THE UNIVERSITY OF BRITISH COLUMBIA

Implementation of a Canadian Willingness to Cross Program: a Strategy to Increase Access to Kidney Transplantation for Highly Sensitized Patients

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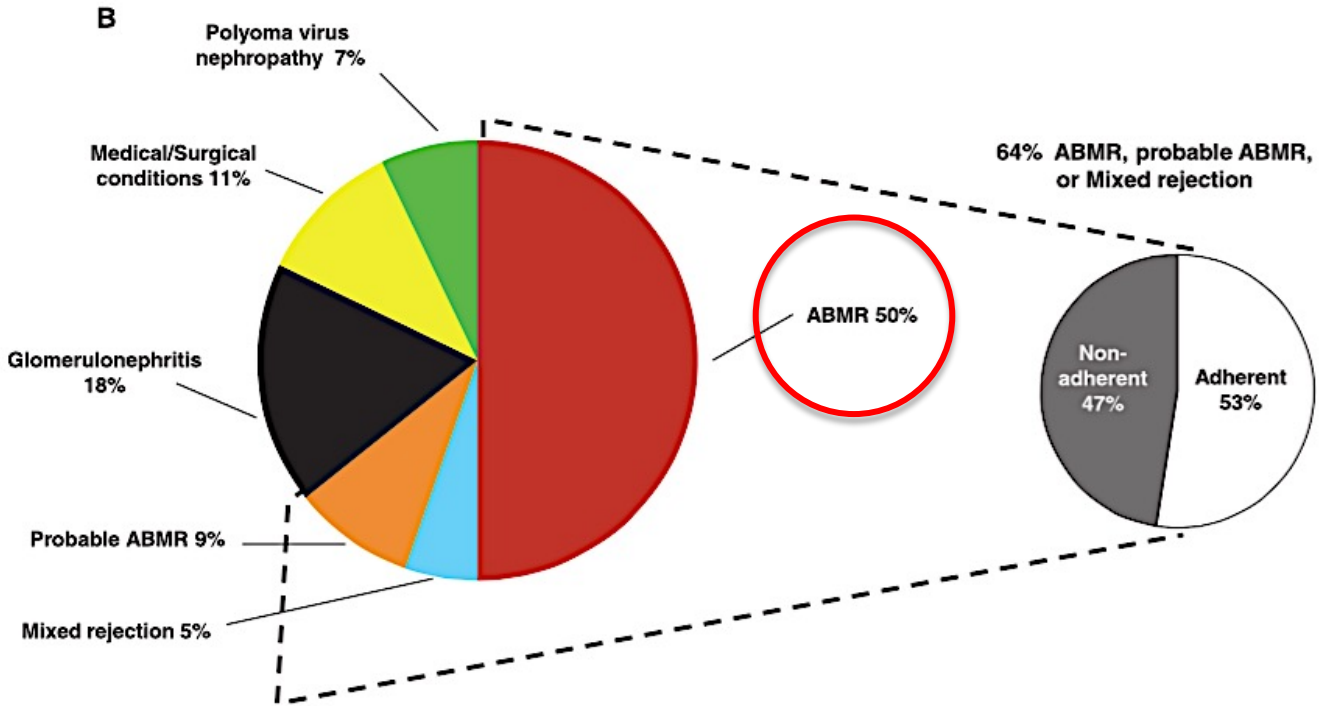
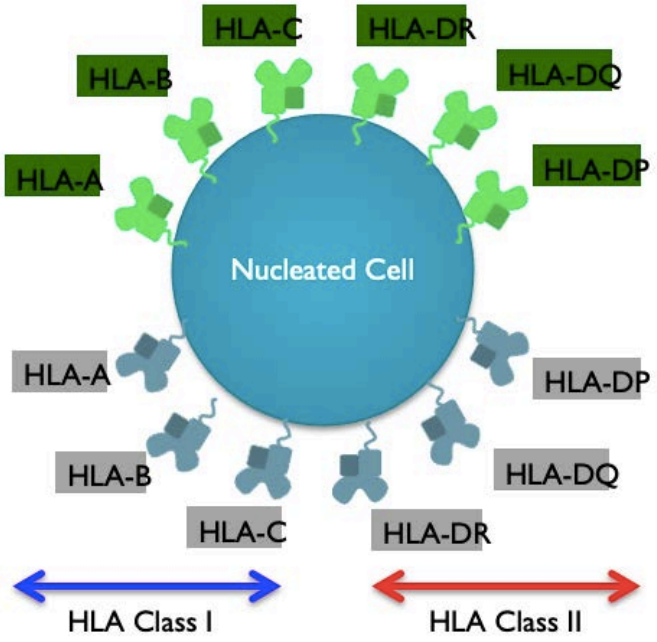
BC Kidney Day, October 4, 2019

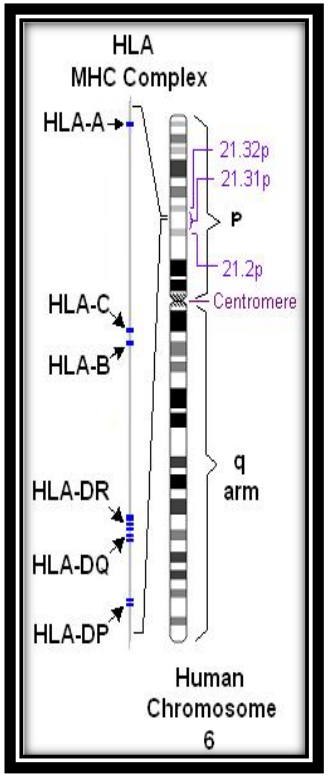
Why do kidney transplants fail?

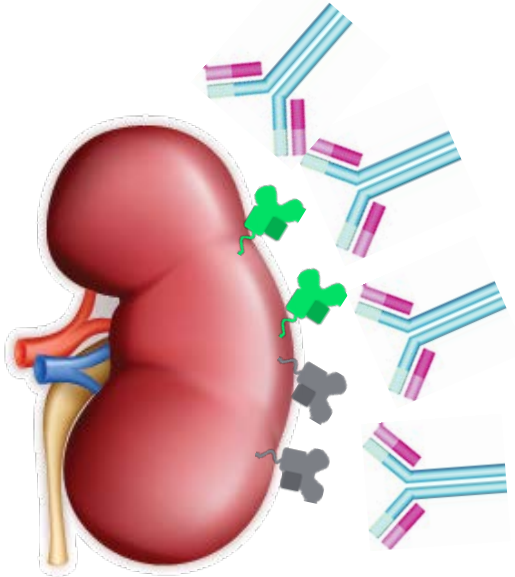


Sellares et al, AJT, 2012

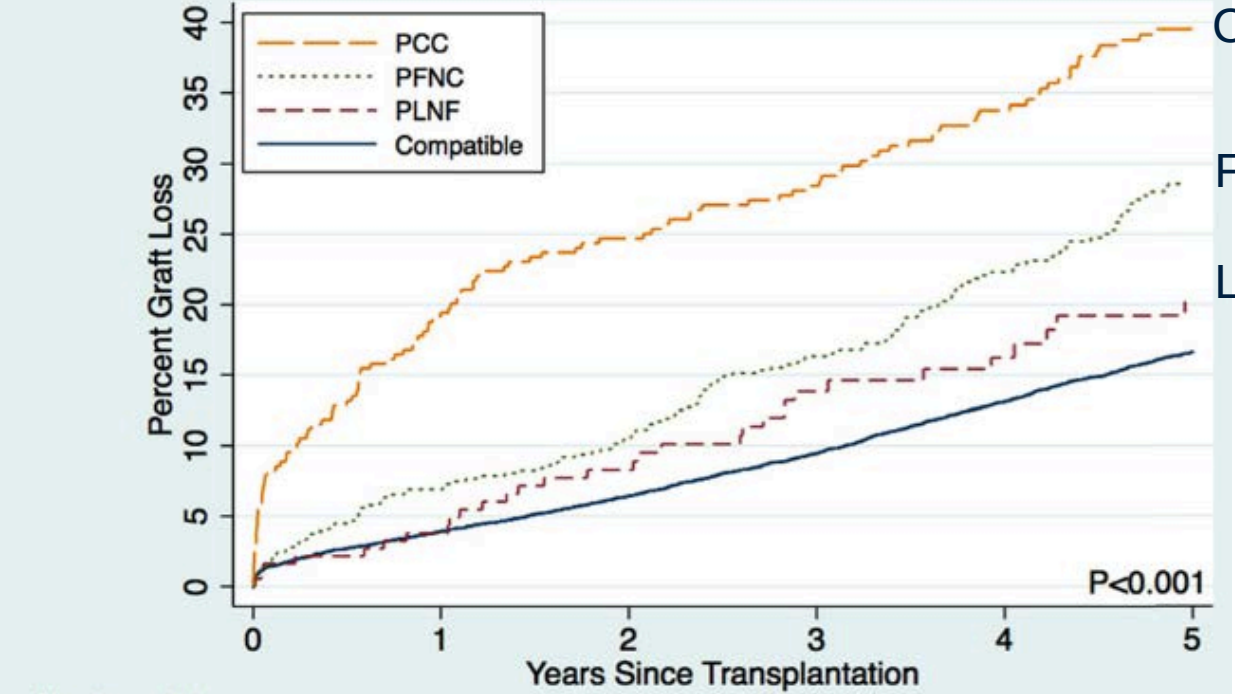
AMR is caused by binding of antibodies to HLA targets on kidney endothelium







Risk of preformed donor-specific antibodies



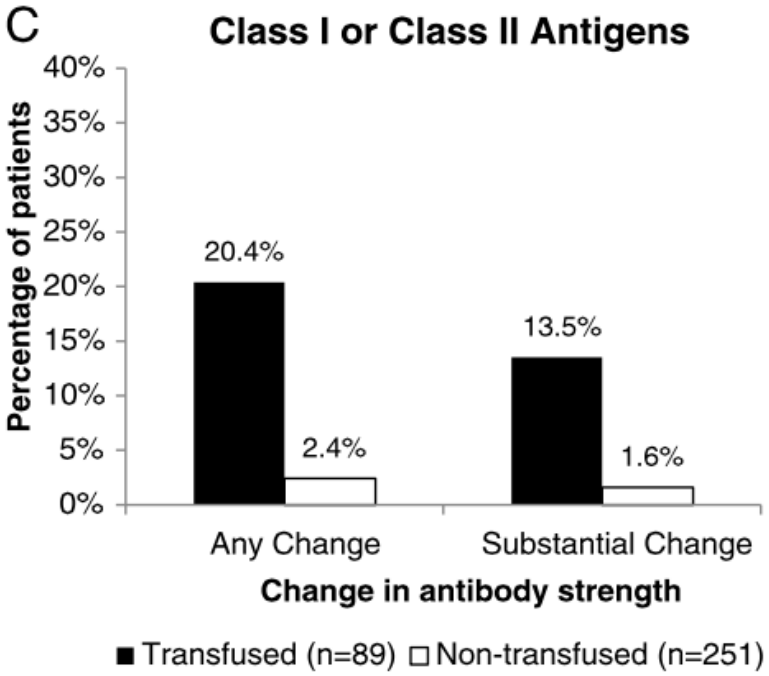
CDC

Flow

Luminex

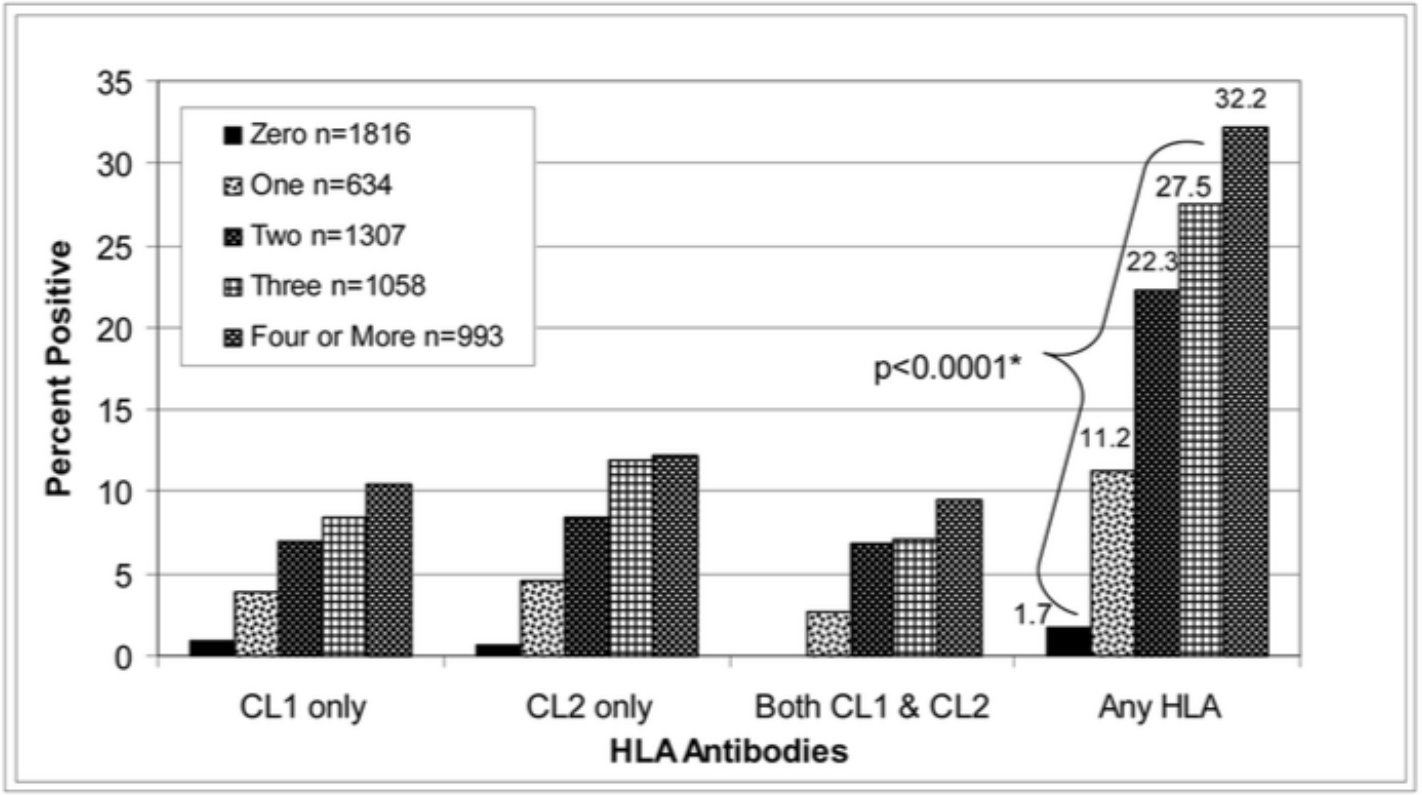
Orandi, AJT 2014

Effect of blood transfusion



Leffell et al, Transplantation 2014

Effect of pregnancy



Triulzi et al, Transfusion 2009

Effect of transplant failure: nephrectomy and IS

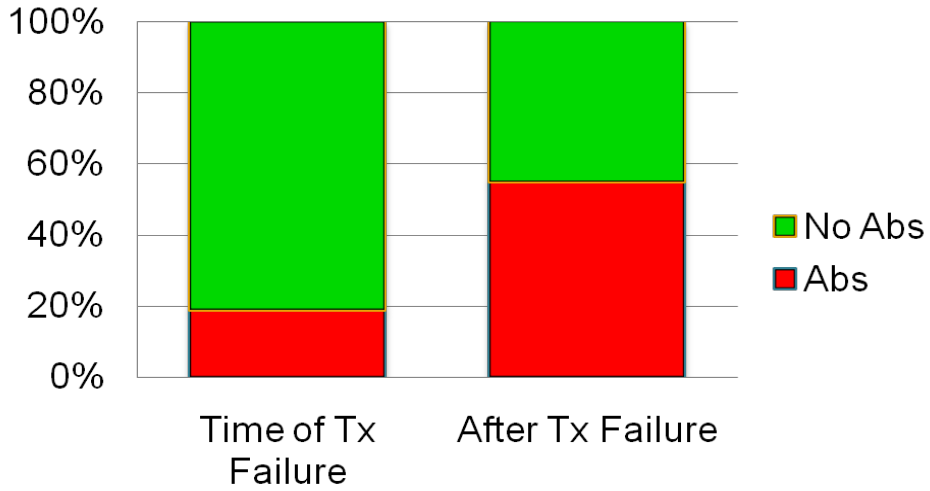


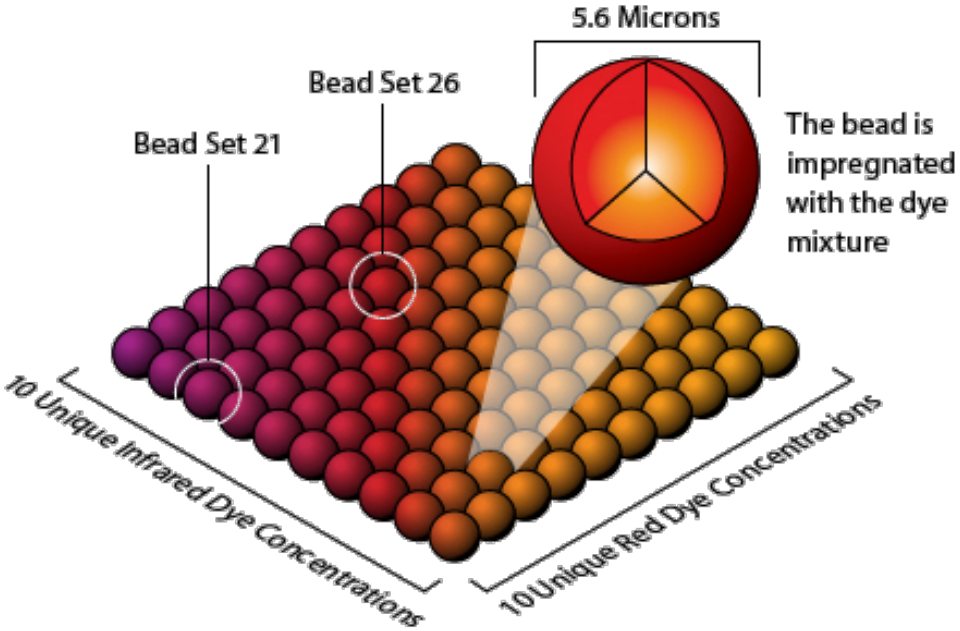
Table 3
Effect of immunosuppression, nephrectomy, and transfusions in sensitization after transplant loss

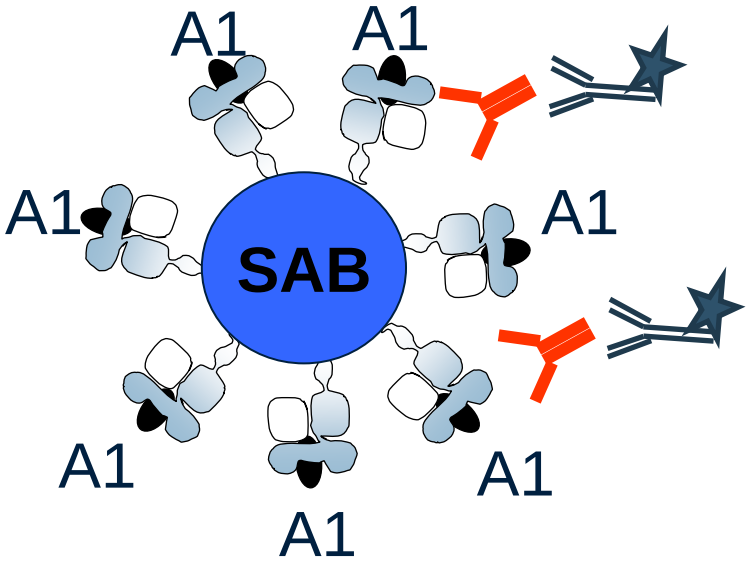
Abs after Tx	*N*	Nephrectomy		Immunosuppression	
		Yes	No	Off	On
Yes	38	31	7	38	0
No	31	8	23	20	11
%	55	79	23	66	0
p value	[a]	<0.001		<0.001	

[a]Fisher exact test.

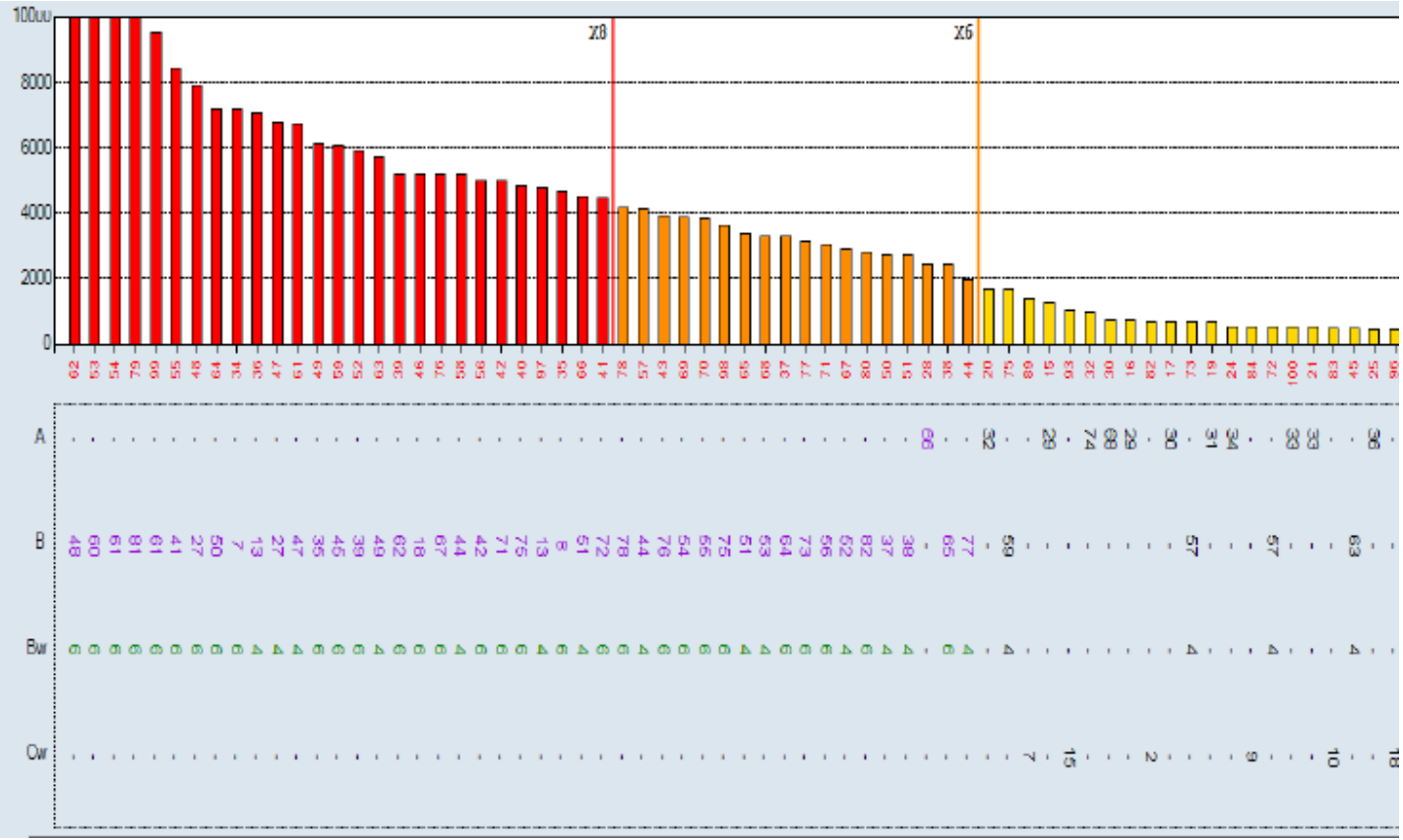
Scornik et al, Human Immunology, 2011

Single antigen bead (SAB) – method of antibody detection

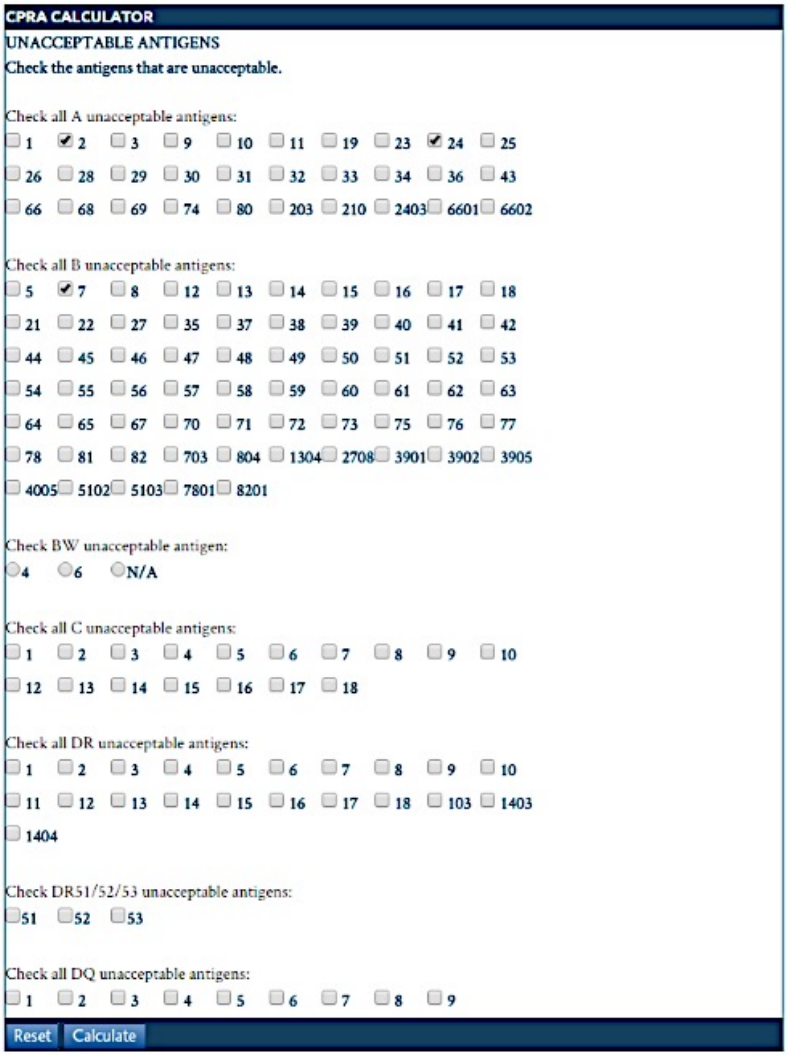




SAB test read-out



CPRA Calculator



CPRA CALCULATOR

UNACCEPTABLE ANTIGENS

Check the antigens that are unacceptable.

Check all A unacceptable antigens:

☐ 1 ☑ 2 ☐ 3 ☐ 9 ☐ 10 ☐ 11 ☐ 19 ☐ 23 ☑ 24 ☐ 25

☐ 26 ☐ 28 ☐ 29 ☐ 30 ☐ 31 ☐ 32 ☐ 33 ☐ 34 ☐ 36 ☐ 43

☐ 66 ☐ 68 ☐ 69 ☐ 74 ☐ 80 ☐ 203 ☐ 210 ☐ 2403 ☐ 6601 ☐ 6602

Check all B unacceptable antigens:

☐ 5 ☑ 7 ☐ 8 ☐ 12 ☐ 13 ☐ 14 ☐ 15 ☐ 16 ☐ 17 ☐ 18

☐ 21 ☐ 22 ☐ 27 ☐ 35 ☐ 37 ☐ 38 ☐ 39 ☐ 40 ☐ 41 ☐ 42

☐ 44 ☐ 45 ☐ 46 ☐ 47 ☐ 48 ☐ 49 ☐ 50 ☐ 51 ☐ 52 ☐ 53

☐ 54 ☐ 55 ☐ 56 ☐ 57 ☐ 58 ☐ 59 ☐ 60 ☐ 61 ☐ 62 ☐ 63

☐ 64 ☐ 65 ☐ 67 ☐ 70 ☐ 71 ☐ 72 ☐ 73 ☐ 75 ☐ 76 ☐ 77

☐ 78 ☐ 81 ☐ 82 ☐ 703 ☐ 804 ☐ 1304 ☐ 2708 ☐ 3901 ☐ 3902 ☐ 3905

☐ 4005 ☐ 5102 ☐ 5103 ☐ 7801 ☐ 8201

Check BW unacceptable antigen:

○ 4 ○ 6 ○ N/A

Check all C unacceptable antigens:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

☐ 12 ☐ 13 ☐ 14 ☐ 15 ☐ 16 ☐ 17 ☐ 18

Check all DR unacceptable antigens:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

☐ 11 ☐ 12 ☐ 13 ☐ 14 ☐ 15 ☐ 16 ☐ 17 ☐ 18 ☐ 103 ☐ 1403

☐ 1404

Check DR51/52/53 unacceptable antigens:

☐ 51 ☐ 52 ☐ 53

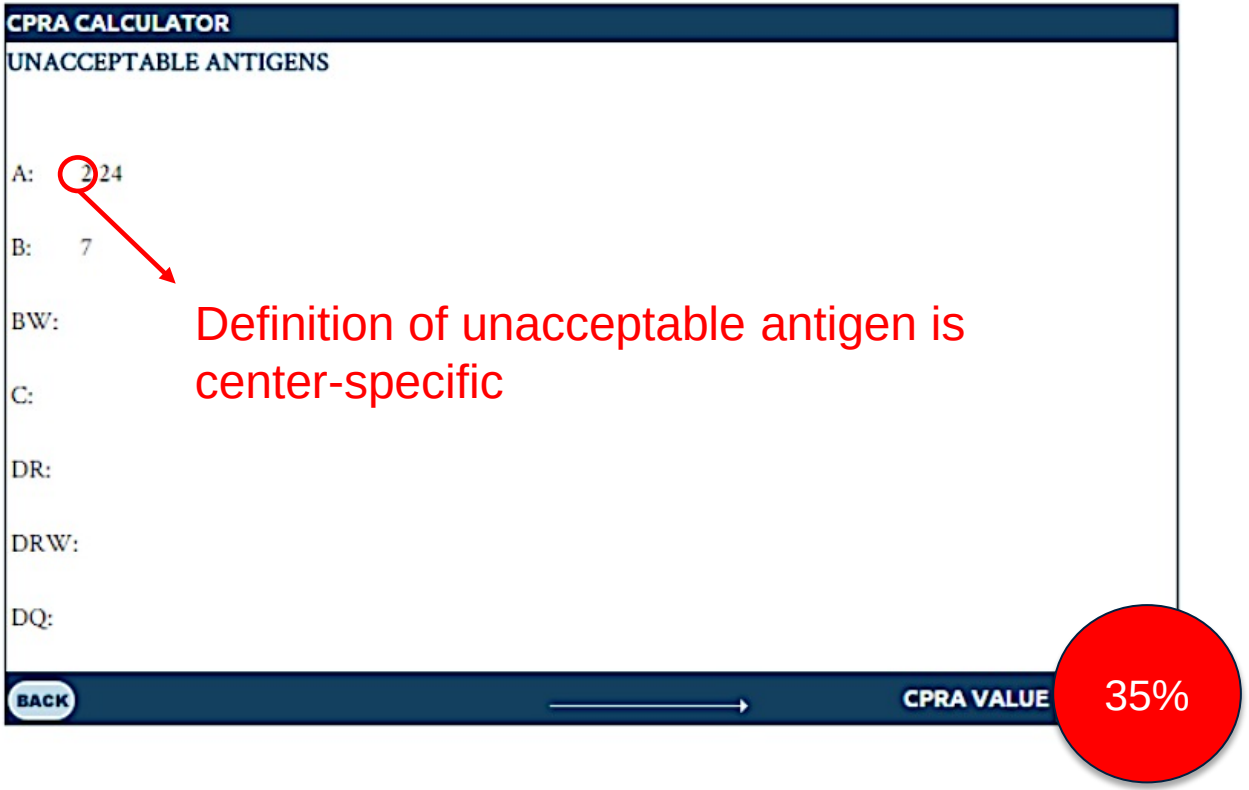
Check all DQ unacceptable antigens:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9

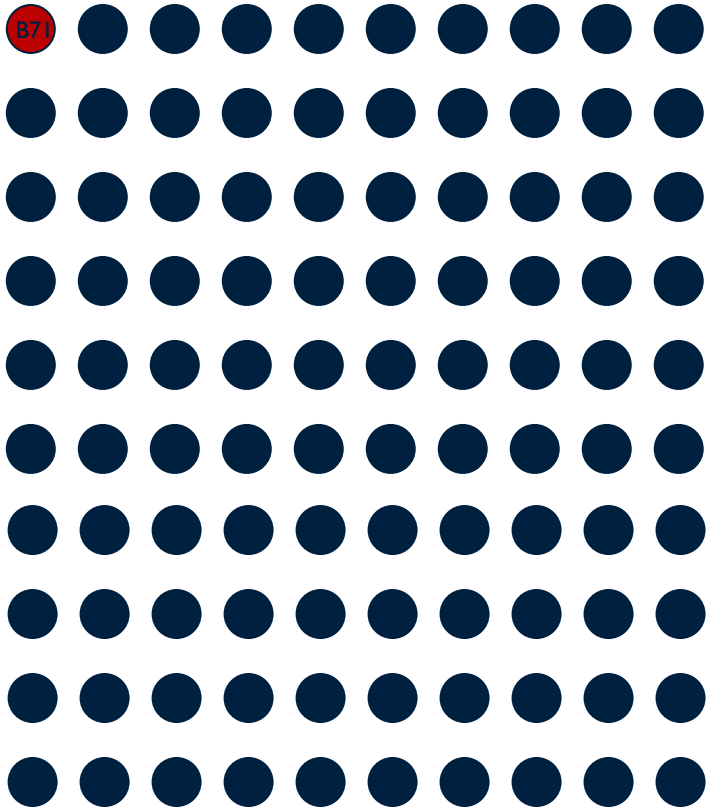
Reset Calculate

CPRA Calculator

CPRA Calculator



Antigen frequency matters



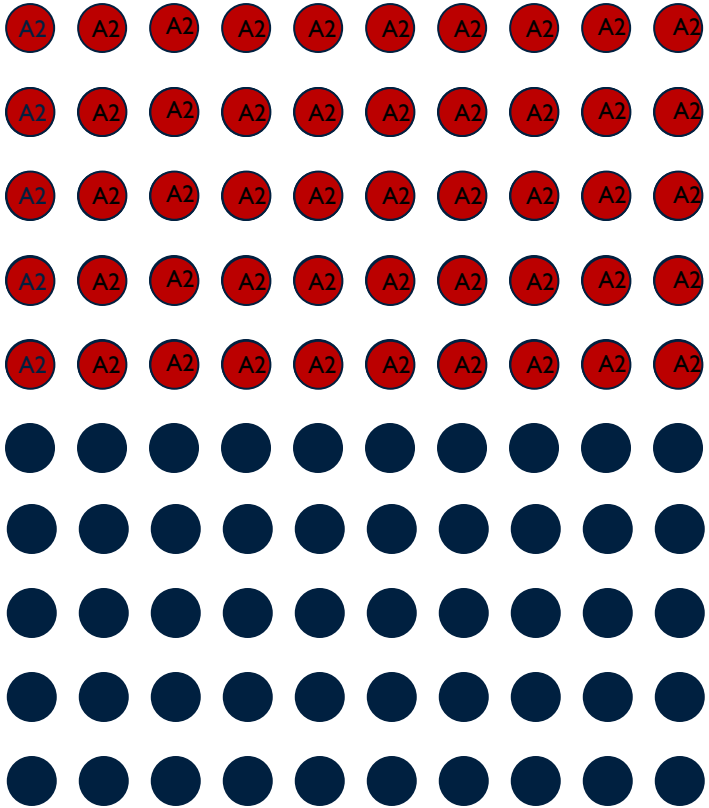
Patient 1:

Antibody: B71

cPRA = 1/100

= 1%

Antigen frequency matters



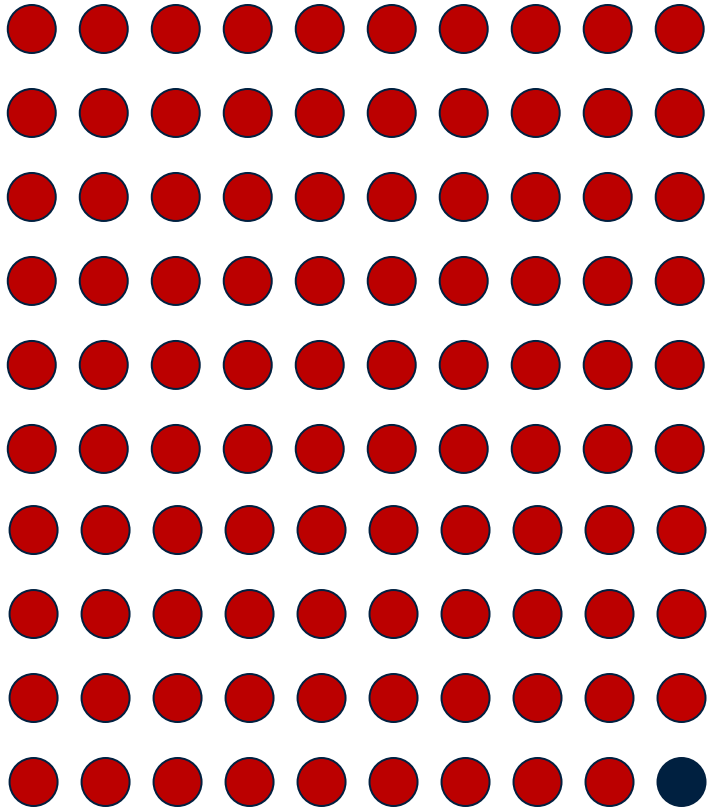
Patient 2:

Antibody: A2

cPRA = 50/100

= 50%

Antigen frequency matters



Patient 3:

cPRA = 99/100

= 99%

Highly sensitized Patient

Cumulative Class I Antibody Specificities

A:24 80

B:35 37 46 49 50 51 52 53 56 62 71 72 75 77 78

Cw:6 7 9 10

Cumulative Class II Antibody Specificities

DR:1 4 8 9 10 11 12 13 14 15 16 17 18 0103

DRw:51 52

DQ:5

DP:3 6 11 13

Cumulative Combined Calculated PRA

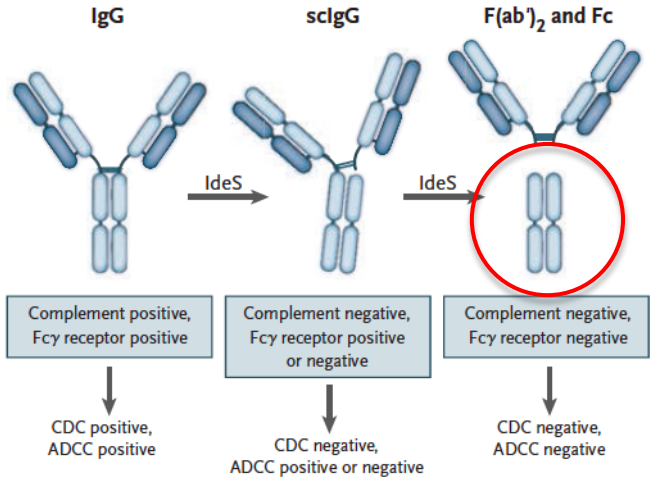
cPRA: 100% Last Date Calculated: 02-Feb-2015

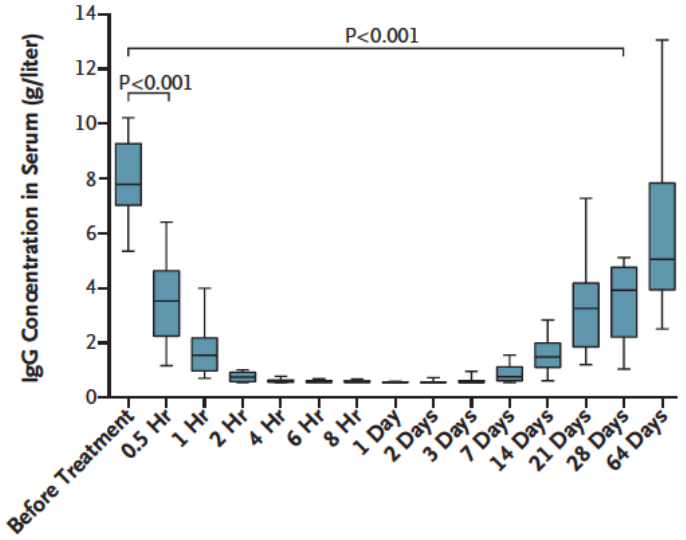
Ides (IgG-degrading enzyme derived from Streptococcus pyrogenes)

IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation

NEJM, 2017

S.C. Jordan, T. Lorant, J. Choi, C. Kjellman, L. Winstedt, M. Bengtsson, X. Zhang, T. Eich, M. Toyoda, B.-M. Eriksson, S. Ge, A. Peng, S. Järnum, K.J. Wood, T. Lundgren, L. Wennberg, L. Bäckman, E. Larsson, R. Villicana, J. Kahwaji, S. Louie, A. Kang, M. Haas, C. Nast, A. Vo, and G. Tufveson

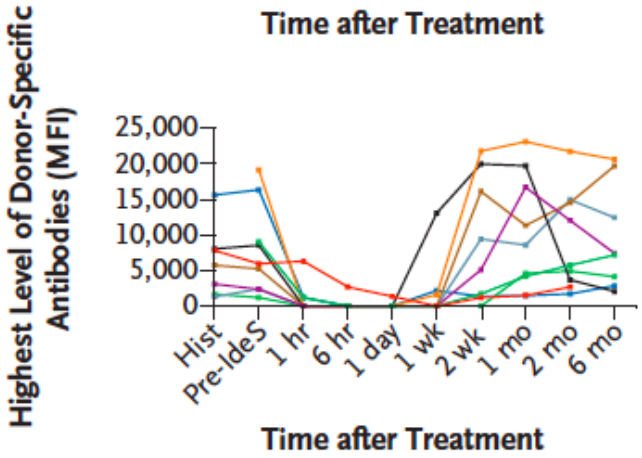




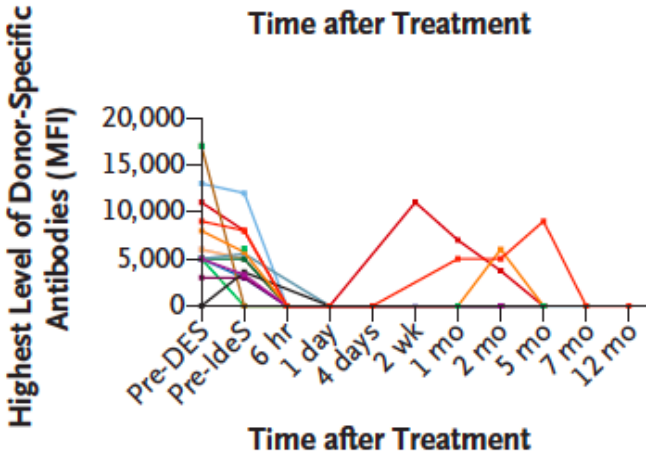
Ides (IgG-degrading enzyme derived from Streptococcus pyrogenes)

- Open-label, phase 1-2, desensitization trial (US, Sweden)
- N=25 highly sensitized patients, cPRA ≥ 95%
- All IgG-DSA eliminated at time of transplantation
- N=10/25 with AMR – ***rebound phenomenon***

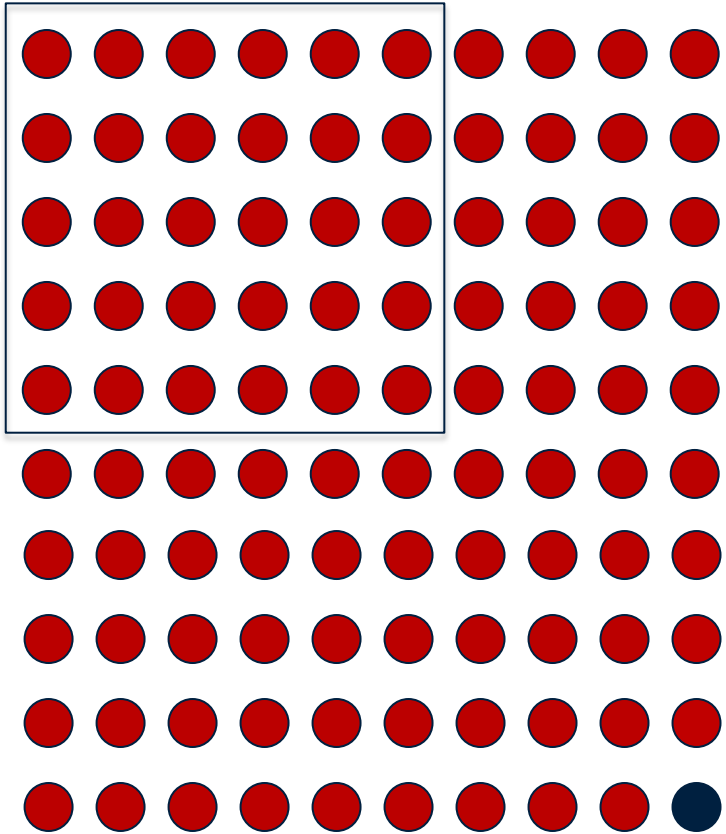
Sweden



US group



Solution for highly sensitized patients

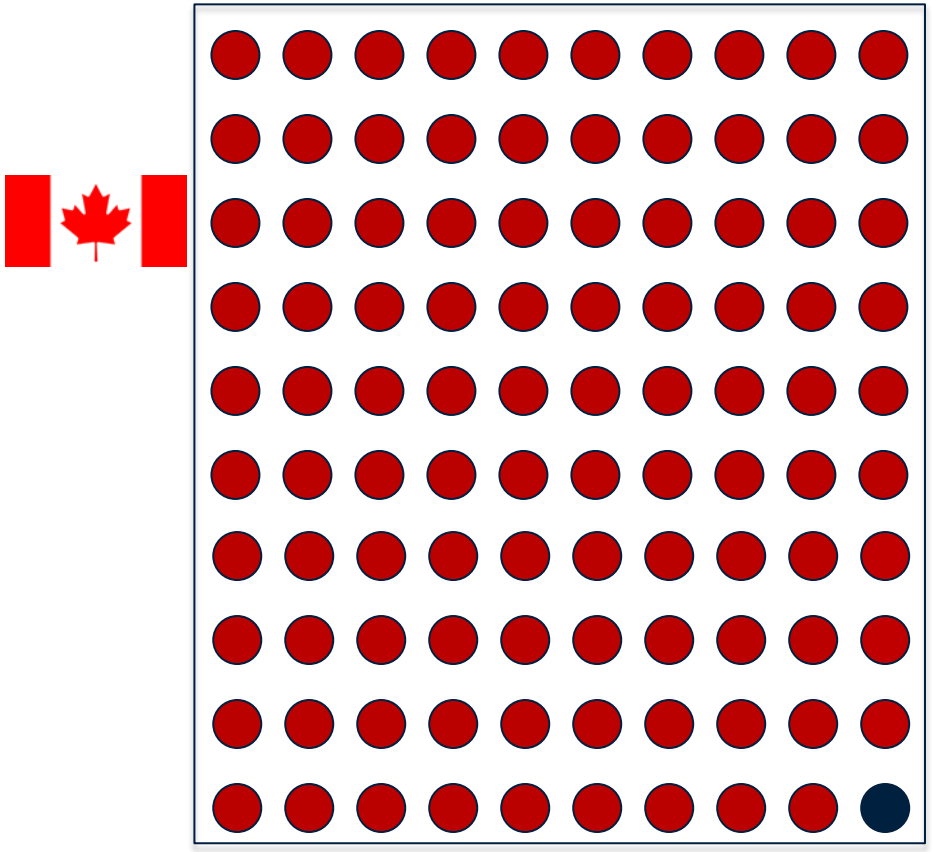


Patient 3:

cPRA = 99/100

= 99%

Solution for highly sensitized patients

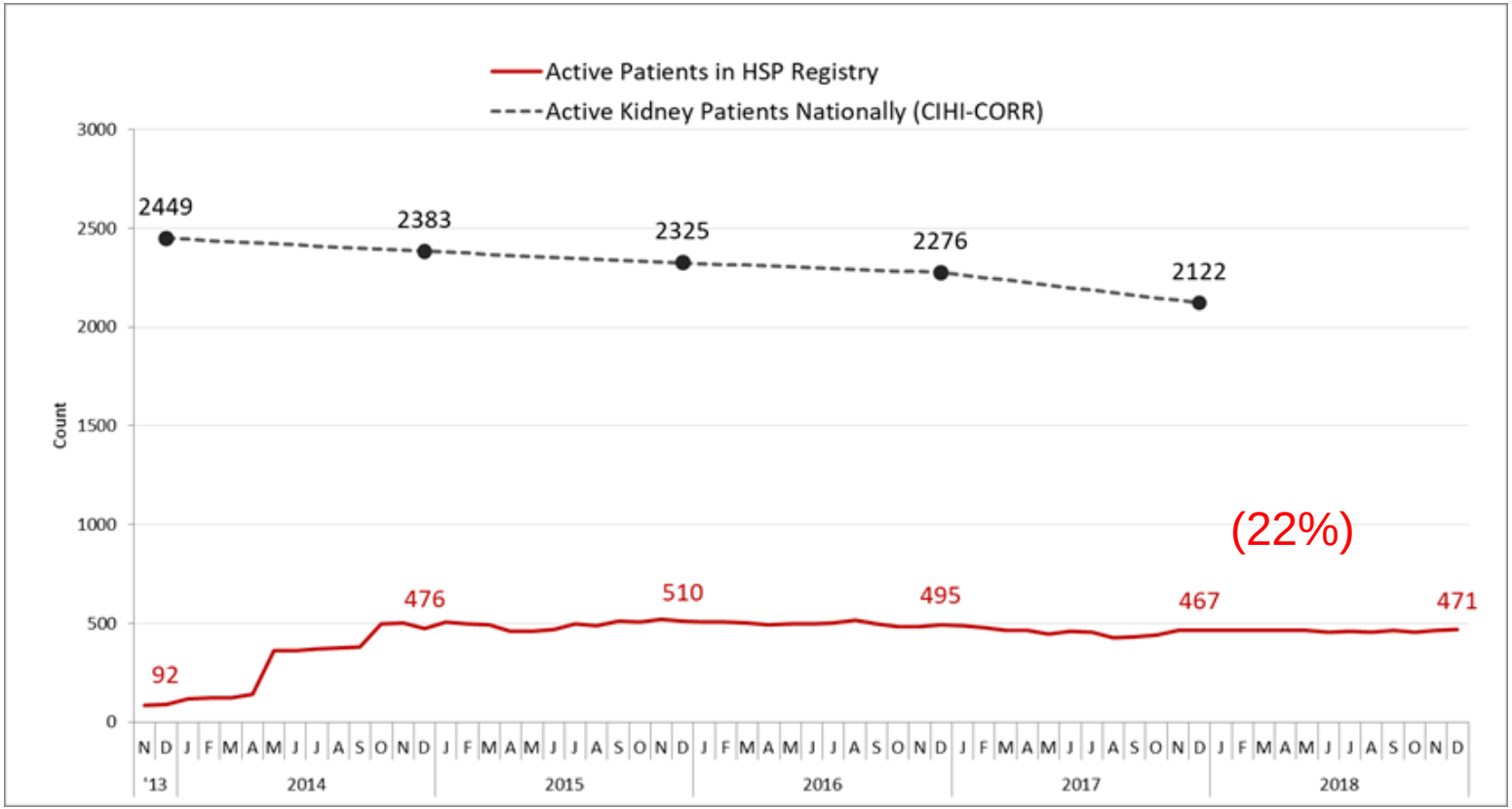


Patient 3:

cPRA = 99/100

= 99%

HSP Program: a solution for highly sensitized patients

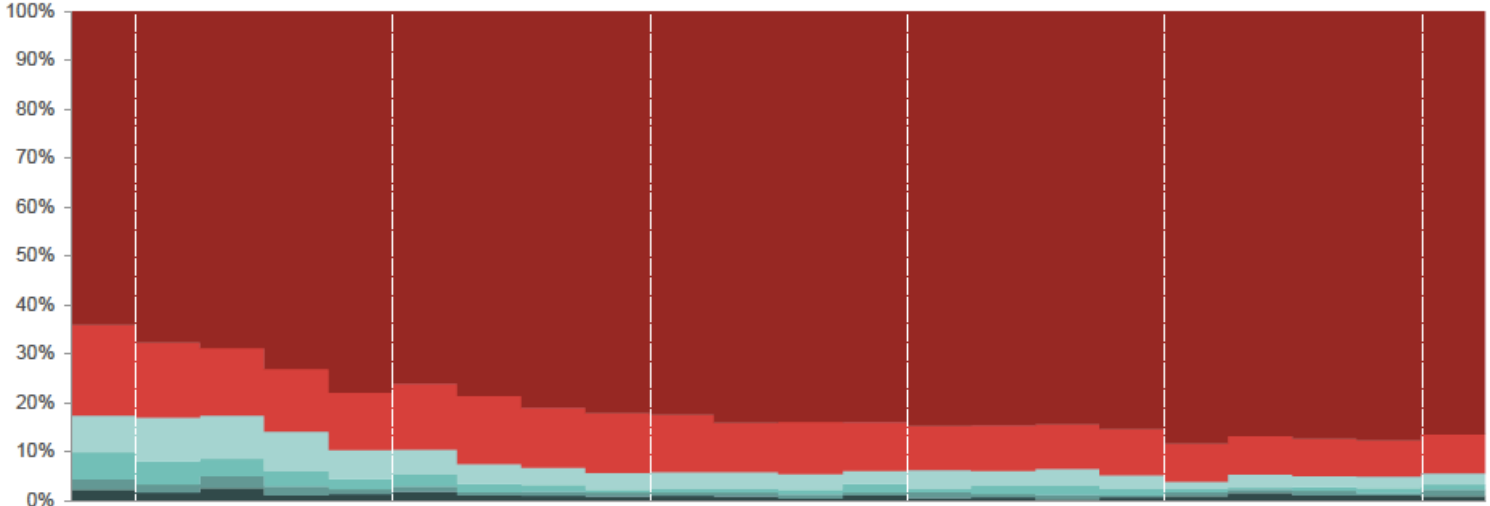


CBS, Feb 28 2019

HSP Activity as of March 31, 2019

Candidates Active on Waitlist: cPRA 99%-100%	439
Candidates Active on Waitlist: cPRA 95%-98%	26
Total Candidates Active on Waitlist	***465***
Total HSP Program Transplants Completed	***515***
Interprovincial Transplants	310
Intraprovincial Transplants	205
Total Donors with HSP Allocation Run	***4,128***

Active HSP candidates over time by cPRA

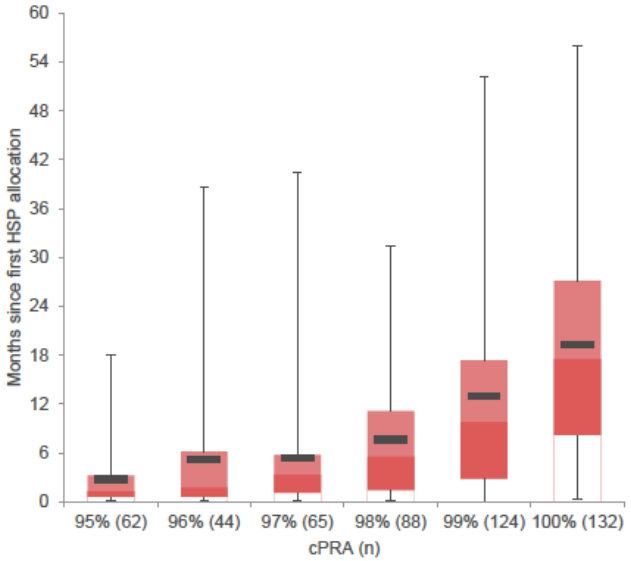


	Oct-Dec 2013	Jan-Mar 2014	Apr-Jun 2014	Jul-Sep 2014	Oct-Dec 2014	Jan-Mar 2015	Apr-Jun 2015	Jul-Sep 2015	Oct-Dec 2015	Jan-Mar 2016	Apr-Jun 2016	Jul-Sep 2016	Oct-Dec 2016	Jan-Mar 2017	Apr-Jun 2017	Jul-Sep 2017	Oct-Dec 2017	Jan-Mar 2018	Apr-Jun 2018	Jul-Sep 2018	Oct-Dec 2018	Jan-Mar 2019
cPRA 100%	59	84	250	280	371	375	368	414	419	415	419	419	416	395	391	364	399	409	395	407	413	402
cPRA 99%	17	19	50	49	56	66	65	63	62	59	50	53	49	42	43	39	44	36	36	36	35	37
cPRA 98%	7	11	32	31	28	25	19	18	18	17	17	16	13	18	14	15	13	7	12	10	11	11
cPRA 97%	5	6	13	12	10	12	8	7	3	4	4	5	9	3	8	8	6	3	2	4	5	5
cPRA 96%	2	2	9	7	5	5	3	4	4	3	4	4	3	6	3	4	2	4	3	4	2	6
cPRA 95%	2	2	9	4	6	9	5	5	4	5	4	2	5	2	3	1	3	4	7	5	5	4

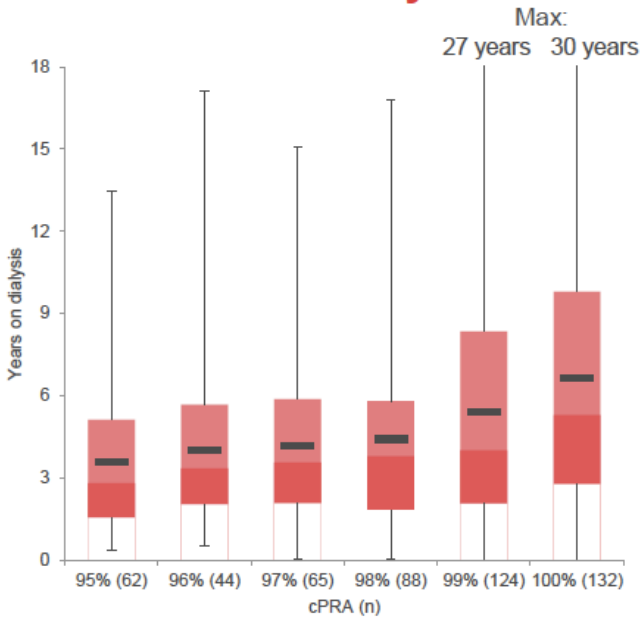
Results shown reflect patient counts at end of quarter.

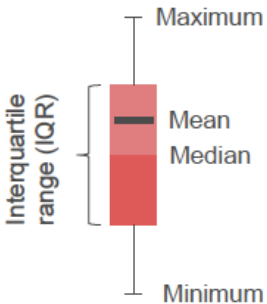
Transplant wait times by cPRA: Profile of transplant recipients

Time in HSP registry



Time on Dialysis



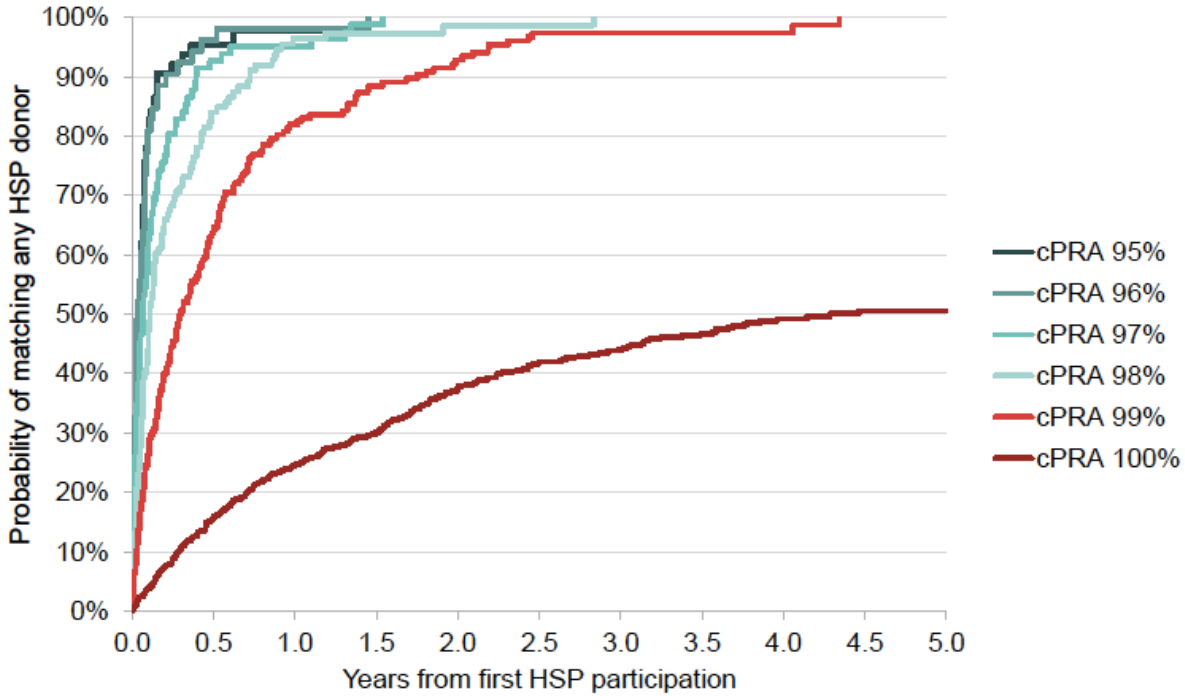


Canadian Blood Services — Blood, Plasma, Stem Cells, Organs & Tissues

Time in registry based on total time from candidate's first inclusion in the HSP matching algorithm.
Time on dialysis based on candidate's most recent dialysis start time prior to transplant.

Match probability over time by cPRA

Approximate time to 90% match probability	
cPRA 95%	2 months
cPRA 96%	3 months
cPRA 97%	5 months
cPRA 98%	9 months
cPRA 99%	21 months

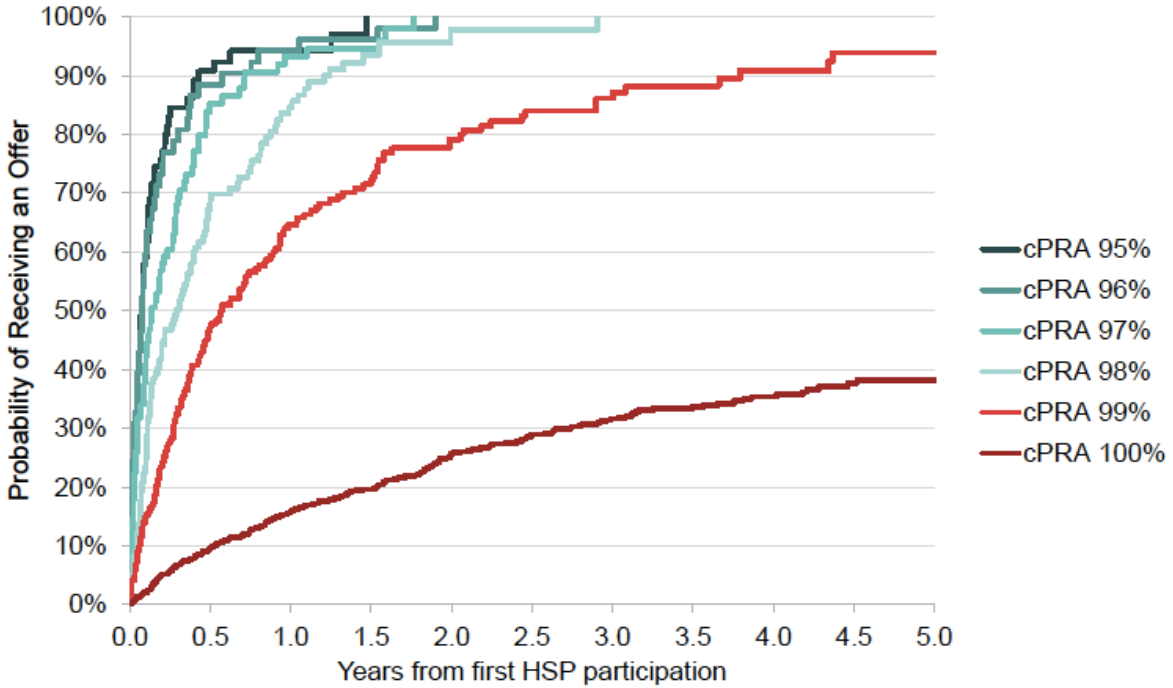


Canadian Blood Services — Blood, Plasma, Stem Cells, Organs & Tissues

Results as of December 31, 2018. Values based on Kaplan-Meier product limit estimator (1 - non-match probability) as calculated for actual program results and reflect current cPRA values in CTR at data collection rather than cPRA at time of match.

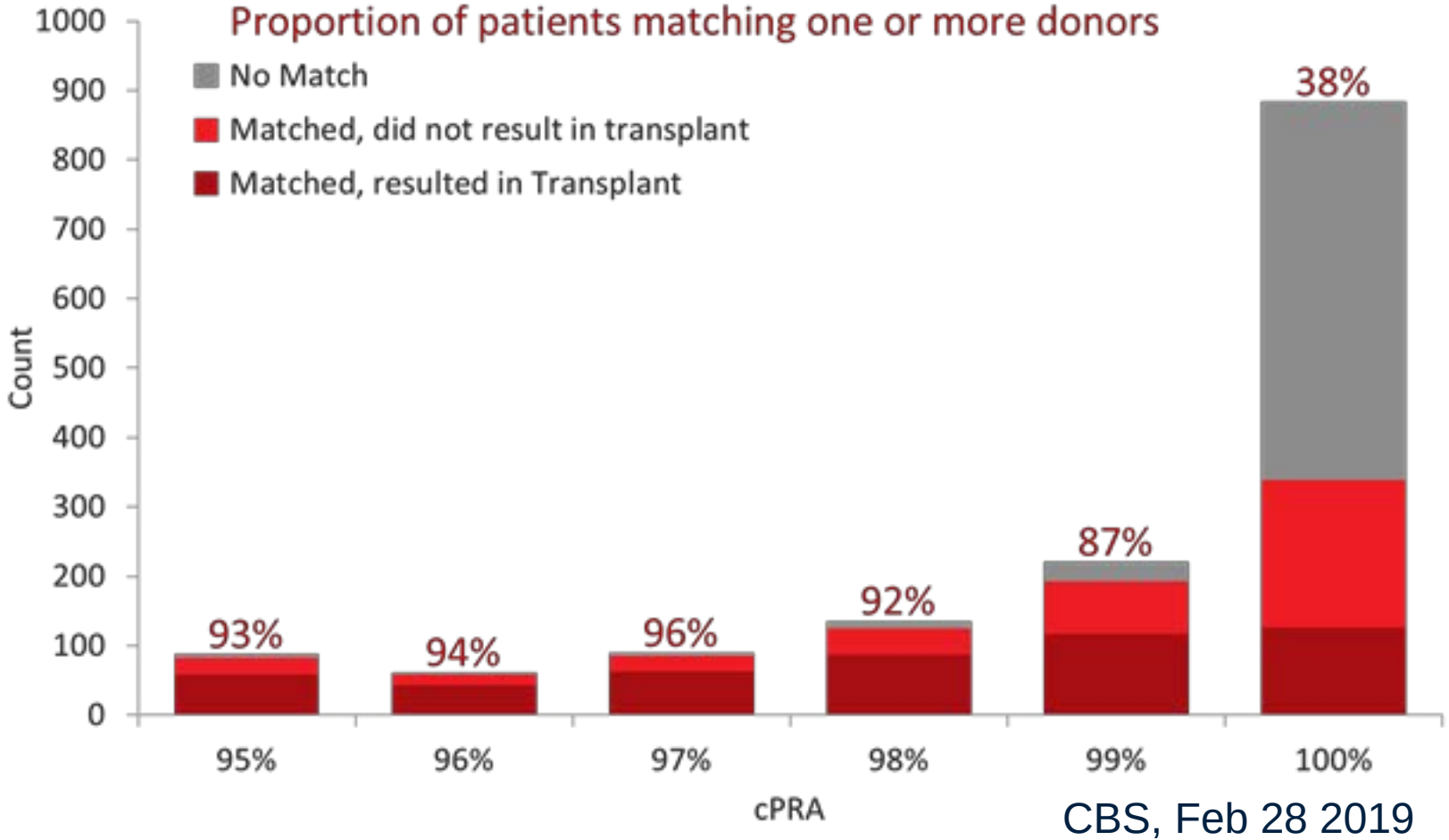
Offer probability over time by cPRA

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



Canadian Blood Services

Results as of December 31, 2018. Values based on Kaplan-Meier product limit estimator (1 - non-match probability) as calculated for actual program results and reflect current cPRA values in CTR at data collection rather than cPRA at time of match.



CBS, Feb 28 2019

Case: MR X.

- 3 failed transplants
- On dialysis since 2002, waiting for his 4th kidney
- Running out of access – thigh graft

Cumulative Class I Antibody Specificities

A:1 3 11 23 24 29 30 31 32 33 34 36 43 66 68 74 80
B:7 13 27 35 37 39 41 42 45 47 48 49 50 52 54 55 56 57 59 60 61 62 63 67 71 72 73 75 76 81 82
Cw:1 2 4 5 6 12 15 17 18

Cumulative Class II Antibody Specificities

DR:1 8 9 15 16 103
DRw:51 53
DQ:4 5 6 8 9
DP:3 6 11 17

Cumulative Combined Calculated PRA

cPRA: 100% Last Date Calculated: 02-Feb-2015

Cumulative Class I Antibody Specificities

A:1 3 11 23 24 29 30 31 32 33 34 36 43 66 68 74 80

B:7 13 27 35 37 39 41 42 45 47 48 49 50 52 54 55 56 57 59 60 61 62 63 67 71 72 73 75 76 81 82

Cw:1 2 4 5 6 12 15 17 18

Cumulative Class II Antibody Specificities

DR:1 8 9 15 16 103

DRw:51 53

DQ:4 5 6 8 9

DP:3 6 11 17

Cumulative Combined Calculated PRA

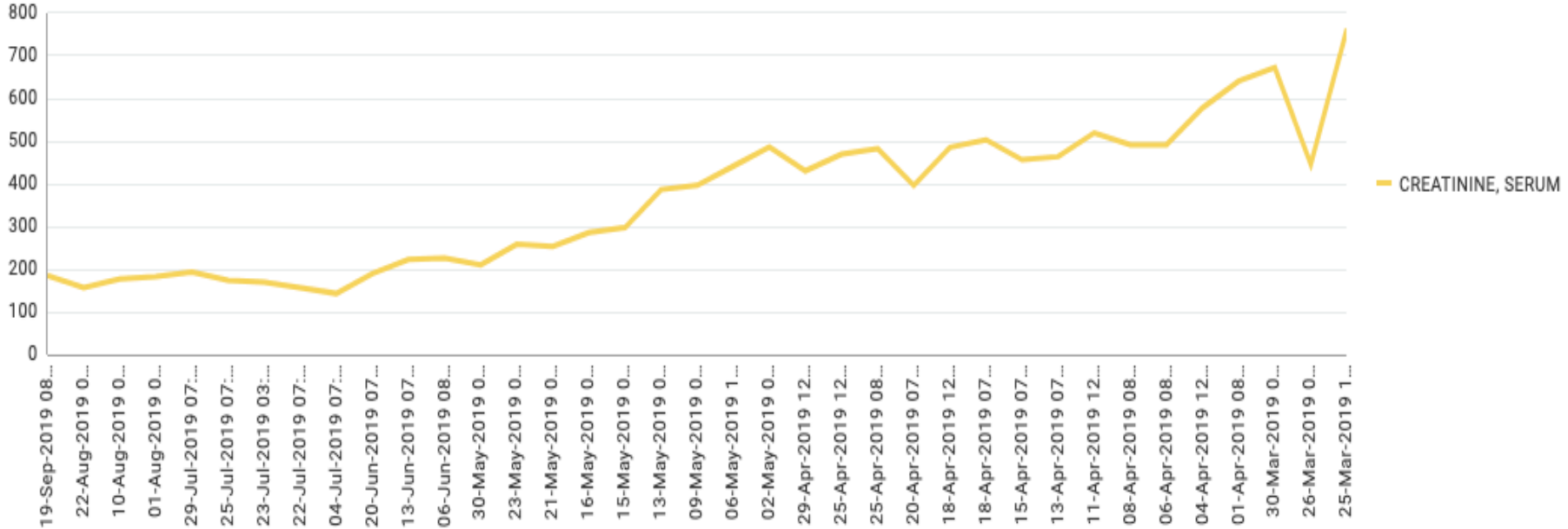
cPRA: 100% Last Date Calculated: 02-Feb-2015

Risk	Antigens Removed	Comments	Adjusted cPRA
Low	Cw: remove all antigens DP: remove all antigens DR53	All present at MFI_{Max}<3000 All present at MFI_{Max}<1100 MFI_{Max}<2500 (detected only once in 2006)	cPRA=99.14%
Low-Med	A23, 24	MFI_{Max}<2800 in 2015, undetectable since	cPRA=98.9%
Med	A3	MFI_{Max}=5000 in 2006, undetectable since	cPRA=98.38%

Case: MR X.

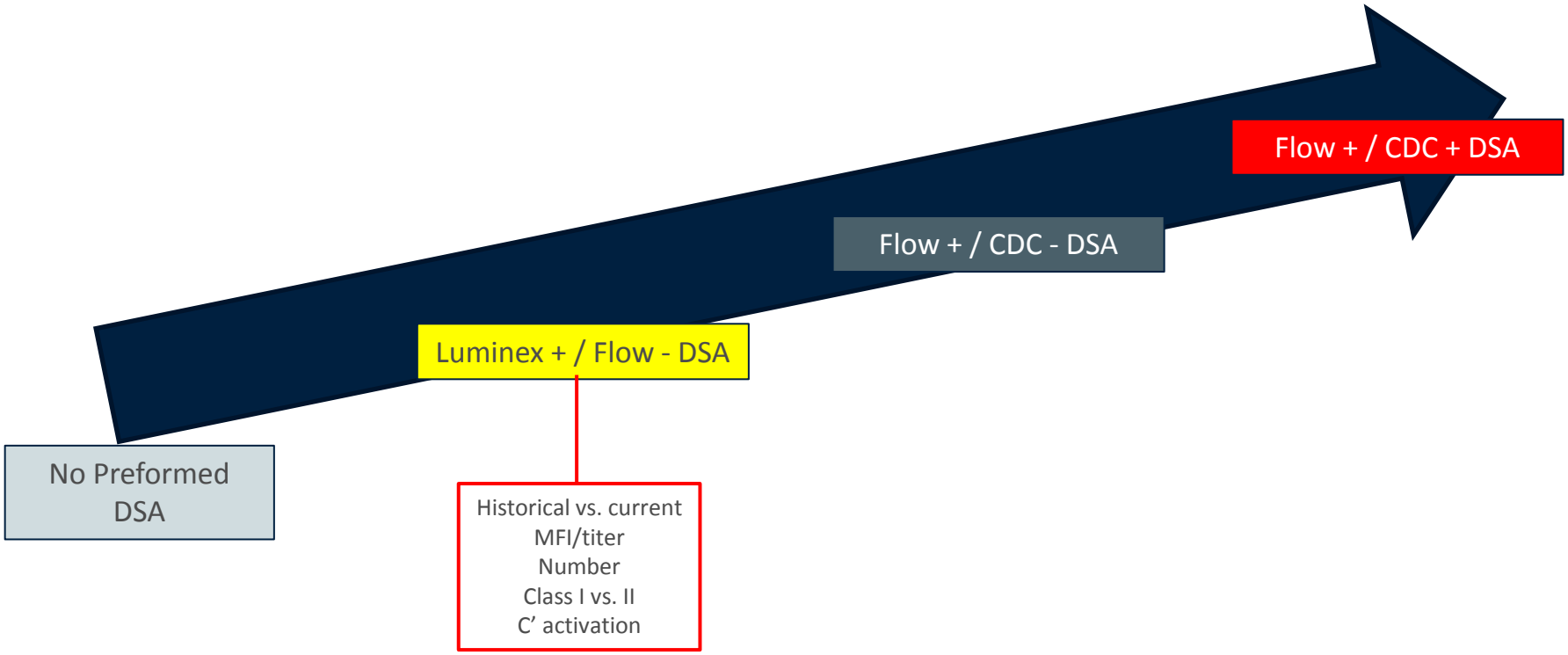
Transplanted across low level Cw15 (MFI 1500) and A24 (historical)

- Significant post-op hypotension
- 3 biopsies: no rejection, all ATN



Implementation of WTC through Adaptive Design

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

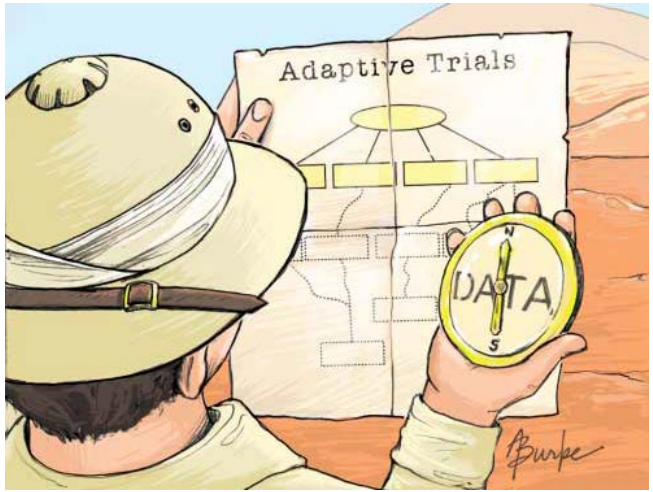
Challenges of Implementing National WTC

- Unlike previous national programs (KPD, HSP), WTC transplants carry real risks to patients and grafts
- No proven treatments for AMR – there is a threshold for unwilling to cross
- Fundamental question – **how to implement WTC without exceeding the threshold for unwilling to cross**
- Can we implement a WTC program which:
    - Maintains patient safety and outcomes
    - Improve our understanding of “risk”

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*

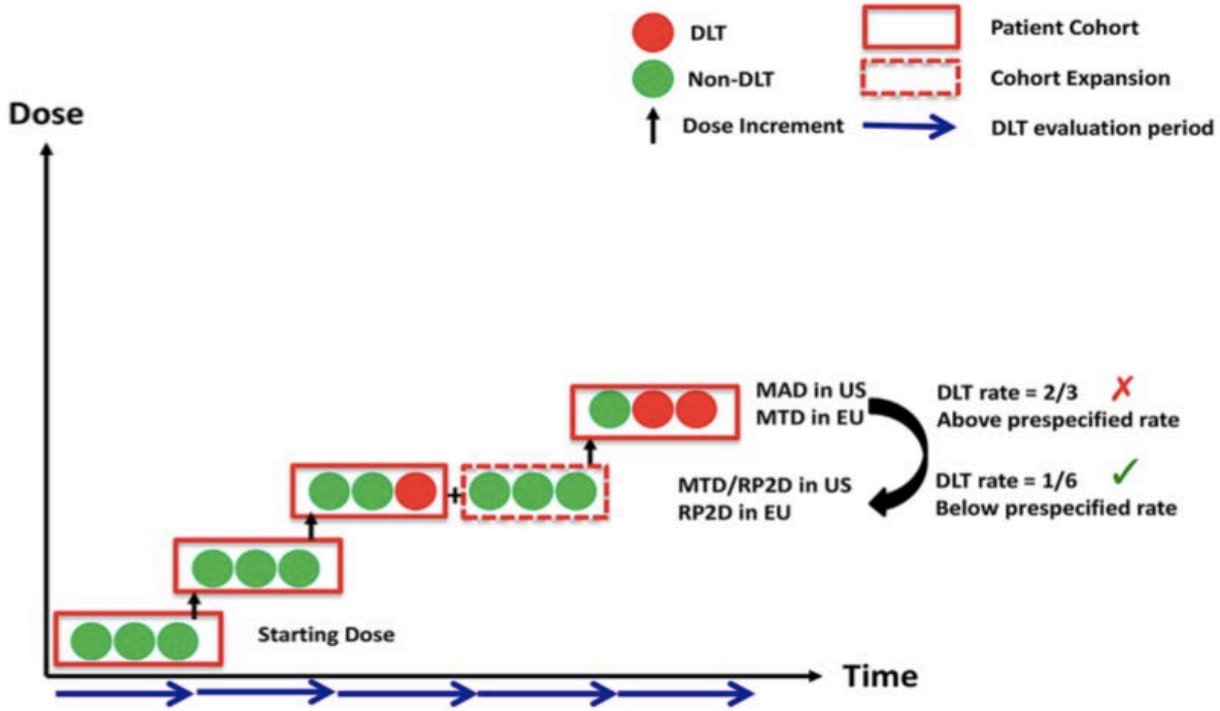
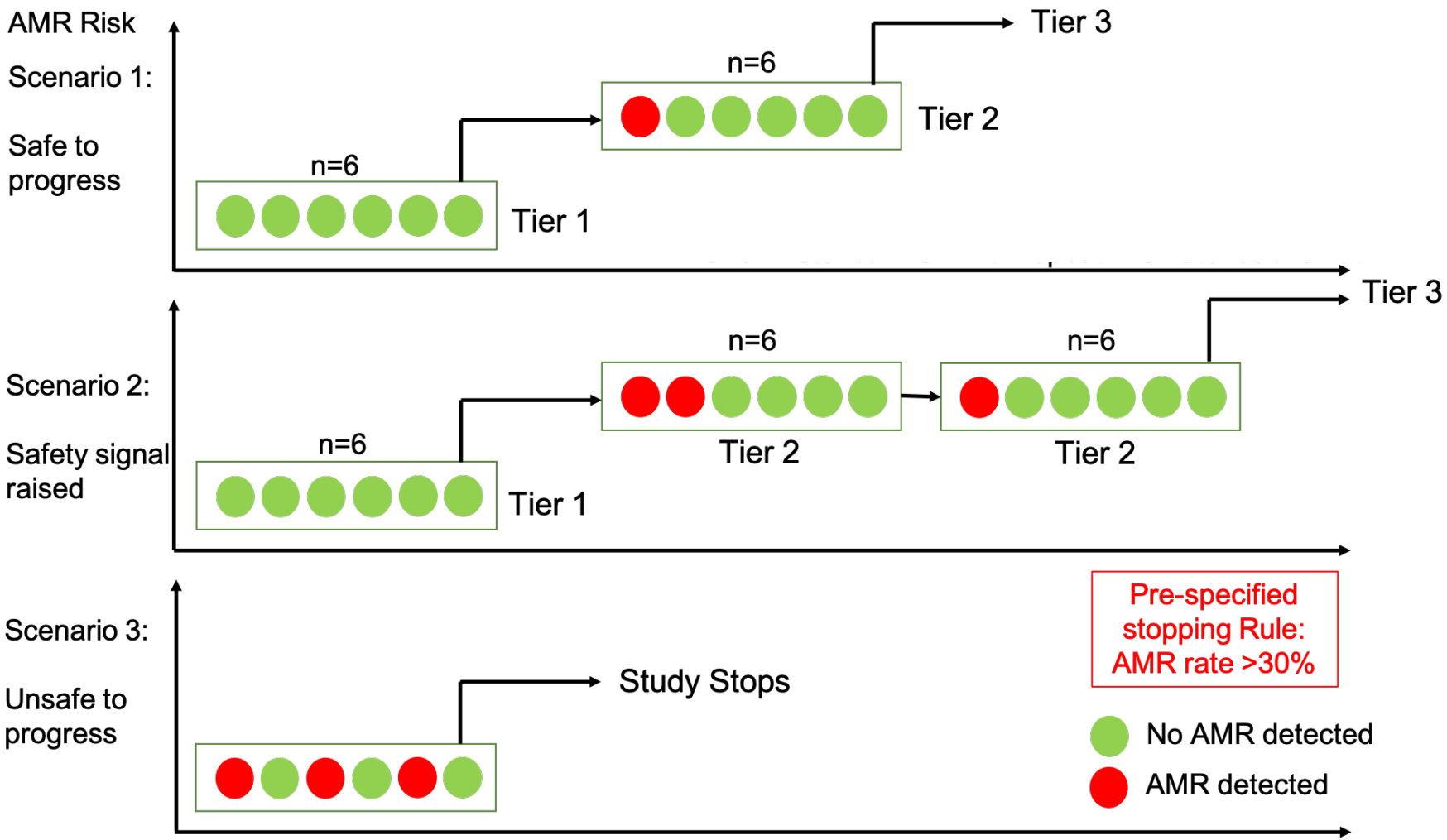


Figure 1 — Elements of a dose escalation study.

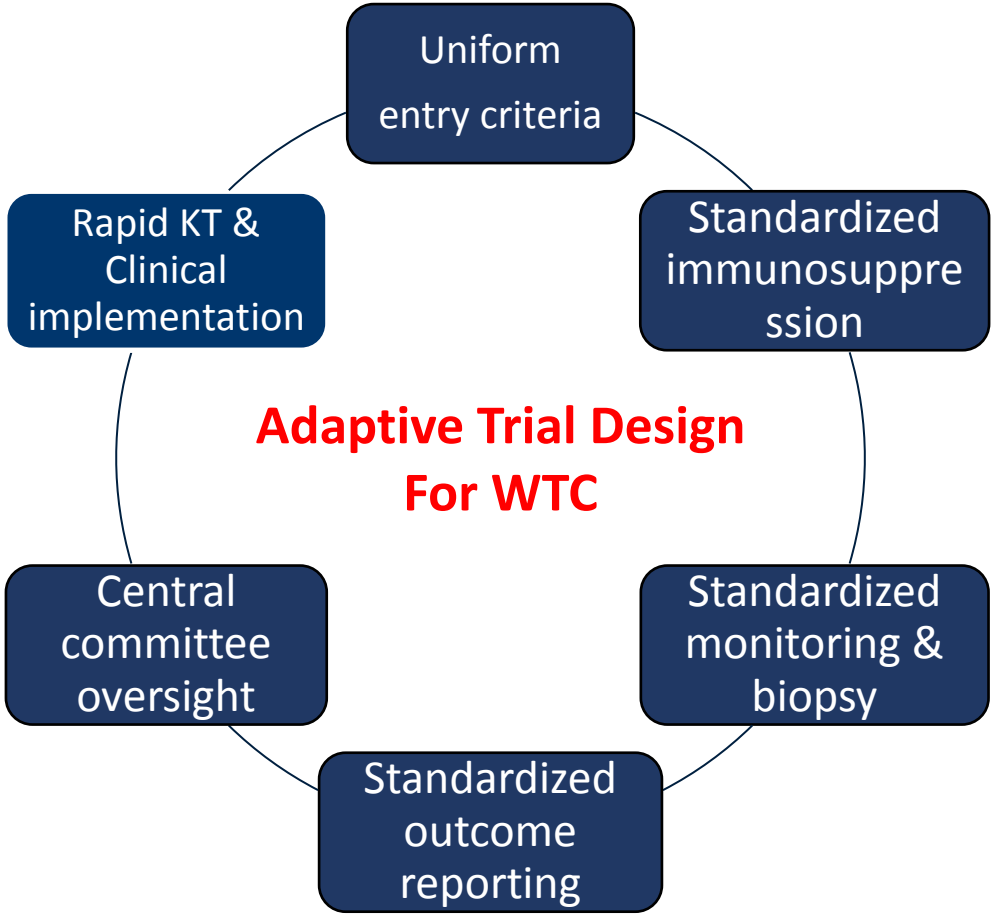
Hansen, Cancer Control 2014


AMR Risk
Scenario 1:
Safe to progress
n=6
Tier 1
n=6
Tier 2
Tier 3
Tier 3
Scenario 2:
Safety signal raised
n=6
Tier 1
n=6
Tier 2
n=6
Tier 2
Scenario 3:
Unsafe to progress
Study Stops
Pre-specified stopping Rule: AMR rate >30%
No AMR detected
AMR detected

Adaptive design advantages[1]

- Efficient method to answer the study question (what is the safety threshold for willing to cross?)
- Flexible: allows modification of protocol tailored to each risk tier
- Ethical benefit (clear stopping rules to prevent the exposure of large number of patients to undue risk)
- Acceptability to stakeholders:
    - Physicians: improved understanding of risk; fairness in sharing organs
    - Patients: a mechanism to improve access within a safe protocol

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


Uniform entry criteria
Standardized immunosuppression
Standardized monitoring & biopsy
Standardized outcome reporting
Central committee oversight
Rapid KT & Clinical implementation
Adaptive Trial Design For WTC

Transplanting Across Historical DSA as a Starting Point

	Cumulative cPRA	Current cPRA
No. Canadian HSP with cPRA ≥ 99% (n)	448	390

13% of patients would have a reduction in cPRA < 99% after removal of historical antibodies as unacceptables

Cumulative cPRA	Current cPRA	Recipient count (n)
100	98	9
100	97	7
100	96	2
100	95	3
100	94	3
100	93	4
100	92	1
100	91	1
100	90	2
100	87	1
100	83	1
100	82	1
100	67	1
100	26	2
99	98	8
99	97	3
99	96	3
99	93	1
99	89	2
99	83	1
99	81	1
99	0	1
Total count		**58**

Principal Investigator: J. Lan

OBJECTIVE	QUARTER - 3 months Start Date (mm/yy)											
	July 2019	Oct 2019	Jan 2020	Apr 2020	Jul 2020	Oct 2020	Jan 2021	Apr 2021	Jul 2021	Oct 2021	Jan 2022	Apr 2022
	Year 1				Year 2				Year 3			
IMPLEMENTATION OF A CANADIAN WTC PROGRAM												
• Interprovincial protocol & consent development												
• Establishment of a central review committee												
• Engagement with CBS to adapt CTR system for WTC												
• Program launch and patient enrollment												
• Central committee review of interim outcomes												
• Analysis and dissemination of interim and final data												

THANK YOU

Questions?

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