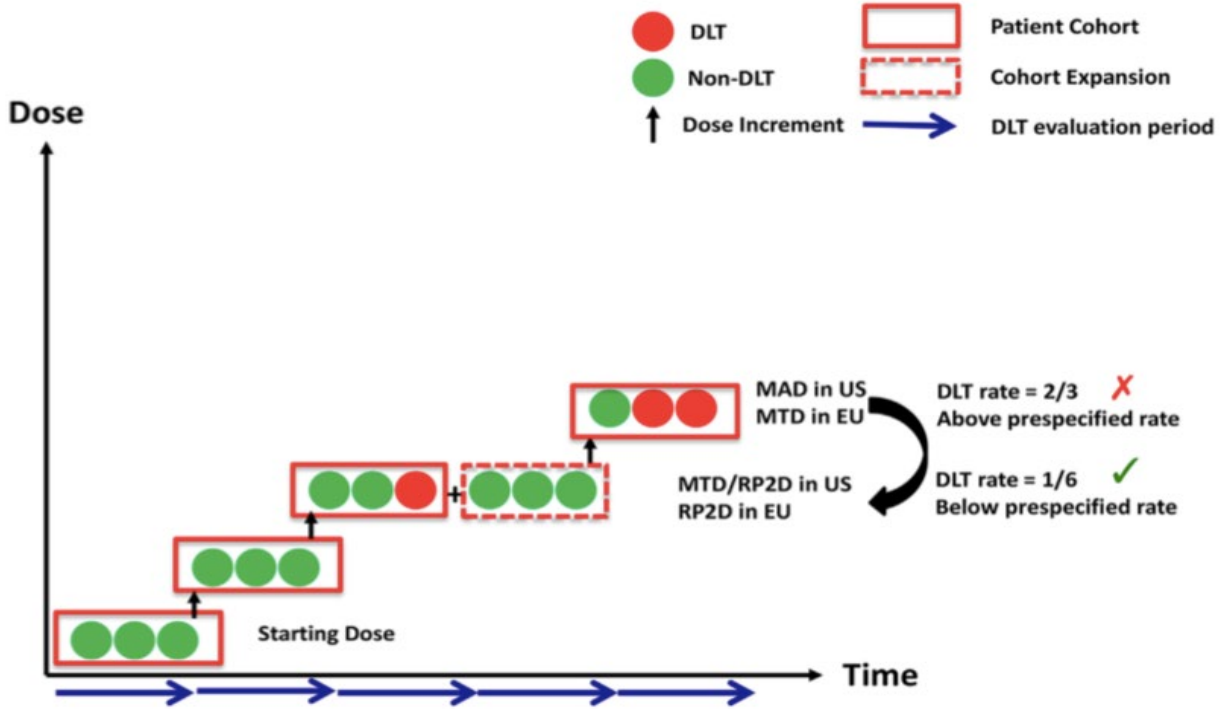
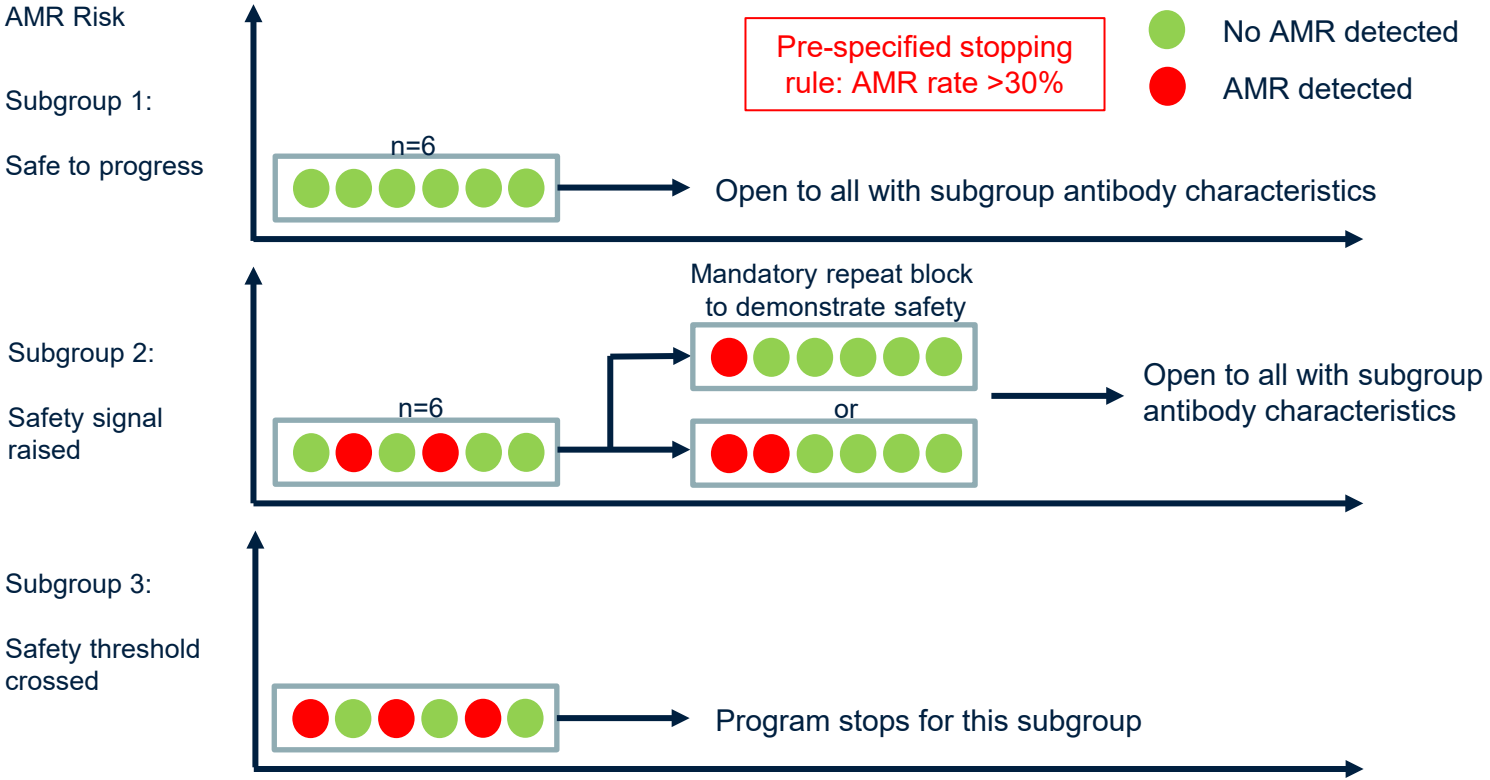


Figure 1 — Elements of a dose escalation study.

Hansen, Cancer Control 2014

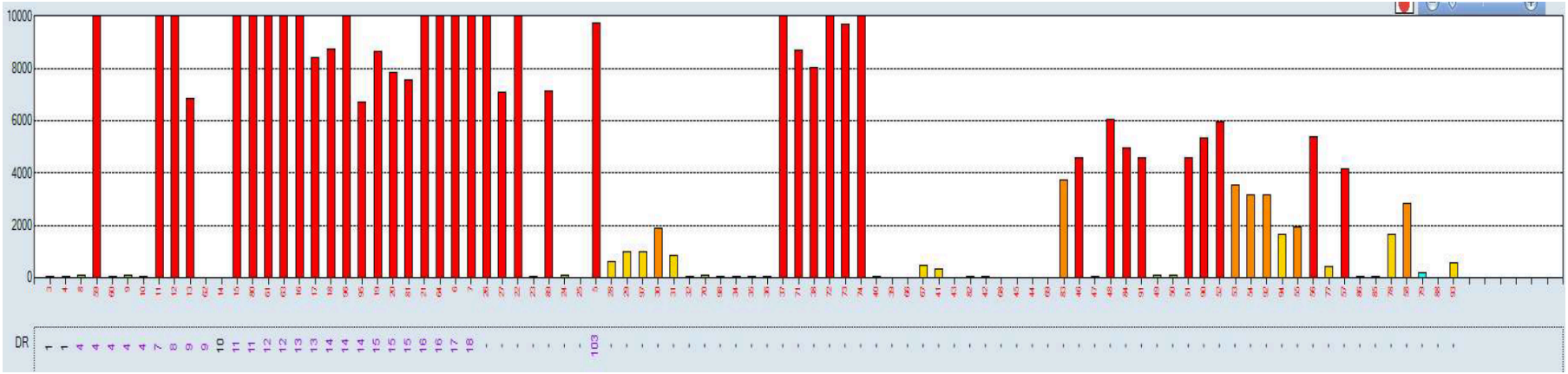

AMR Risk
Subgroup 1:
Safe to progress
Pre-specified stopping rule: AMR rate >30%
No AMR detected
AMR detected
n=6
Open to all with subgroup antibody characteristics
Mandatory repeat block to demonstrate safety
Subgroup 2:
Safety signal raised
n=6
or
Open to all with subgroup antibody characteristics
Subgroup 3:
Safety threshold crossed
Program stops for this subgroup

Transplanting Across Historical DSA – BC’s Experience

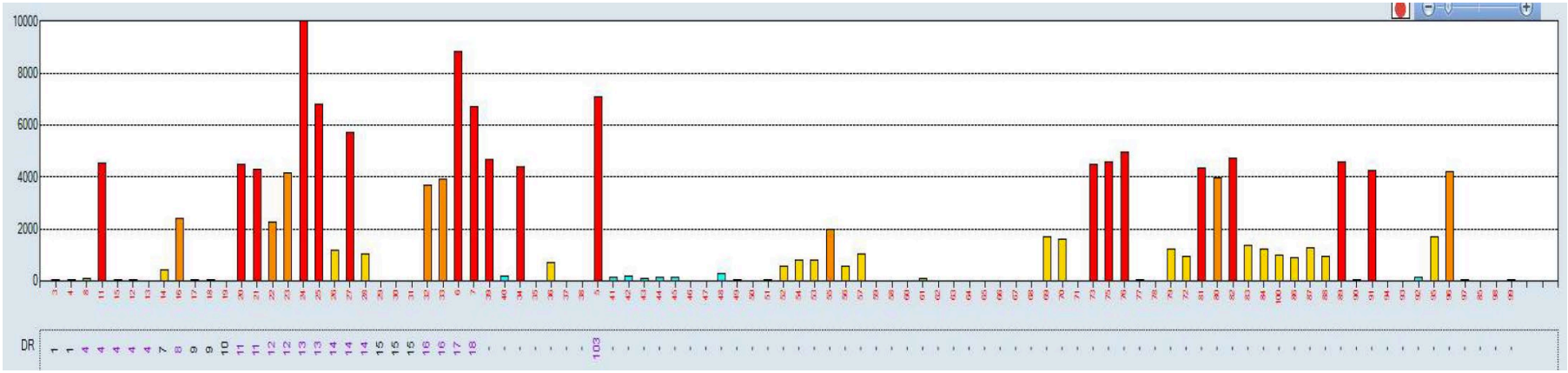
HSP Case: Mrs T

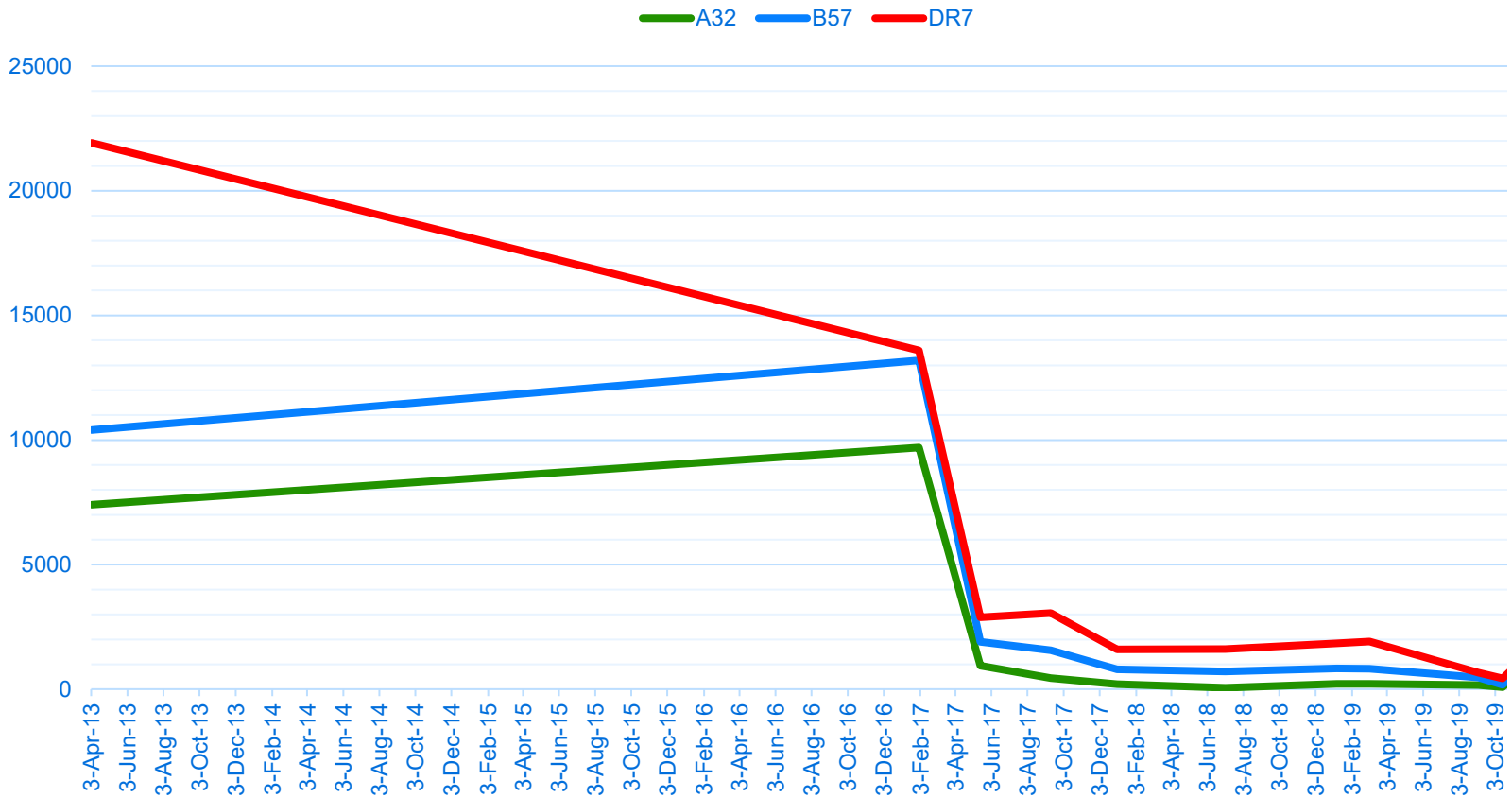
- 40 F, blood group A, ESRD from IgA
- On dialysis since 2010, KPD with 2 sisters
- No kidney offers despite being in HSP
- History of severe peritonitis → PD no longer possible
- Multiple attempts at fistula creation all failed
- Line access no longer possible → thigh graft
- cPRA = 100% (history 1 pregnancy, 2 blood transfusions)

April 2013



Oct 2019




A32
B57
DR7
25000
20000
15000
10000
5000
0
3-Apr-13
3-Jun-13
3-Aug-13
3-Oct-13
3-Dec-13
3-Feb-14
3-Apr-14
3-Jun-14
3-Aug-14
3-Oct-14
3-Dec-14
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3-Apr-18
3-Jun-18
3-Aug-18
3-Oct-18
3-Dec-18
3-Feb-19
3-Apr-19
3-Jun-19
3-Aug-19
3-Oct-19

Transplant
(Nov 13, 2019)

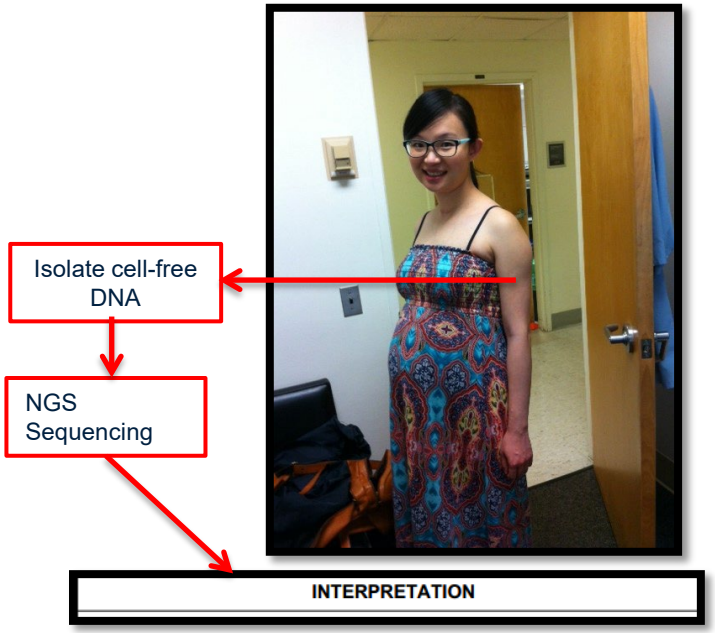
DSA	15-Oct-19	14-Nov-19	19-Nov-19	26-Nov-19
POD			POD 6	POD 13
A32	80	700	950	2400
B57	100	110	340	2200
DR7	250	300	4900	10400

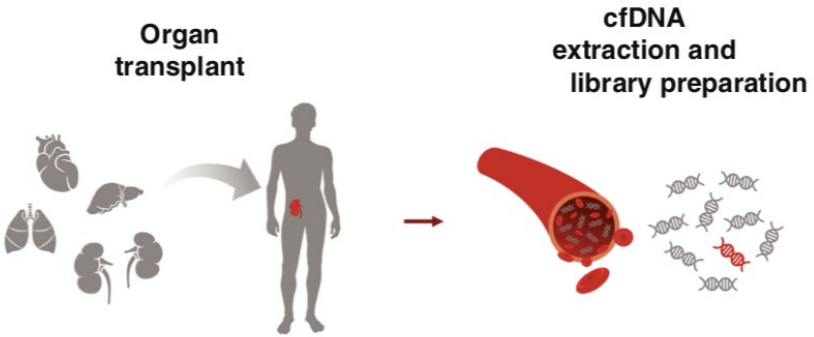
Plasmapheresis
Rituximab

DSA	15-Oct-19	14-Nov-19	19-Nov-19	26-Nov-19	10-Dec-19	23-Dec-19	07-Jan-20	07-Feb-20	06-Mar-20
POD			POD 6	POD 13	POD 28				
A32	80	700	950	2400	80	40	10	25	25
B57	100	110	340	2200	70	30	10	20	10
DR7	250	300	4900	10400	500	200	10	30	20

Can we apply precision medicine to post-transplant monitoring?

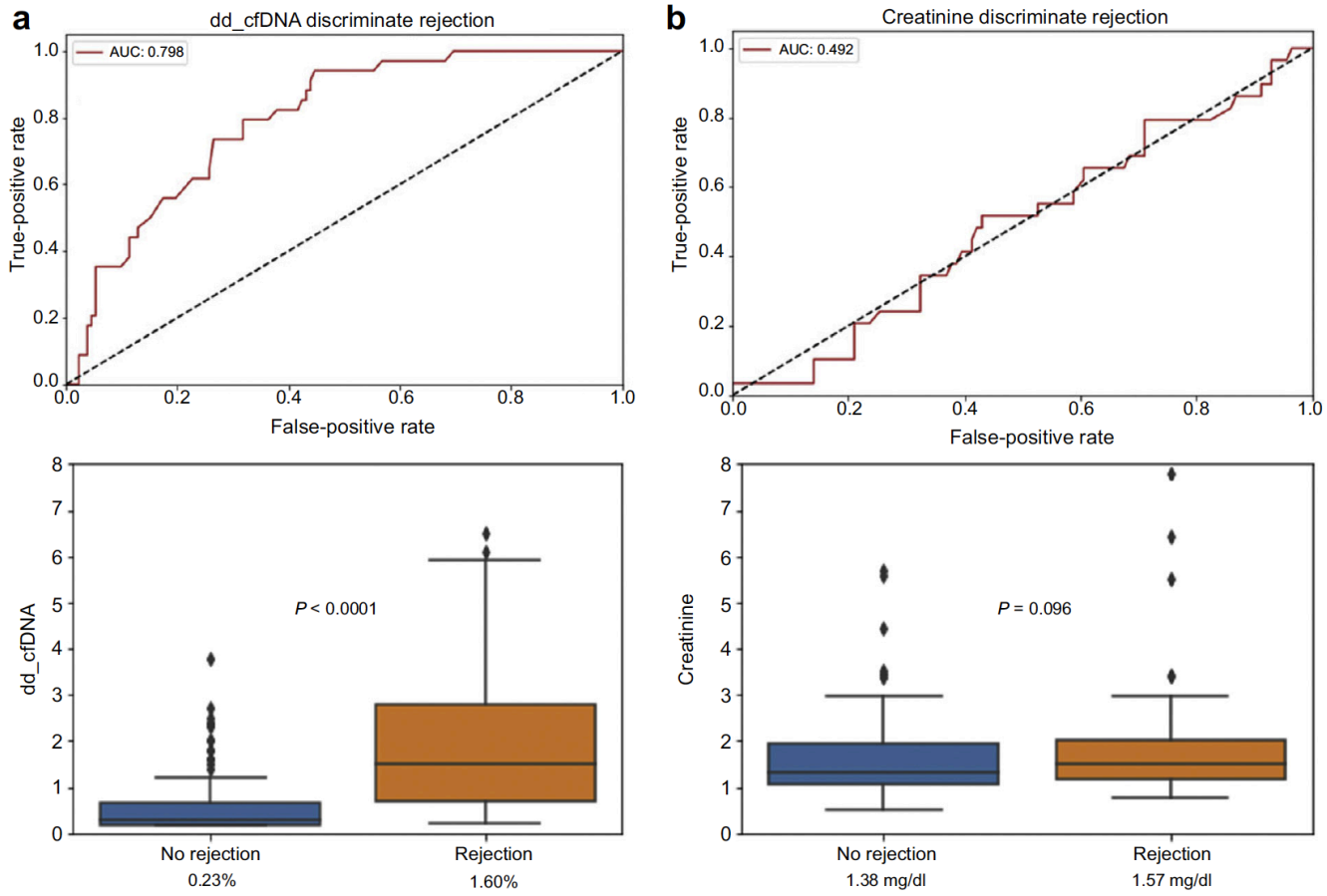
Non-invasive monitoring: donor-derived cell-free DNA





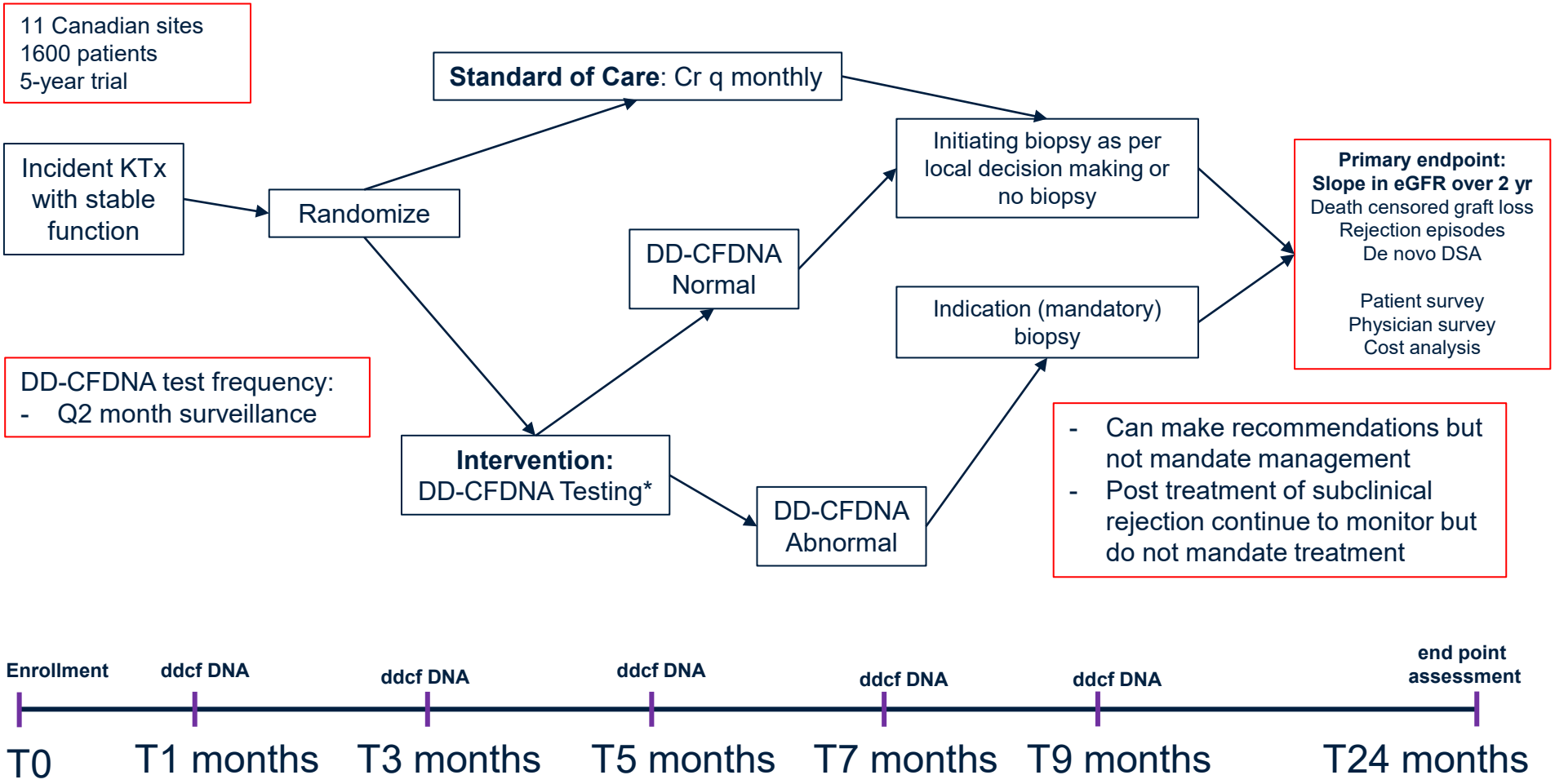
JASN 2017

Donor-derived cell free DNA is a more sensitive biomarker for renal injury than serum creatinine



Bu, KI 2022

Canadian Multicenter RCT: **Cl**inical **e**valuation of cell-free DN**A** for **R**enal Allograft Injury (CLEAR)



Acknowledgements

VGH Immunology Lab

Karen Sherwood
Jenny Tran
Yoojin Choi
Franz Fenninger
Doris Chang
Sabina Dobrer
Logan Tate
Oliver Gunther
Vivian Wu
Vince Benedicto
Jennifer Beckrud
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MICHAEL SMITH FOUNDATION FOR HEALTH RESEARCH
BC's health research funding agency

The Kidney Foundation of Canada / La Fondation canadienne du rein

Vancouver Coastal Health Research Institute

TRANSPLANT RESEARCH FOUNDATION of British Columbia

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