

Not all Pre-formed donor-specific HLA antibodies are pathogenic in transplantations



Rajalingam Raja, PhD, FRCP, F(ACHI)
Professor of Clinical Surgery &
Director of Immunogenetics and Transplantation Laboratory
University of California, San Francisco (UCSF)

Lecture Outline

- **HLA testing support for UCSF transplant programs.**
- **Histocompatibility and HLA systems.**
- **HLA and transplant Immunology.**
- **Histocompatibility testing – HLA antibody testing.**
- **Successful kidney transplantation of highly sensitized candidates across strong preformed DSA without desensitization.**
- **Transfusion-induced HLA antibodies are not stable and do not rebound following heart transplantation.**
- **DSA and simultaneous liver and kidney/heart transplantation.**
- **IVIg infusions deplete HLA antibodies in lung transplant recipients.**

UCSF transplant statistics for 2023: Waitlisted = 4,850;

Transplanted = 965

Transplants

Waitlist

Waitlist

Transplants

97

40



30

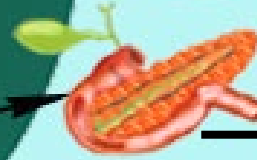
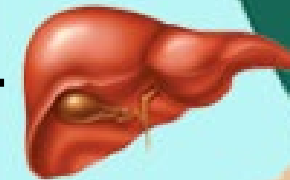
79

(SHLT 2)

201

LD=26 (ped 2)
DD=164 (ped 9)
(SLKT 19)

475

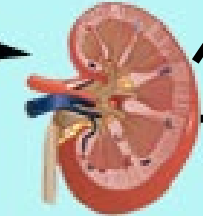


103

8

109

Adult=84
Pediatric=25



4,031

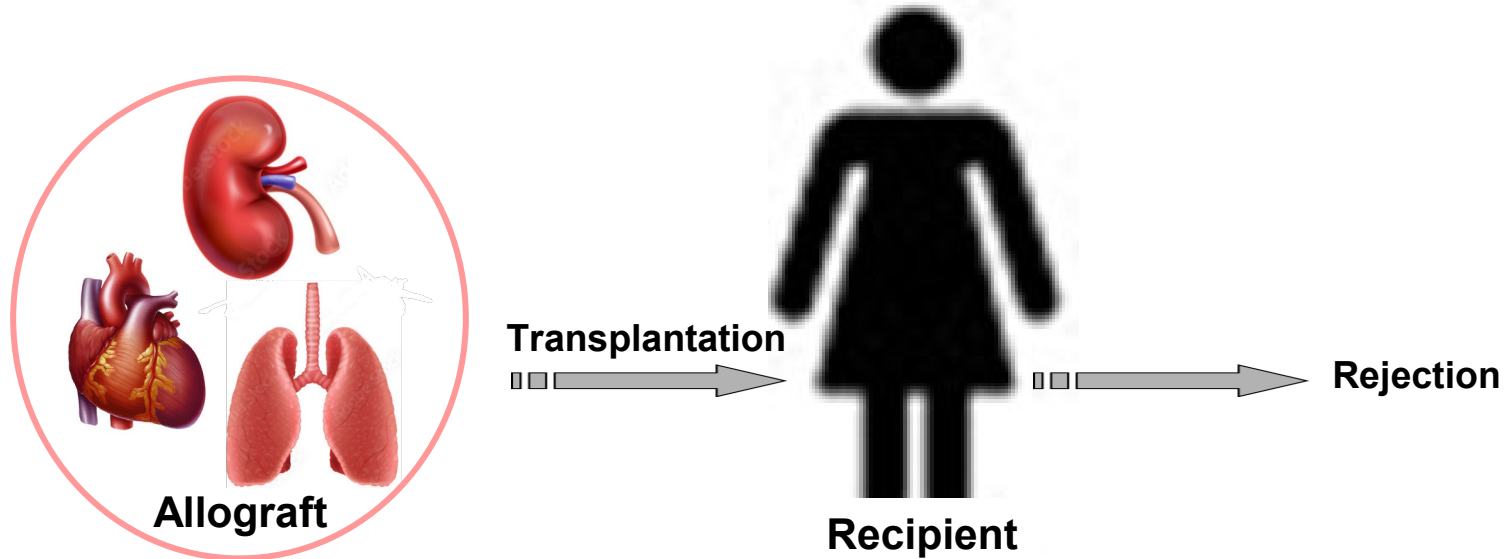
(4.4% of UNOS)

471

LD=117 (ped 8)
DD=322 (ped 8)
(SHKT 13)

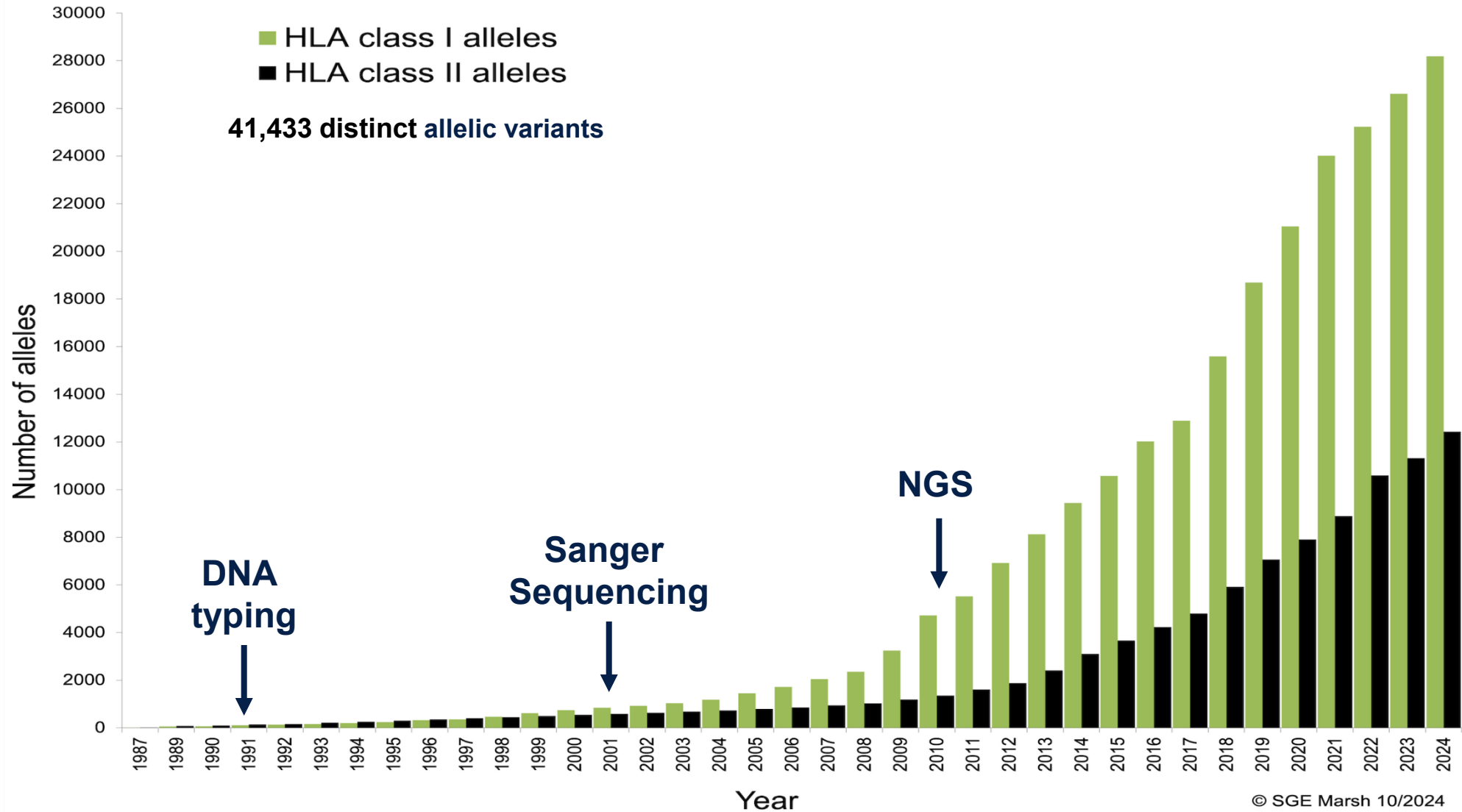
- Local OPO – 627 DD
- USC -200KTx, 1500 waitlisted
- Non-UCSF -BMT
- Clinical trials/research

Histocompatibility System

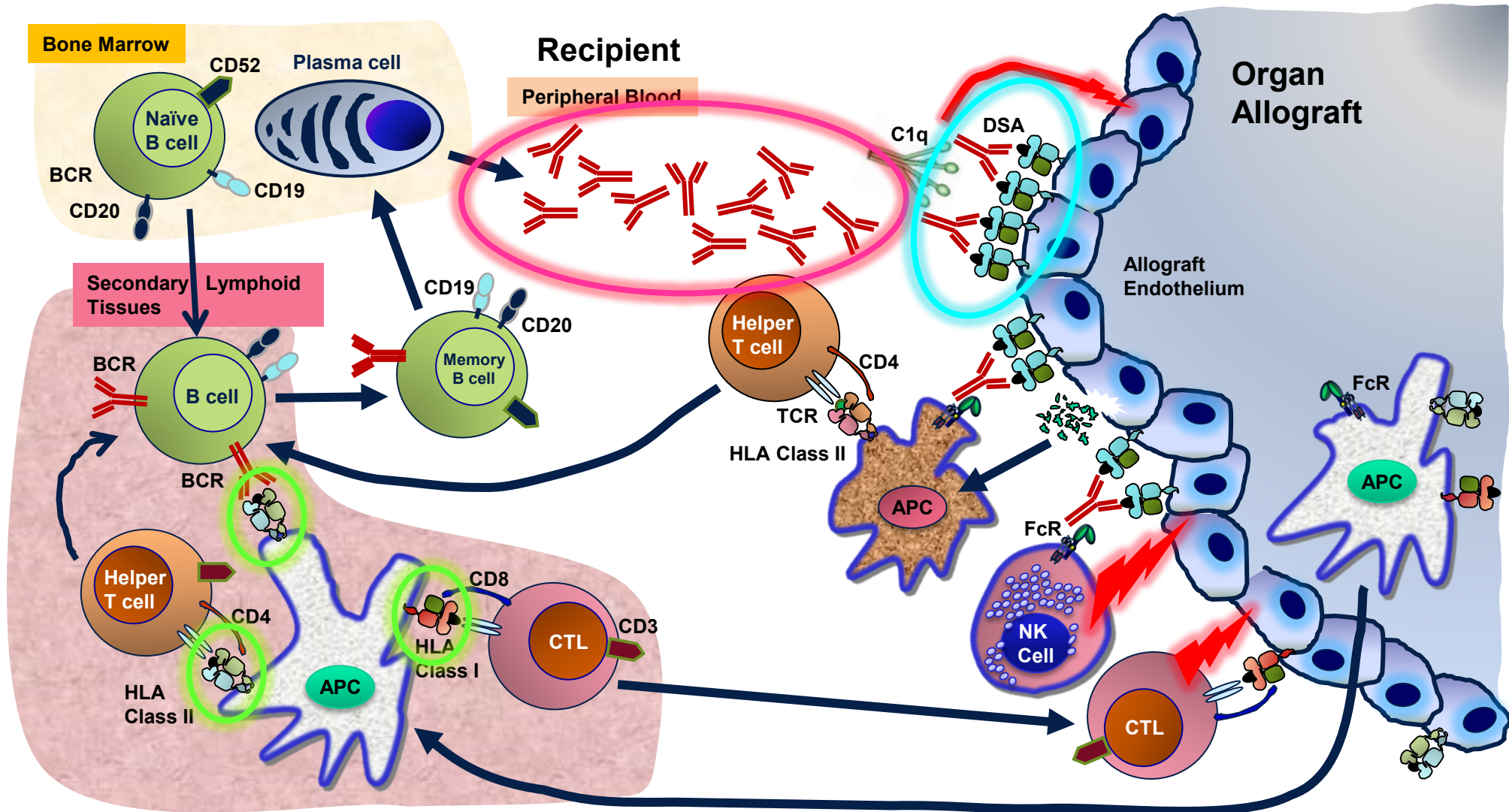


	Components	Polymorphism	Immunogenicity
1	Blood Group Antigens: ABO	Few	Very High
2	Minor Histocompatibility Antigens: HA-1, HA-2, HA-3, H-Y...	Too Many	Low
3	Major Histocompatibility Antigens: Human Leukocyte Antigen (HLA)	Many	High

Numbers of HLA alleles named since 1987, up to October 9, 2024



Transplant Immunology



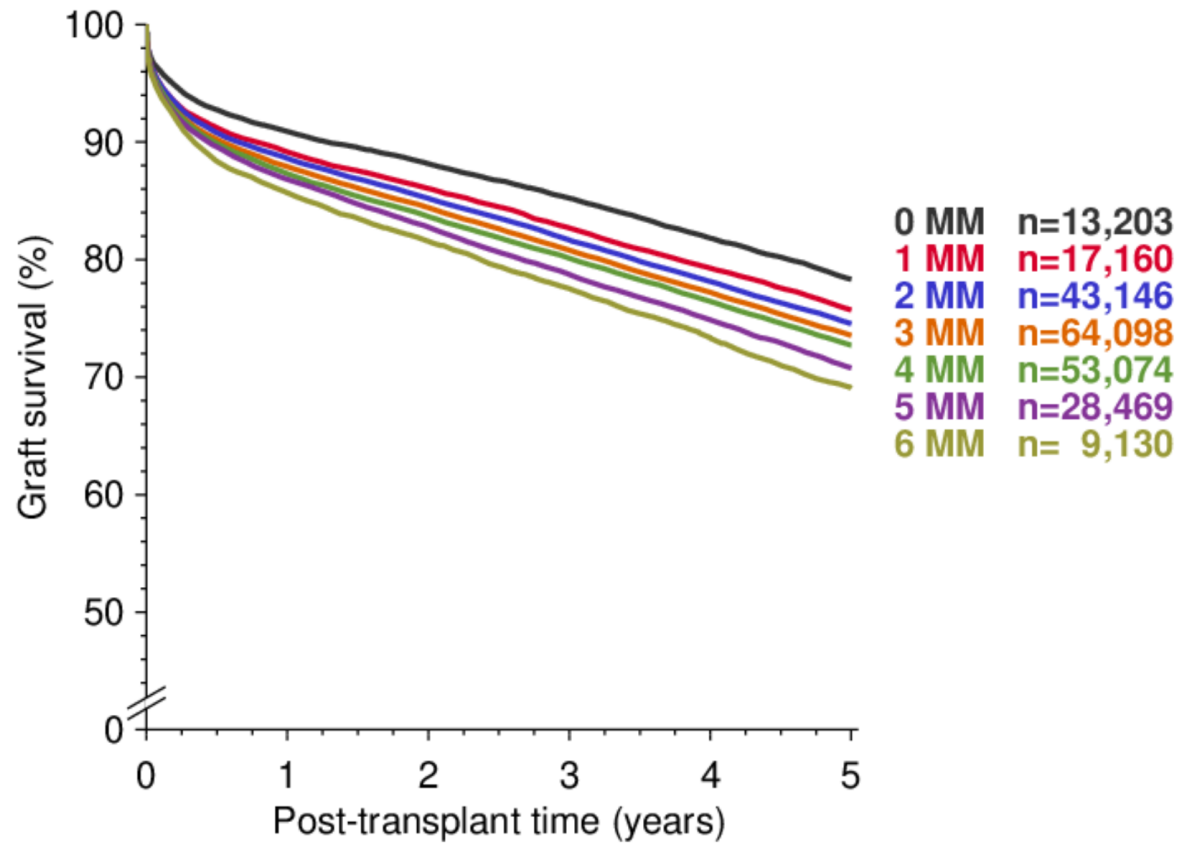
Histocompatibility testing

	Old methods	Cutting Edge
HLA typing	SSP PCR	Hybrid capture NGS
HLA antibody measurement	Multiantigen bead screening	Single antigen bead assay
Crossmatch	CDC/Flow crossmatch	Virtual crossmatch

HLA typing

HLA-A+B+DR Mismatches

Deceased Donor, First Kidney Transplants 1990-2018 (n=228,280)



HLA typing workflow at UCSF ITL

RT-PCR

- Deceased donors (DD)
- Emergency listing

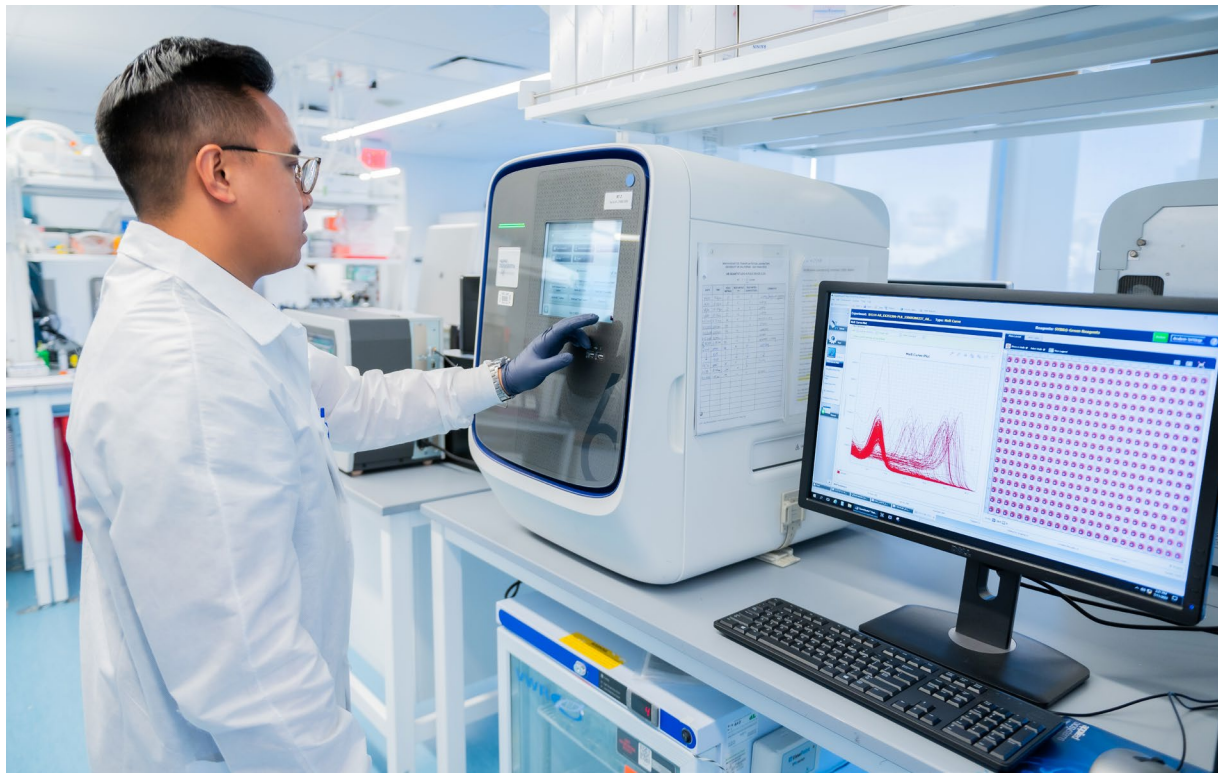
2023 DD volume = 627

NGS

- SOT patients
- Living donors
- HSCT: patients and donors
- Confirmatory typing for HSCT
- Confirmatory typing for import DD
- Disease and pharmacogenetic markers

2023 volume = 4800

Real-time PCR method

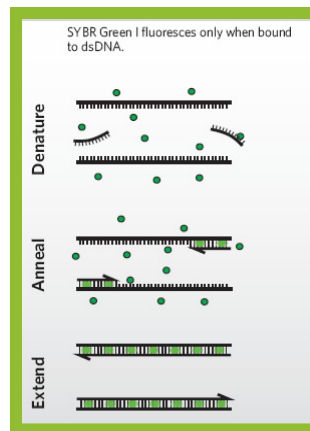


ADD
Add DNA and reagents into pre-aliquoted buffer then add to LinkSēq™ Plates
10 min
MANUAL TASK

AMPLIFY
Amplify DNA and perform melt curve analysis on a real-time PCR instrument
70 min
AUTOMATED STEP

ANALYZE
Analyze data in SureTyper™ and report results
10 min
AUTOMATED STEP

TOTAL TIME
One manual step—results in hand—90 minutes
90 min

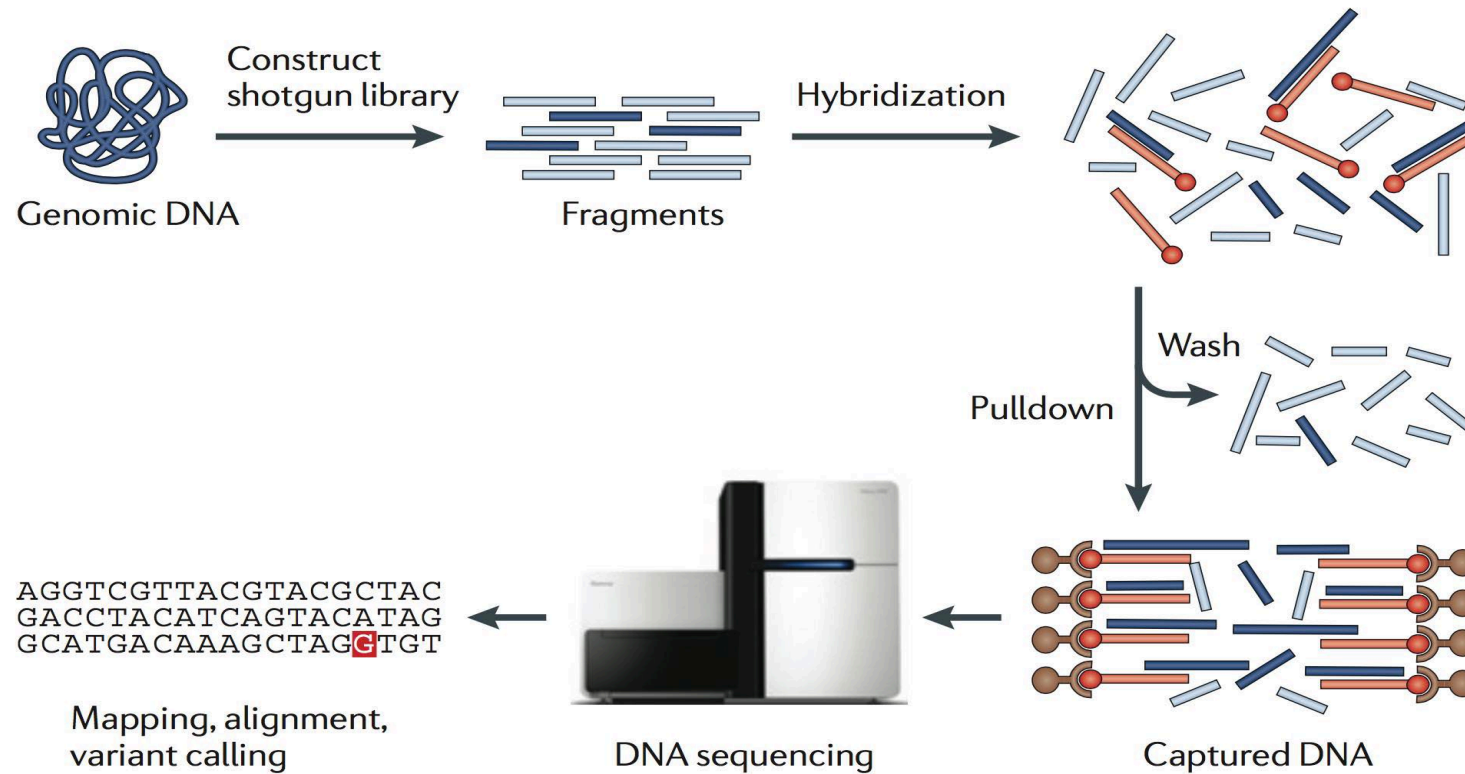


SureTyper - Tray 1 - Assays

Trey	Test	Group	Alide	Assay																				
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	
A	+	+	+	+																				
B																								
C																								
D																								
E																								
F																								
G																								
H																								
I																								
J																								
K																								
L																								
M																								
N																								
O																								
P																								

SYBR™ GREEN – 384 wells

Capture-based NGS for HLA typing



The American Journal of Human Genetics 99, 375–391, August 4, 2016

ARTICLE

Defining KIR and HLA Class I Genotypes at Highest Resolution via High-Throughput Sequencing

Paul J. Norman,^{1,*} Jill A. Hollenbach,² Neda Nemat-Gorgani,¹ Wesley M. Marin,² Steven J. Norberg,³ Elham Ashouri,¹ Jyothi Jayaraman,⁴ Emily E. Wroblewski,¹ John Trowsdale,⁴ Raja Rajalingam,⁵ Jorge R. Oksenberg,² Jacques Chiaroni,⁶ Lisbeth A. Guethlein,¹ James A. Traherne,⁴ Mostafa Ronaghi,³ and Peter Parham¹

JANUS® G3 Liquid Handler Workstations for NGS Automation



Importance of HLA typing and matching

- **Reduce the Risk of Graft Rejection**
- **Improve Long-Term Graft Survival**
- **Prevent Antibody-Mediated Rejection (AMR)**
- **Support Donor Selection in Paired Exchange and Living Donor Programs**
- **Guide Desensitization Protocols for Sensitized Patients**
- **Improve Access to Transplantation**
- **Support Personalizing Immunosuppressive Therapy**

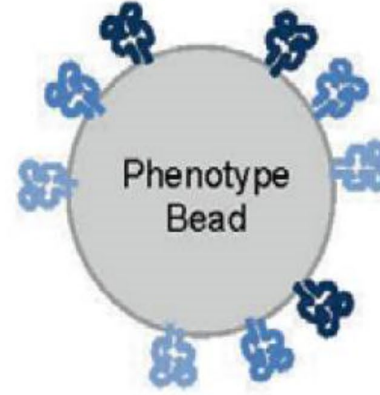
HLA antibodies testing

HLA Antibody Testing Methods

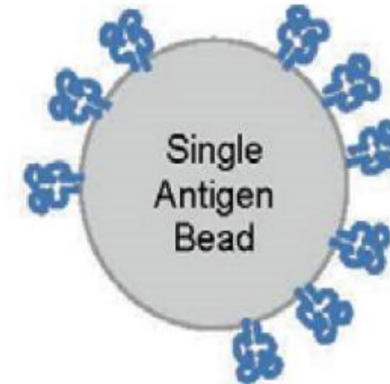
Mixed Antigen Beads



Multi Antigen Beads

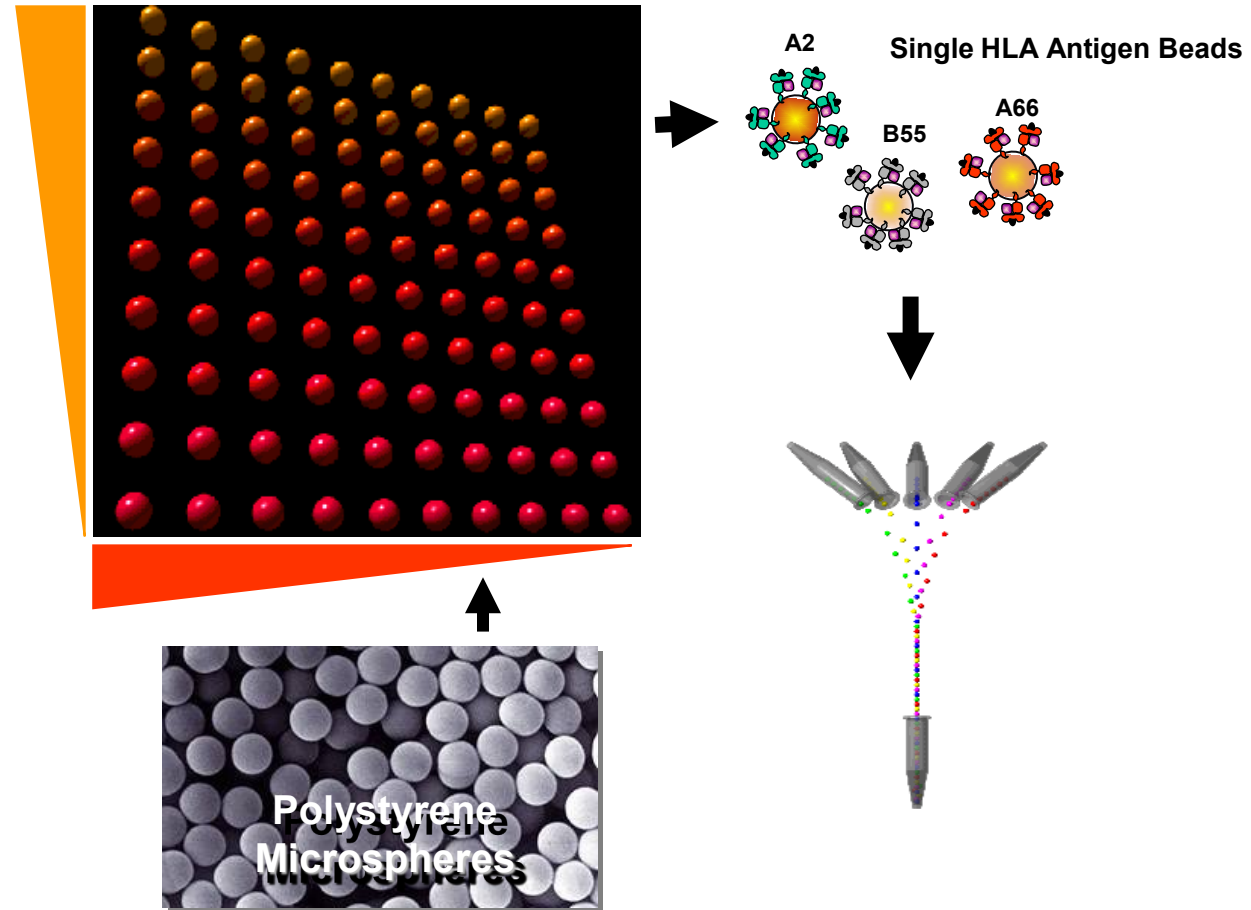


Single Antigen Beads

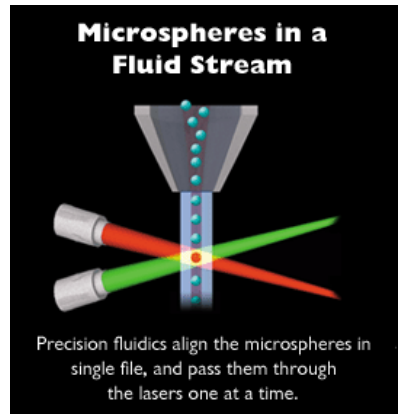
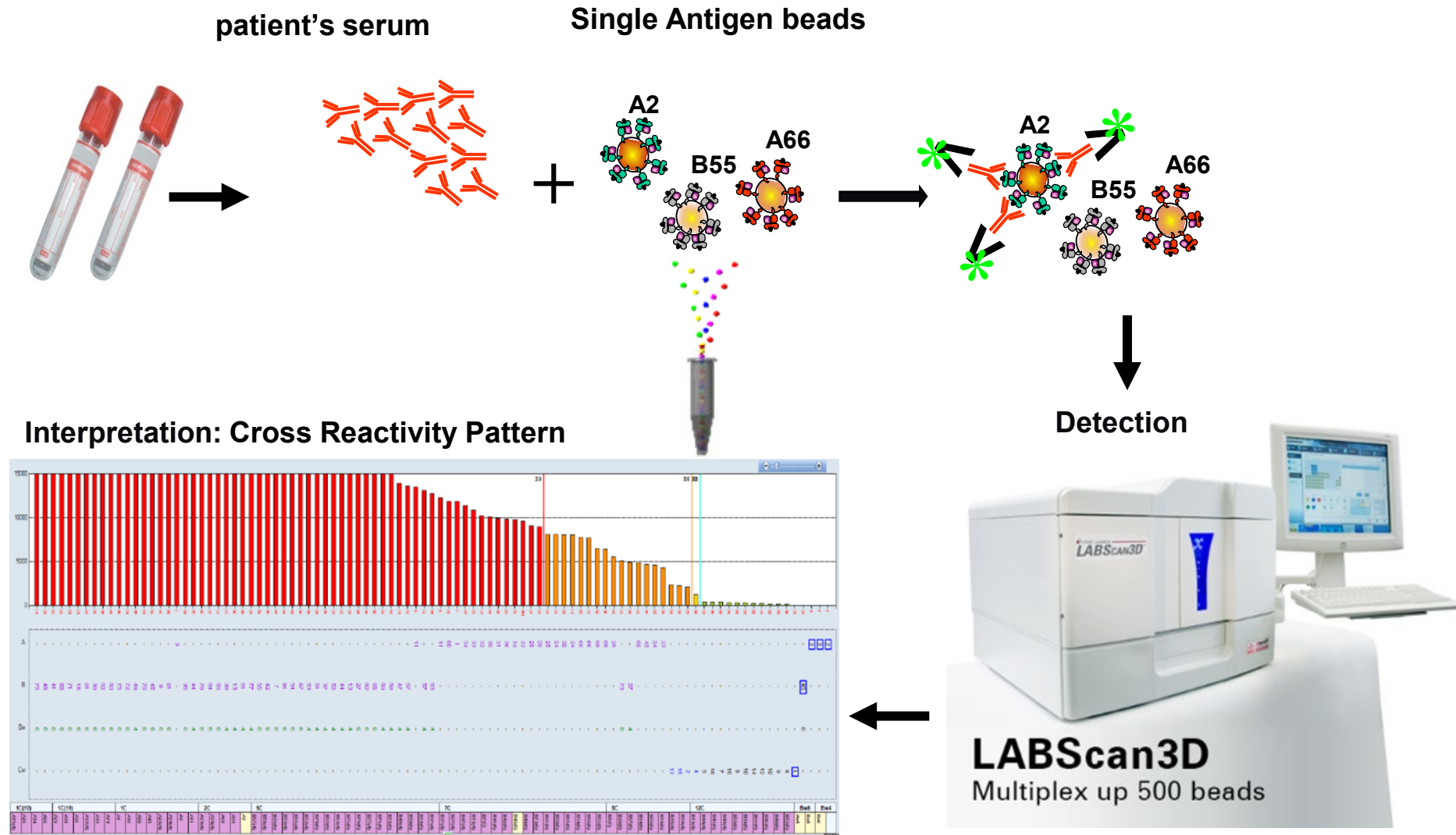


<i>Application</i>	screening	specification	specification
<i>Relative antigen density</i>	low Positive / Negative	intermediate % PRA	high Specificity and Strength (MFI)
<i>Resolution</i>	—	★	★★★
<i>Antigen source</i>	Platelets, EBV-transformed cell line	EBV-transformed cell line	Recombinant cell line
<i>Antigen composition per bead</i>	Complete class I or II phenotype of 3–5 individuals	Complete class I or II phenotype of 1 individual	Single allelic antigen

Luminex single antigen bead-based HLA antibody testing: Design



Luminex single antigen bead-based HLA Antibody Testing



Precision fluidics align the microspheres in single file, and pass them through the lasers one at a time.

UCSF standards for HLA Antibody Testing: Luminex Single Antigen Bead Assay

Serum pre-treatment: dithiothreitol (DTT)

- to prevent aggregation of high titer antibodies
- to remove interfering factors to increase the sensitivity


High throughput automation: Lab Express

- to minimize inter-assay MFI variation
- to maximize the efficiency

Interpretation standards:

- Cross REactive Group (CREG) Signatures (e.g., A2: A2, A68, A69, B57, B58, A23, A24) & split antigens (e.g., B12: B44, B45)
- no a set MFI cutoff for HLA antibody assignment
- consider the mode of Prior Sensitization: transplant, pregnancy, transfusion
- incorporate cell-binding ability assessed by Flow Cytometry crossmatch

Pre-transplant HLA Antibody Report

 <p>Immunogenetics and Transplantation Laboratory University of California San Francisco Laurel Heights Campus 3333 California Street, Suite 150 San Francisco, CA 94118 Office: 415-476-3883; Laboratory: 415-476-3886 Facsimile: 415-476-0379 ASHI: 02-6-CA-14-1 State of CA: CLF3207 CLIA: 05D0720389 HCFA: 05-HL-06 Director: Rajalingam Raja, Ph.D., D(ABHI)</p>	<p>Name: DOB; Age & Gender: MRN: Category: Provider: UCSF Renal Transplant Service</p>	<p>Report Date: 1/13/2020 cPRA: A100% Probability of 0 ag MM offer - National: 12% Probability of 0 ag MM offer - Local: 3%</p>	
---	---	---	--

HLA Antibody Report

Patient HLA Types

Name	ABO	A	B	Bw	Cw	DR (DRB1)	DR (DRB3/4/5)	DQ (DQB1)	DQA1	DP (DPB1)	DPA1
(O	2 68	35 35	6 6	4 4	4 8	53	8 4	03 04:01	04:02 04	01:03 01

For HLA type that has NMDP codes, please refer to the HLA typing report for translations. The ABO typing was obtained from patient medical records.

Prior Allografts

Date of Transplant	Organ	Donor Name UNOS ID	HLA Type
06/30/2019	Kidney	AGFZ466	A*02B*MYF.02B*MYF B*35:04,35:17 B*6,6C*04B*PPRH,04B*PPRJ DRB1*04AMSCX,08B*PKSS DRB4*01B*PHSW, DQA1*03RV,04AEDQB1*03B*MPA,04B*PMPCDPA1*01B*PGMP,01 B*PGMPDPB1*04:01,04:02
05/19/2011	Kidney	YDZ787	A*02,30 B*13,35 C*04,06 DRB1*04,15 DRB3*NEG, DRB4*POS, DRB5*POS, DQB1*03(8),06


Antibody Test Results

Sample Date	Tested Date	Test Description
01/06/2020	01/09/2020	HLA Antibody - Class I Single Antigen
Strong: A:32 B:13 27 38 44 47 48 49 51 53 57 58 59 60 61 63 7 73 77 81 Bw:4		
Moderate: A:23 24 25 29 30 31 66 B:37 39 41 42 45 52 55 62 75 67 76 Cw:2		
Weak: A:74 B:50 82		
Comments: Unacceptables:(A:23 24 25 26 29 30 31 32 33 34 66 80 74 B:13 27 37 38 39 41 42 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 7 75 67 73 76 77 81 82 Bw:4 Cw:2 6)		
01/06/2020	01/09/2020	HLA Antibody - Class II Single Antigen
Strong: DR:1 15 9 103 DRw:51 DQ:5 6		
Moderate: DR:10 16 DQ:2		
Weak: DR:7		
Comments: Unacceptables:(DR:1 10 11 12 13 15 16 7 9 103 DRw:51 DQ:2 5 6)		

Antibody testing was performed by solid phase methods that detect only IgG antibodies. Strong: >8500 MFI; Moderate: 2000-8499 MFI; Weak: 1000-1999 MFI. The MFI values listed below are average values for all positive beads with a particular antigen. These may not match the antibody specificities and strengths listed above, which represent the Director's interpretation.

Sample Date: 01/06/2020	Sample #:2001H213847	Sample Date: 01/06/2020	Sample #:2001H213847
-------------------------	----------------------	-------------------------	----------------------

Class I Specificity	MFI	Class II Specificity	MFI
B13	24940	DR51	27752
B27	22785	DQ5	25841
B7	22755	DQ6	24350
B60	21503	DR15	21813

 <p>Immunogenetics and Transplantation Laboratory University of California San Francisco Laurel Heights Campus 3333 California Street, Suite 150 San Francisco, CA 94118 Office: 415-476-3883; Laboratory: 415-476-3886 Facsimile: 415-476-0379 ASHI: 02-6-CA-14-1 State of CA: CLF3207 CLIA: 05D0720389 HCFA: 05-HL-06 Director: Rajalingam Raja, Ph.D., D(ABHI)</p>	<p>Name: DOB; Age & Gender: MRN: Category: Kidney Recipient Provider: UCSF Renal Transplant Service</p>	<p>Report Date: 1/13/2020 cPRA: A100% Probability of 0 ag MM offer - National: 12% Probability of 0 ag MM offer - Local: 3%</p>	
---	--	---	--


HLA Antibody Report

Sample Date: 01/06/2020 Sample #:2001H213847 Sample Date: 01/06/2020 Sample #:2001H213847

Class I Specificity	MFI	Class II Specificity	MFI
B61	21363	DR103	17630
B81	21276	DR9	15073
B48	19146	DR1	14018
B47	17242	DR16	7554
B59	12614	DQ2	4997
B49	12508	DR10	3846
B57	12178	DR7	1461
B73	12038		
A32	11850		
B38	11712		
B58	10622		
B51	10439		
B63	9520		
B53	9214		

Comments

This candidate does NOT qualify for virtual crossmatch and requires physical flow cytometry crossmatch.



01/13/2020

Owen Buenaventura, B.S., CHT(ABHI), CLS Date
Rajalingam Raja, Ph.D., D(ABHI), Director

These tests were developed and their performance characteristics determined by the UCSF Immunogenetics and Transplantation Laboratory (ITL). They have not been cleared or approved by the U.S.FDA. FDA approval is not necessary since the ITL is certified under CLIA for high complexity testing.



Immunogenetics and Transplantation Laboratory
 University of California San Francisco
 Laurel Heights Campus
 3333 California Street, Suite 150
 San Francisco, CA 94118
 Office: 415-476-3883; Laboratory: 415-476-3886
 Facsimile: 415-476-0379
 ASHI: 02-6-CA-14-1 State of CA: CLF3207
 CLIA: 05D0720389 HCFA: 05-HL-06
 Director: Rajalingam Raja, Ph.D., D(ABHI)

Name: xxxxxxx, xxx
 DOB; Age & Gender: xxxxxxx; 59M
 MRN: xxxxxxxx
 Category: Kidney Recipient
 Provider: Kaiser Permanente San Francisco
 Medical Ctr
 Report Date: 12/5/2018

Donor-specific antibody (DSA) Report (page-1)

Post Transplant DSA Antibody Report

HLA Types

Name	Relation	ABO	A	B	Bw	Cw	DR (DRB1)	DR (DRB345)	DQ (DQB1)	DQA1	DP (DPB1)	DPA1
xxxxxxx, xxx	Patient	O	2	7	6	5	8	51	4	01	04:02	01:03
			3	44	4	7	15	6	04:02	04:02	01:03	
58704253	Friend		26	64	4	2	4	53	2	02:01	05:01	02:01
			26	27	6	8	7	53NULL	8	03	17:01	02:01

For HLA type that has NMDP codes, please refer to the HLA typing report for translations. The ABO typing was obtained from patient medical records.

Prior Allografts

Date of Transplant	Organ	UNOS ID	HLA Type
12/19/2016	Kidney	ADKO696	A*26,26 B*14(64),27 B*4,6C*02,08 DRB1*04,07 DRB4*01:03,01:03N DQA1*02:01,03MNDQB1*02,03(8)DPA1*02:01,02:01DPB1*05:01,17:01

Antibody Test Results

Sample Date	Tested Date	Test Description
12/03/2018	12/04/2018	HLA Antibody - Class I Single Antigen
Weak: A:24		
Comments: No donor-specific HLA Class I antibodies were detected in this serum against donor ADKO696, Tx. Date: 12/19/2016.		
12/03/2018	12/04/2018	HLA Antibody - Class II Single Antigen
Strong: DQ:8 9 DQA:03		
Moderate: DQ:2 7		
Weak: DRw:53		
Comments: The patient displays donor-specific HLA Class II antibodies, HLA-DQ2 (MFI=5855), DQ8 (MFI=8502), and DR53 (MFI=1030) against donor ADKO696, Tx. Date: 12/19/2016., which indicates an increased risk of antibody-mediated rejection.		

Antibody testing was performed by solid phase methods that detect only IgG antibodies. Strong: >8500 MFI; Moderate: 2000-8499 MFI; Weak: 1000-1999 MFI. The MFI values listed below are average values for all positive beads with a particular antigen. These may not match the antibody specificities and strengths listed above, which represent the Director's interpretation.

The trends of donor-specific antibodies (DSA) in the historical sera are shown in the table and graph in the subsequent pages. The table and graph exclude DSAs that are directed against DQA1,DPA1, and to specific allele types. Please refer the original reports for complete listing of DSAs and comments that are essential for using the test results.

Sample Date: 12/03/2018 Sample #:1812H190773 Sample Date: 12/03/2018 Sample #:1812H190773

Class I Specificity	MFI
A24	1132

Class II Specificity	MFI
DQ4	9487
DQ9	8788
DQ8	8502



Immunogenetics and Transplantation Laboratory
 University of California San Francisco
 Laurel Heights Campus
 3333 California Street, Suite 150
 San Francisco, CA 94118
 Office: 415-476-3883; Laboratory: 415-476-3886
 Facsimile: 415-476-0379
 ASHI: 02-6-CA-14-1 State of CA: CLF3207
 CLIA: 05D0720389 HCFA: 05-HL-06
 Director: Rajalingam Raja, Ph.D., D(ABHI)

Name: xxxxxxxx, x
 DOB; Age & Gender: xxxxxxxxx; 59M
 MRN: xxxxxxxxx
 Category: Kidney Recipient
 Provider: Kaiser Permanente San Francisco
 Medical Ctr
 Report Date: 12/5/2018

DSA Report (page-2)

Post Transplant DSA Antibody Report

Donor-Specific Antigens and Antibodies

		A26	B27	B64	Cw2	Cw8	DR4	DR53	DR7	DQ2	DQ8	DP17	DP5	Txp
9/1/15	Pre	0	0	0	0	0	0	0	0	0	0	0	0	0
12/12/16	Pre	0	0	0	0	0	0	0	0	0	0	0	0	0
12/19/16	Txp	0	0	0	0	0	0	0	0	0	0	0	0	
6/9/17	Post	0	0	0	0	0	0	0	0	0	0	0	0	0
11/2/17	Post	0	0	0	0	0	0	3271	0	8942	10377	0	0	0
11/13/17	Post	0	0	0	0	0	0	6336	0	11002	12066	0	0	0
1/14/18	Post	0	0	0	0	0	0	2566	0	7318	11093	0	0	0
2/11/18	Post	0	0	0	0	0	0	2806	0	8490	13218	0	0	0
3/9/18	Post	0	0	0	0	0	0	2433	0	7758	12020	0	0	0
4/16/18	Post	0	0	0	0	0	0	7789	0	11065	16260	0	0	0
6/5/18	Post	0	0	0	0	0	0	1792	0	7558	9021	0	0	0
7/7/18	Post	0	0	0	0	0	0	1350	0	6601	8186	0	0	0
7/27/18	Post	0	0	0	0	0	0	1345	0	6673	8418	0	0	0
9/3/18	Post	0	0	0	0	0	0	1538	0	7336	9540	0	0	0
9/30/18	Post	0	0	0	0	0	0	1227	0	4716	9852	0	0	0
12/3/18	Post	0	0	0	0	0	0	1030	0	5855	8502	0	0	0

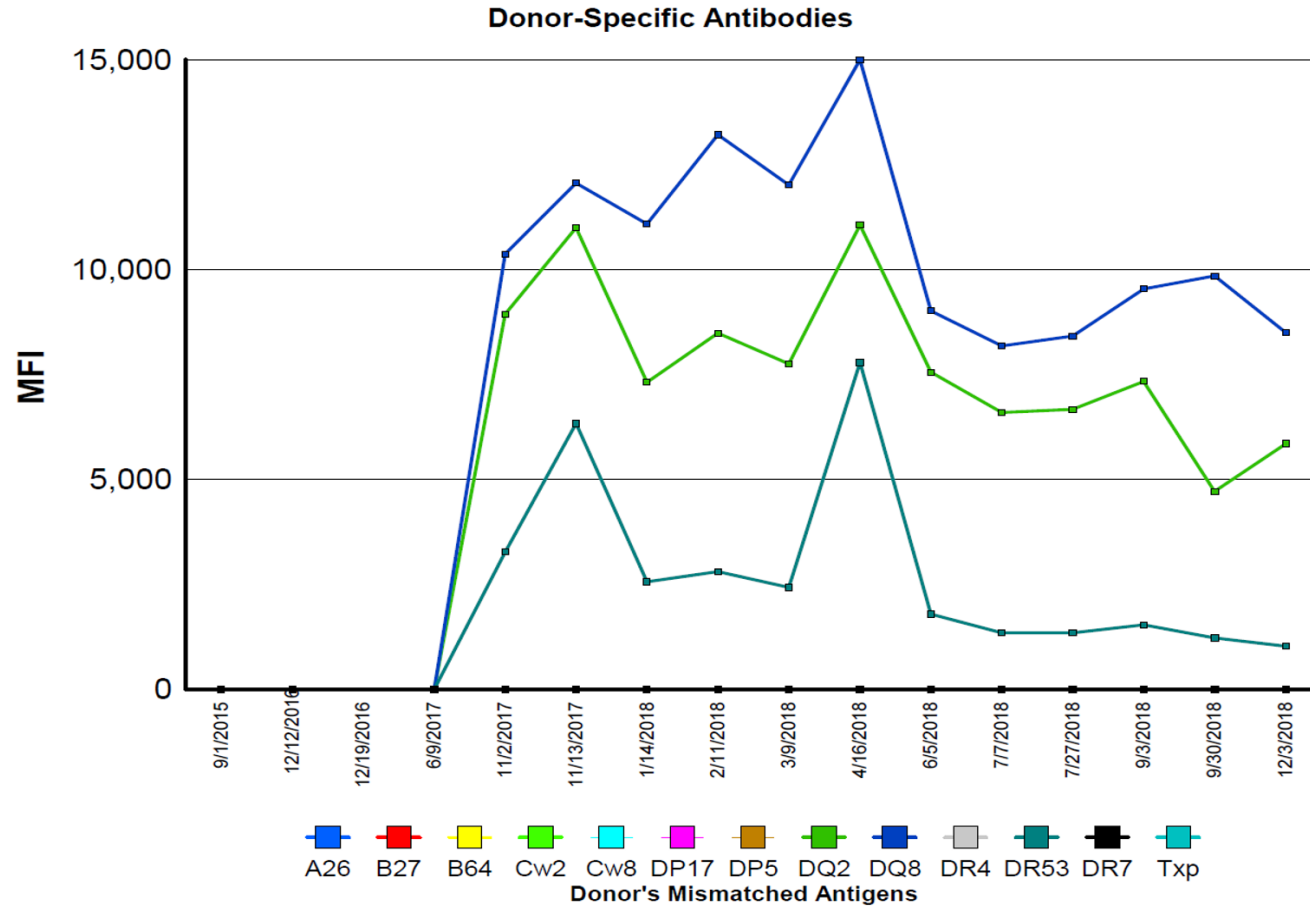


Immunogenetics and Transplantation Laboratory
 University of California San Francisco
 Laurel Heights Campus
 3333 California Street, Suite 150
 San Francisco, CA 94118
 Office: 415-476-3883; Laboratory: 415-476-3886
 Facsimile: 415-476-0379
 ASHI: 02-6-CA-14-1 State of CA: CLF3207
 CLIA: 05D0720389 HCFA: 05-HL-06
 Director: Rajalingam Raja, Ph.D., D(ABHI)

Name: xxxxxxx, xxx
 DOB; Age & Gender: xxxxxxx; 59M
 MRN: xxxxxxxxxx
 Category: Kidney Recipient
 Provider: Kaiser Permanente San Francisco
 Medical Ctr
 Report Date: 12/5/2018

DSA Report (page-3)

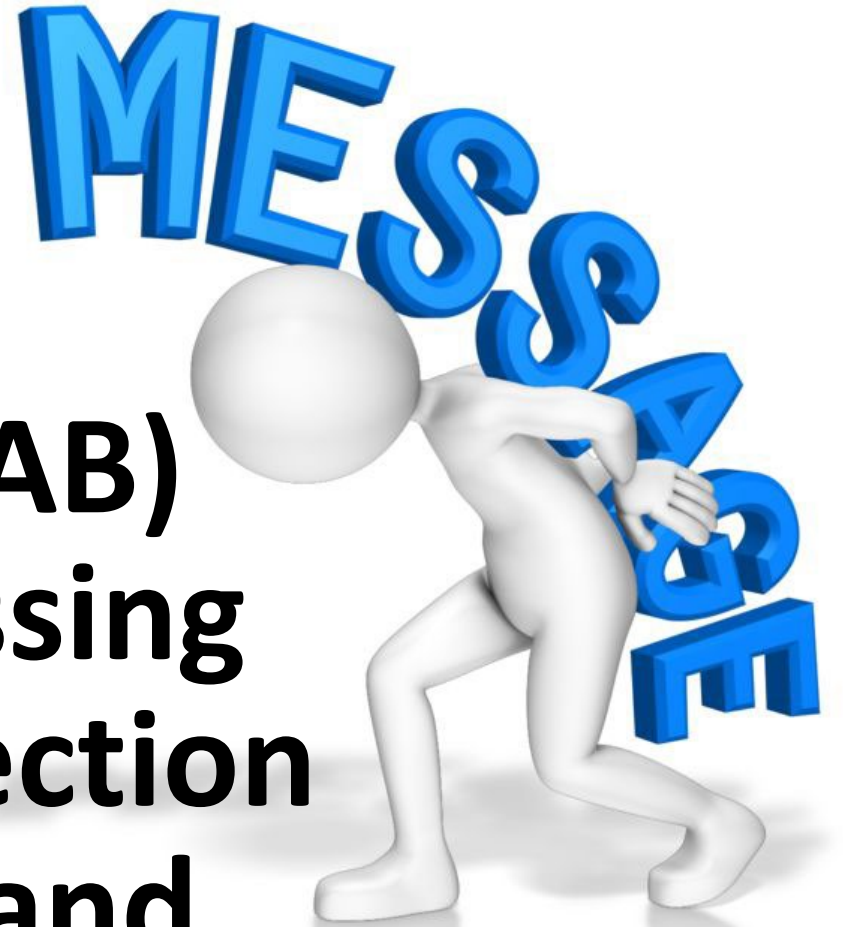
Post Transplant DSA Antibody Report



Advantages of single antigen bead assay (SAB) for HLA antibody testing

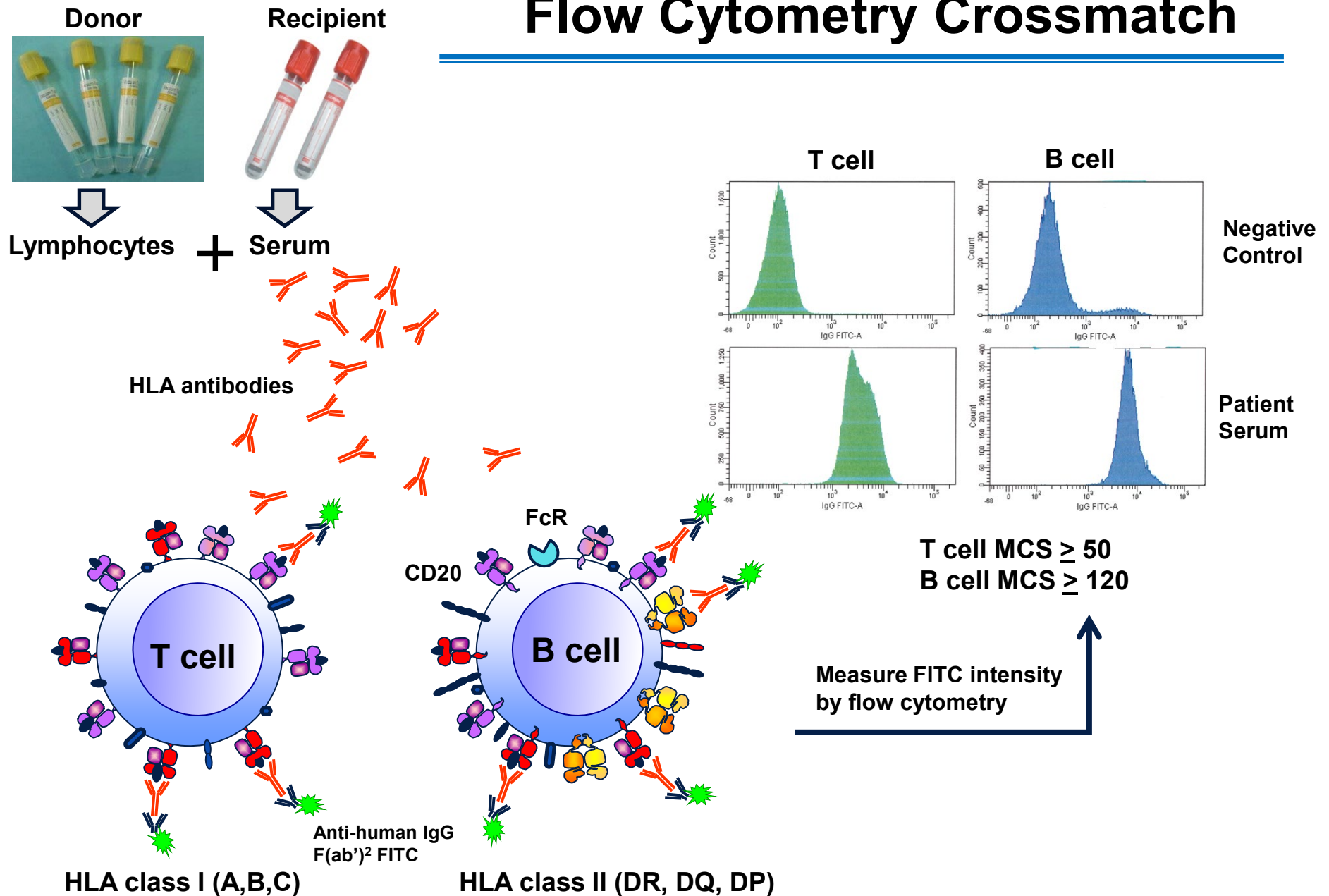
- 1. High Sensitivity and Specificity**
- 2. Detailed Antibody Profiling**
- 3. Quantitative Results – MFI values**
- 4. Ability to Detect Broad and Narrow Specificities**
- 5. Reduced Cross-Reactivity**
- 6. Useful to Assess the Breadth of Sensitization - CPRA**
- 7. Standardization and Reproducibility**
- 8. Supports Virtual Crossmatching**
- 9. Minimizes the Need for Cell-Based Assays**
- 10. Risk Assessment for Transplant Outcomes – DSA assessment**

**Single Antigen Bead (SAB)
assay is critical for assessing
the risk of transplant rejection
in both pre-transplant and
post-transplant settings**



Crossmatch

Flow Cytometry Crossmatch



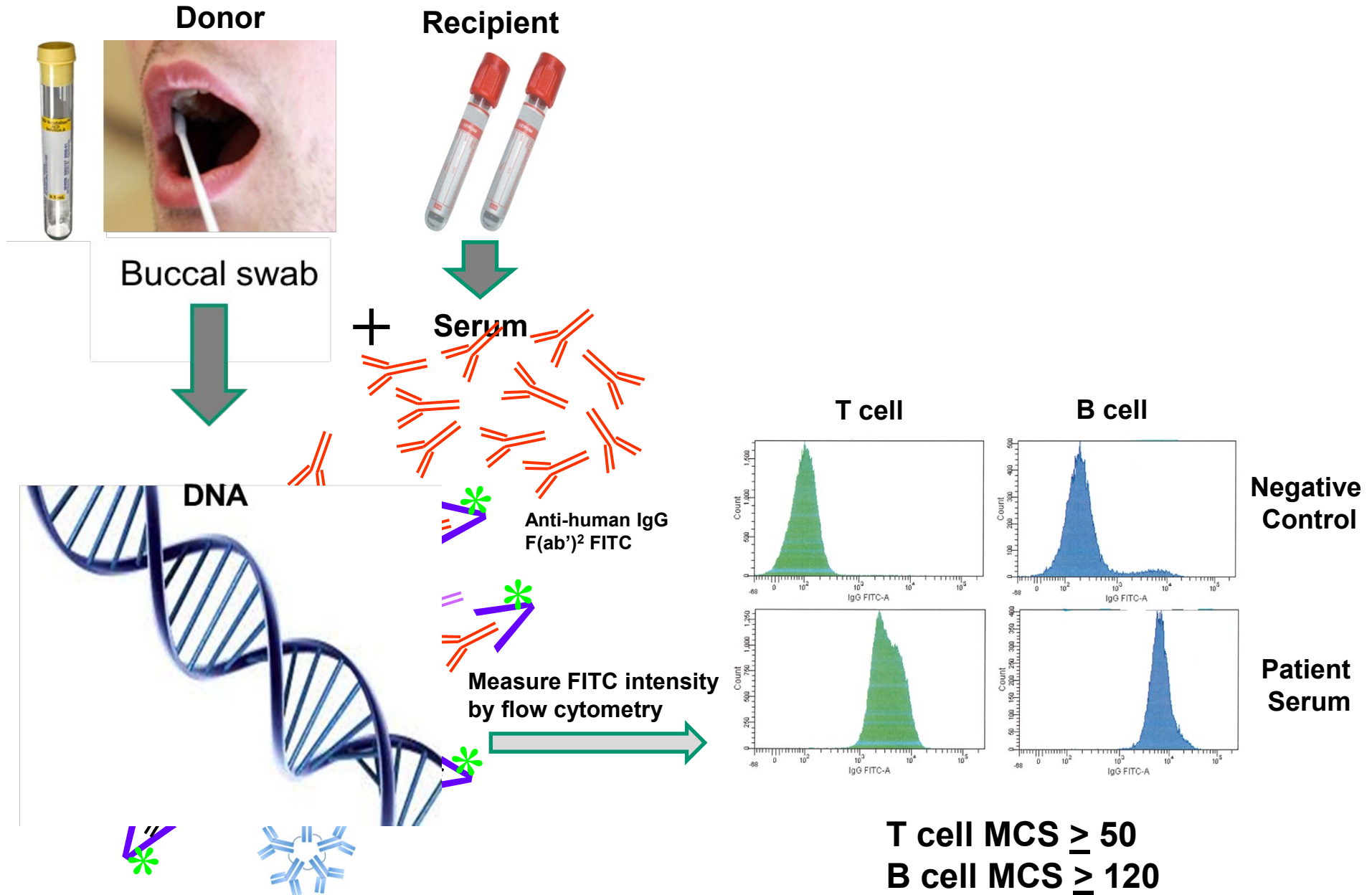
Flow cytometry crossmatch workspace



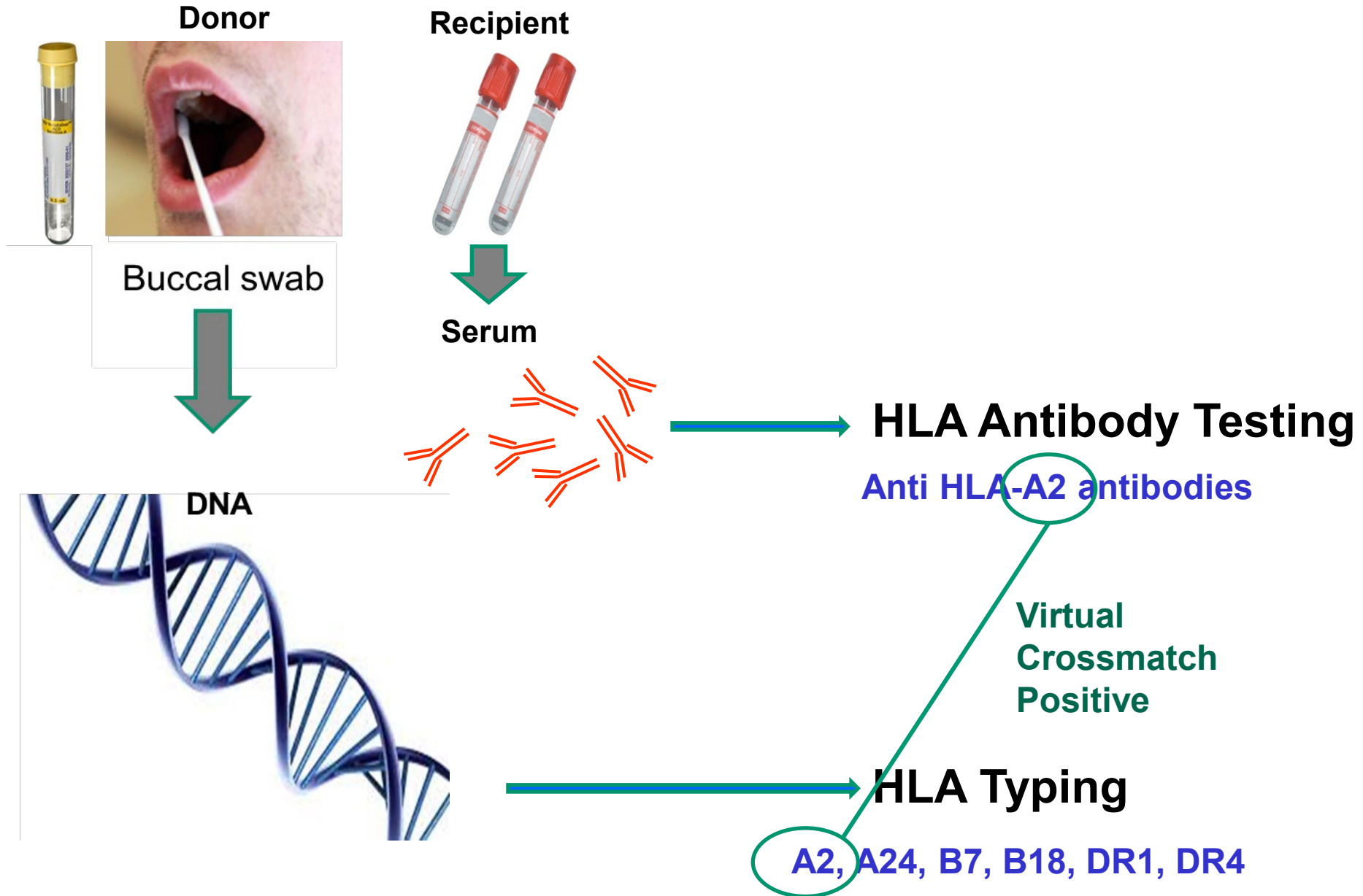
Flow Crossmatch - problems

- **~8% of flow crossmatches false positive – unnecessary exclusion**
- **~7% of flow crossmatches false negative – risk to patient**

Virtual ~~Flow Cytometry~~ Crossmatch



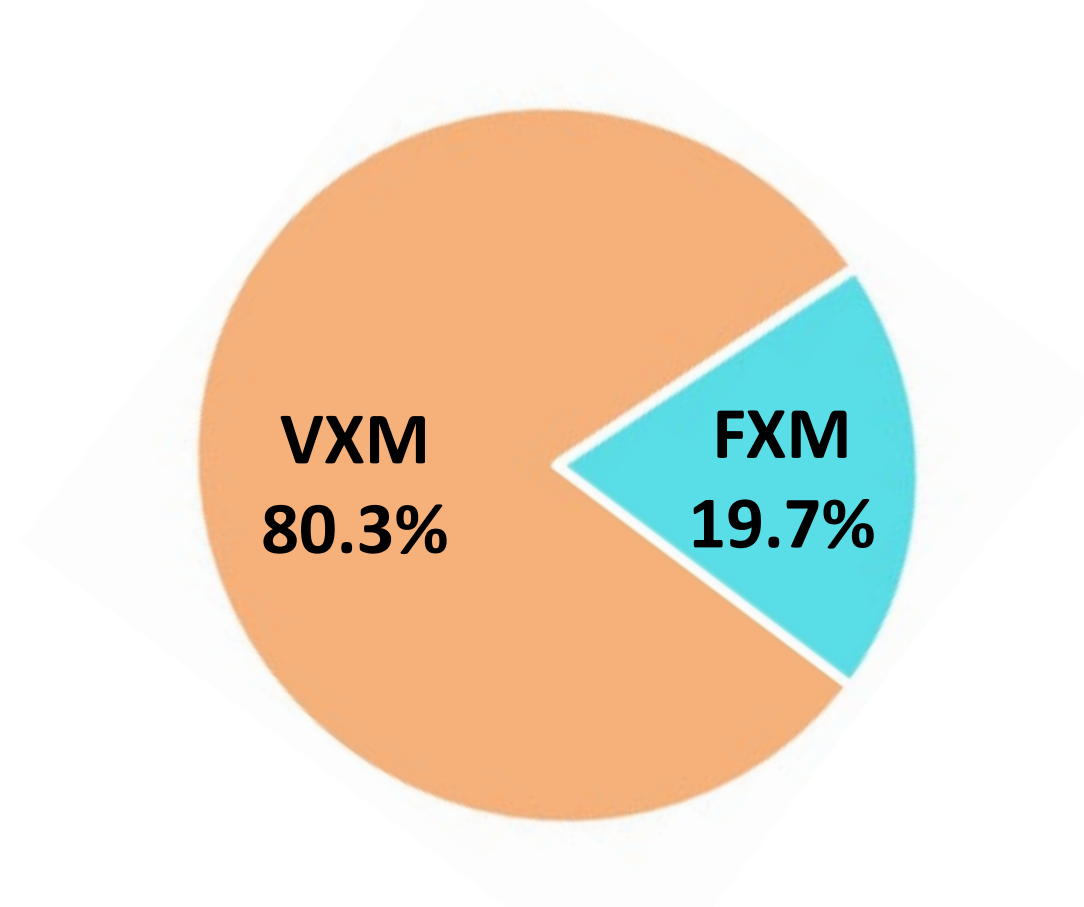
Virtual Crossmatch - Essentials



Benefits of virtual crossmatch

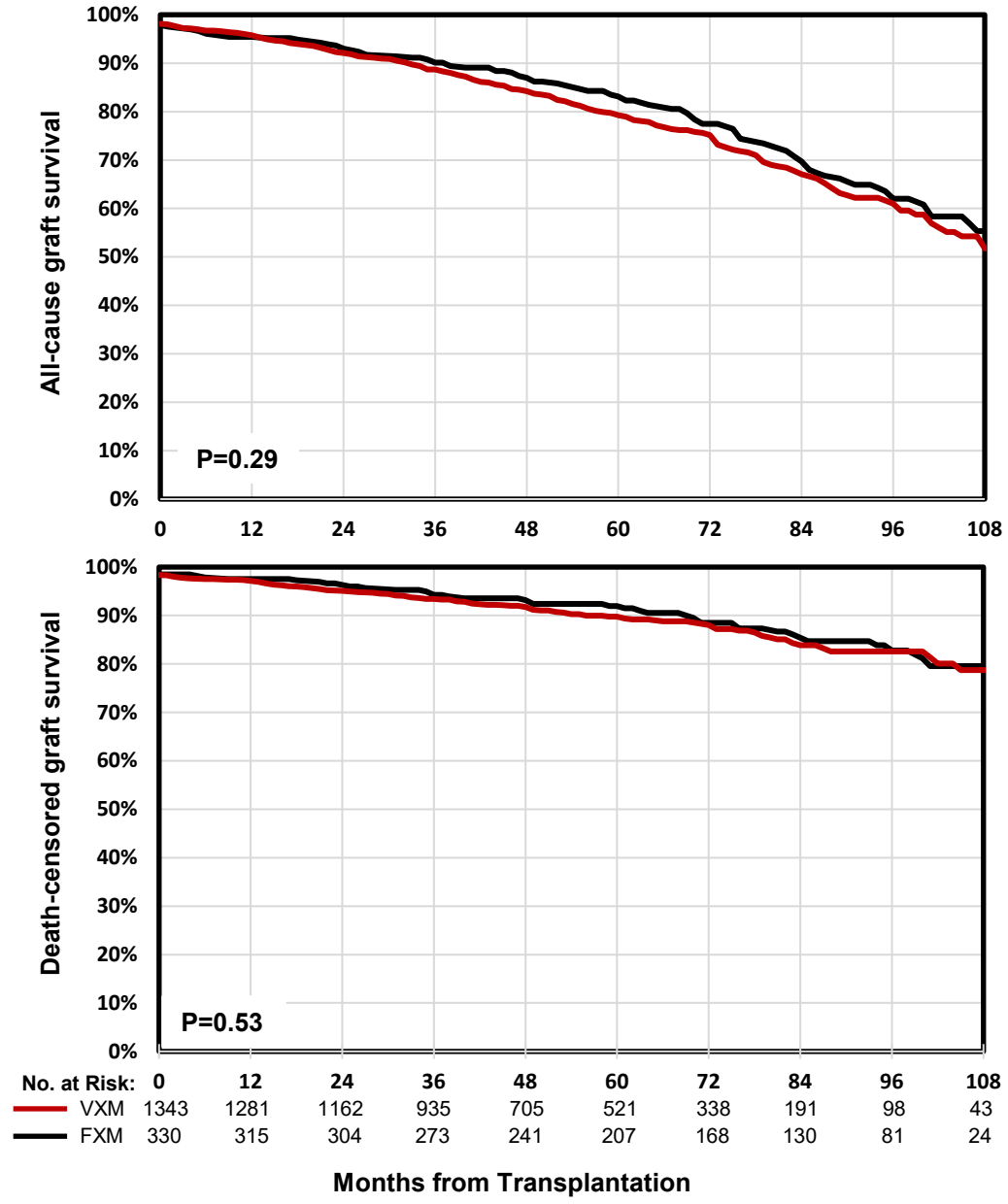
- 1. Speed and Efficiency**
- 2. Reduced Organ Discard Rate**
- 3. Improved Access for Highly Sensitized Patients**
- 4. Facilitates Paired Exchange & Living Donor Programs**
- 5. Cost-Effective**
- 6. Supports Extended Donor Pools**
- 7. Optimizes Organ Allocation Process**
- 8. Decreases Cold Ischemia Time**
- 9. Enables Better Planning and Coordination**

Deceased Donor Adult Kidney Tx, n=1673 1/1/2013 and 12/31/2020



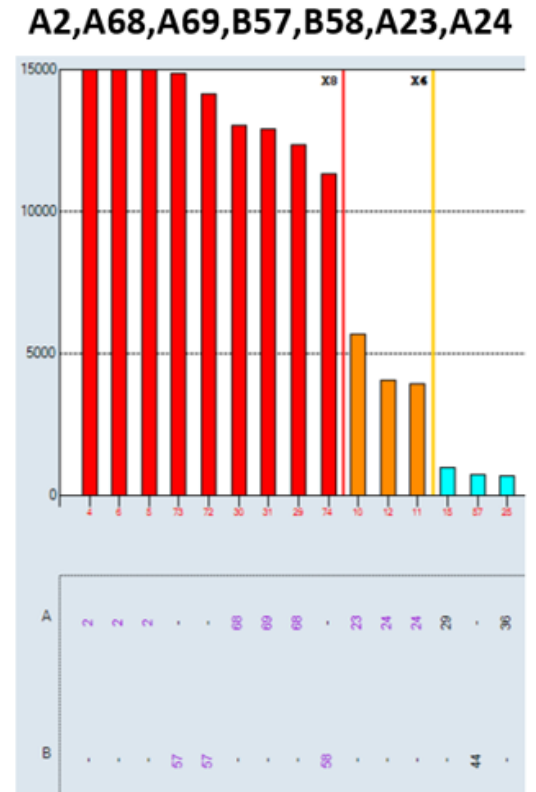
Post-transplant follow-up through 3/31/2022 was evaluated for patient and graft survival outcomes.

Outcomes of VXM-based KTx are comparable to PXM-based KTx in deceased donor cohorts

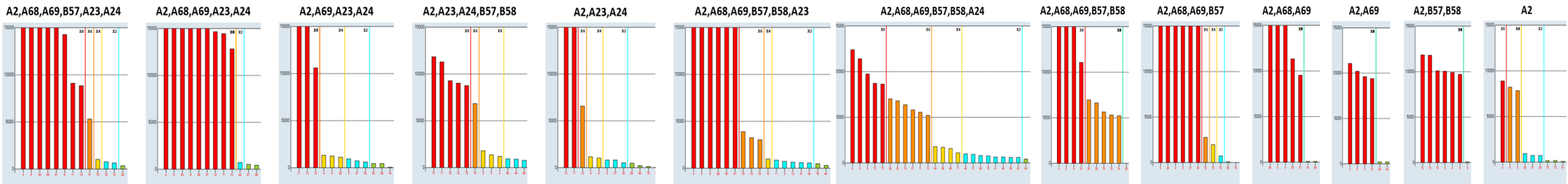


**Are All HLA Antibodies Detected by
Single Antigen Assays Equally
Capable of Binding to Cells and
Harming the Allograft?**

A comprehensive analysis of the cell-binding ability of HLA antibodies in the state of standalone and with its variable cross-reactive constellations.

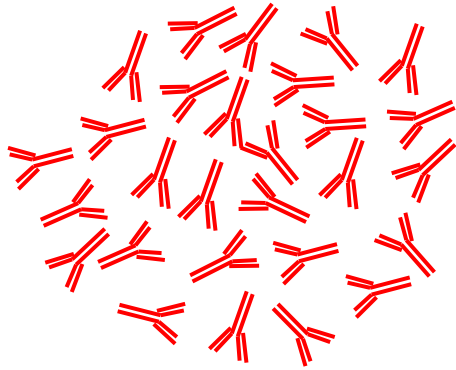


14 distinct patterns of HLA-A2 CREG antibodies

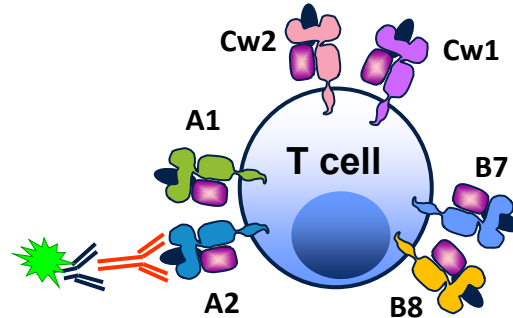


Multi-million \$ experiment

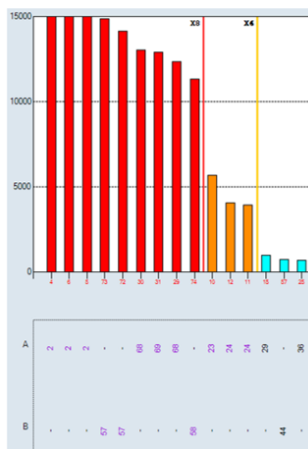
to define the cell-binding ability of various HLA DSA



+



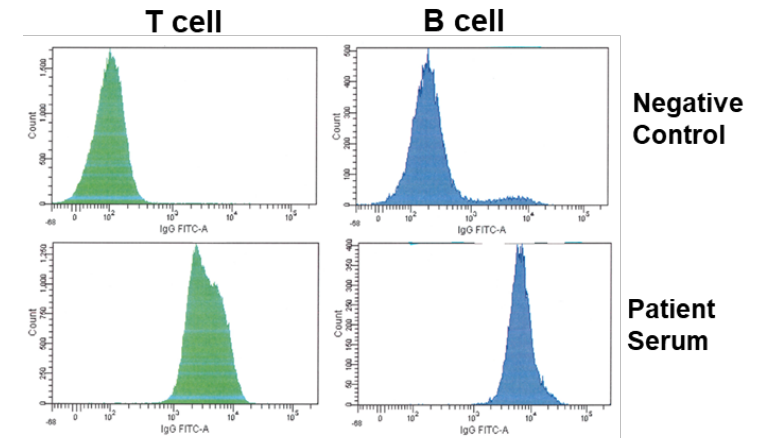
A2,A68,A69,B57,B58,A23,A24



304 patients making HLA antibodies to a single CREG

Each patient was crossmatched with a minimum 4 different donors targeting a single DSA

Flow cytometry Crossmatch (FXM)



T cell MCS \geq 50
B cell MCS \geq 120

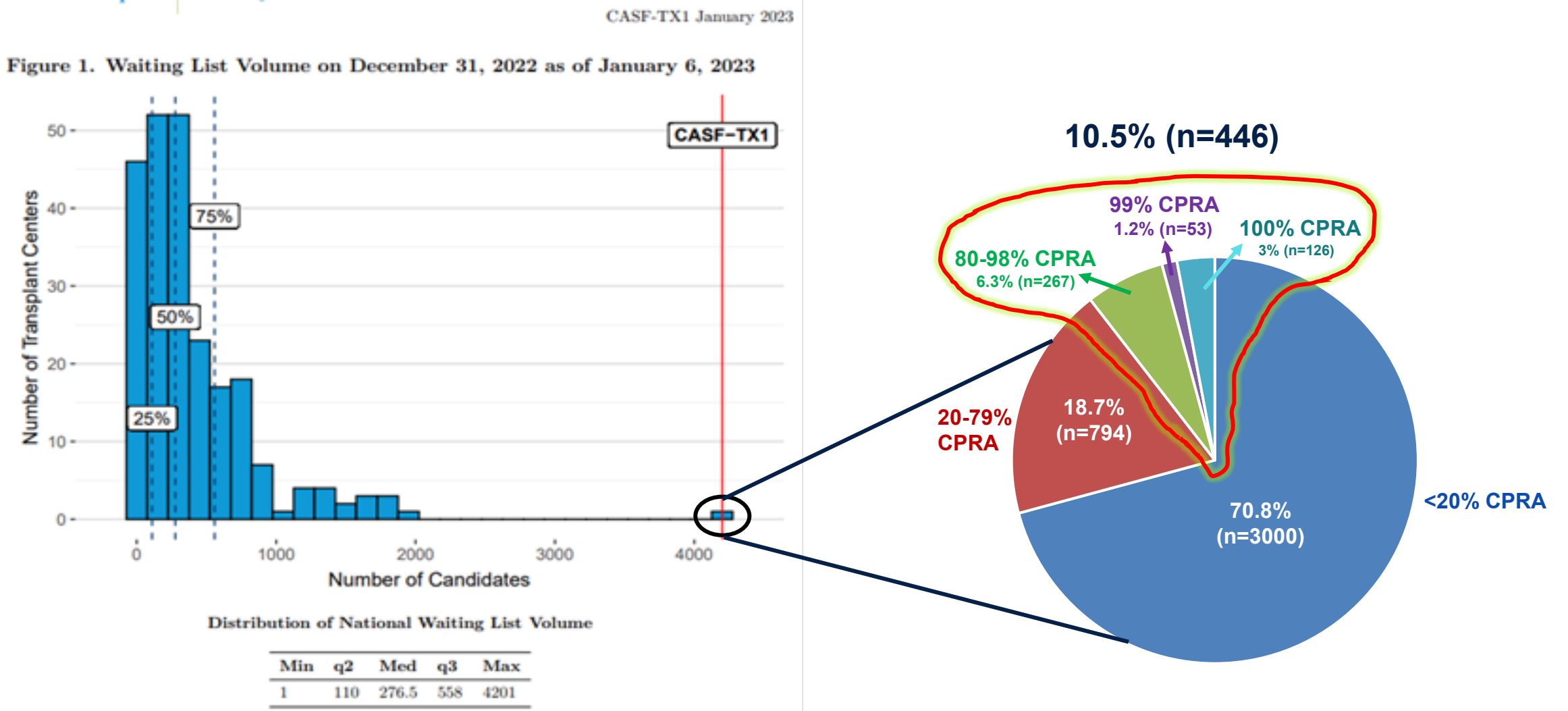
total FXM=1831

Some HLA antibodies detected by Single Antigen Bead assays do not bind to cells and, therefore, may not be involved in allograft rejection.



What forced us crossing HLA antibodies in the UCSF transplant programs?

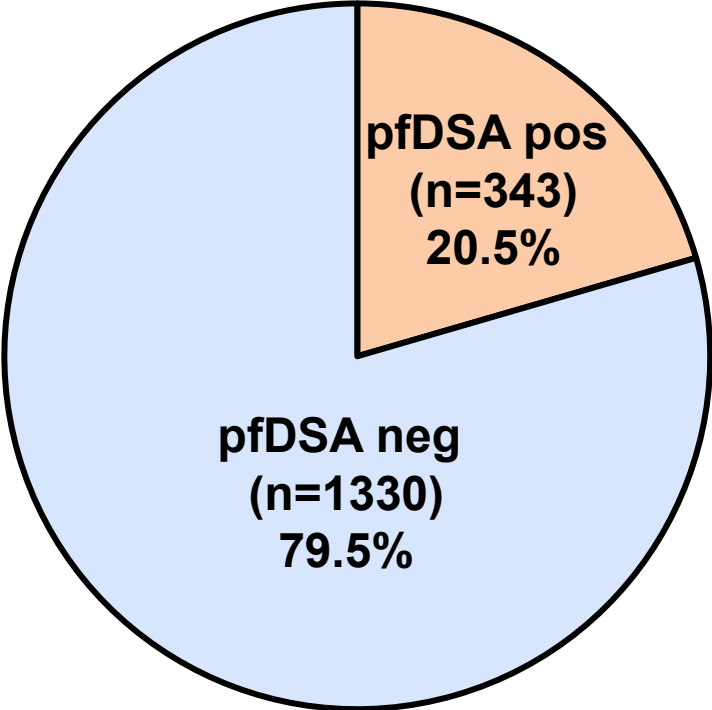
UCSF kidney waitlist (n=4201) is the largest in the USA; 10.5% of them with a CPRA $\geq 80\%$



UCSF protocol for immunosuppression in kidney transplant recipients, who had preformed DSA

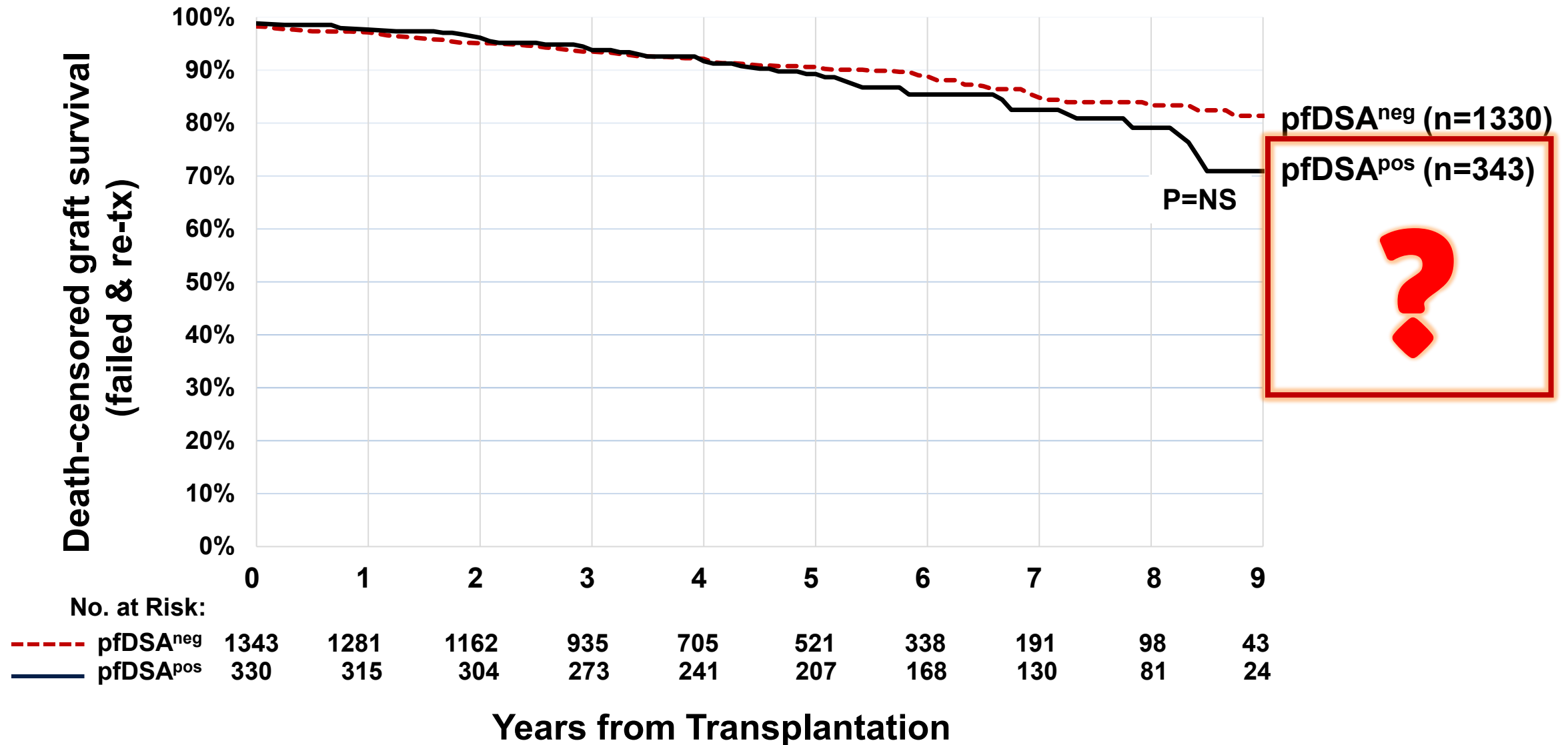
- **Initial induction:** Thymoglobulin 6 mg/kg
- **Post-operative:**
 - **IVIg 1 gm/kg on POD-1 and 2.**
 - **No additional desensitization therapies.**
- **Maintenance:** triple immunosuppression with Tac/MMF/Pred

1673 consecutive adult deceased donor kidney transplants performed at UCSF (1/1/2013 - 12/31/2020)

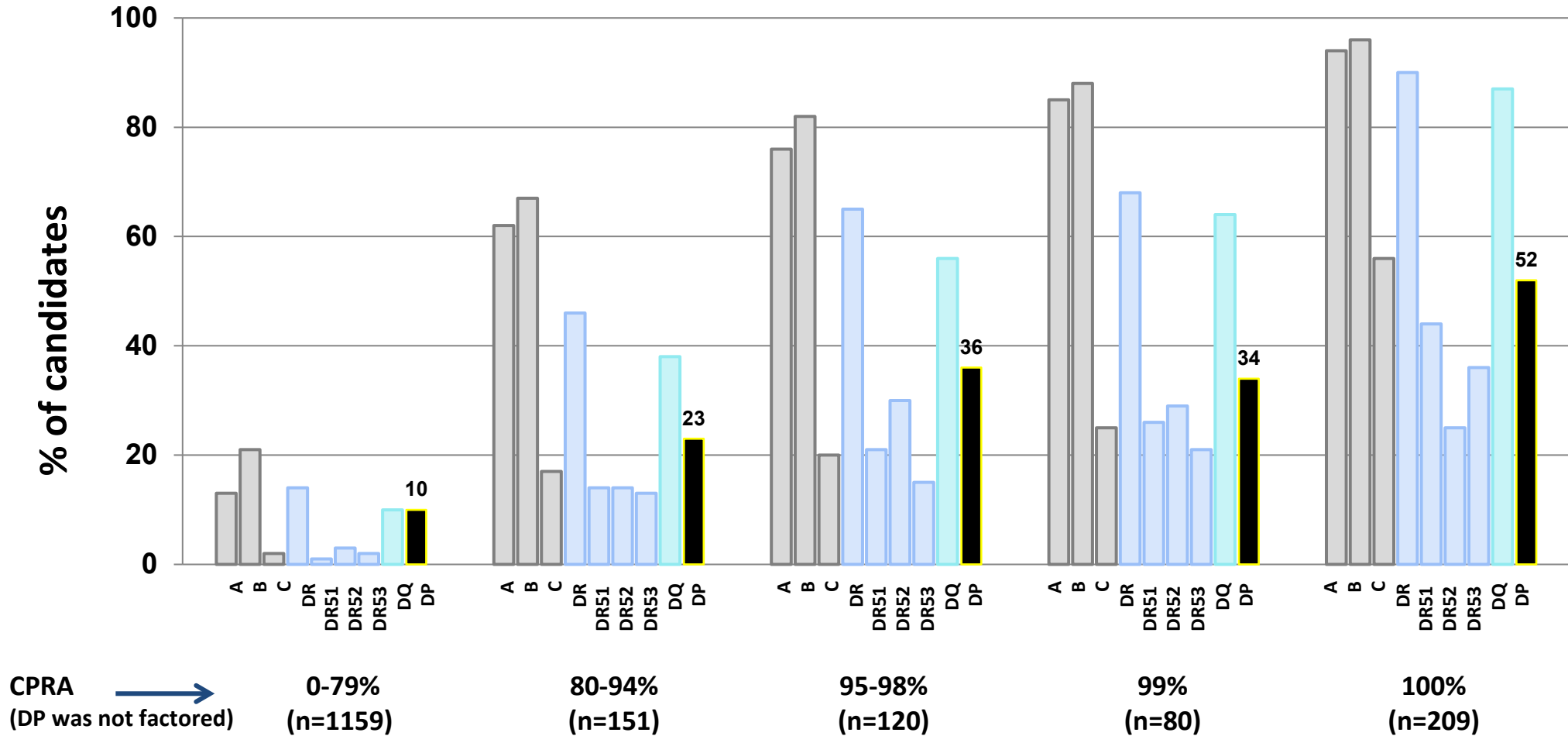


Post-transplant follow-up through 3/31/2022 was evaluated for patient and graft survival outcomes

Pre-formed DSAs do not impact kidney transplant outcomes

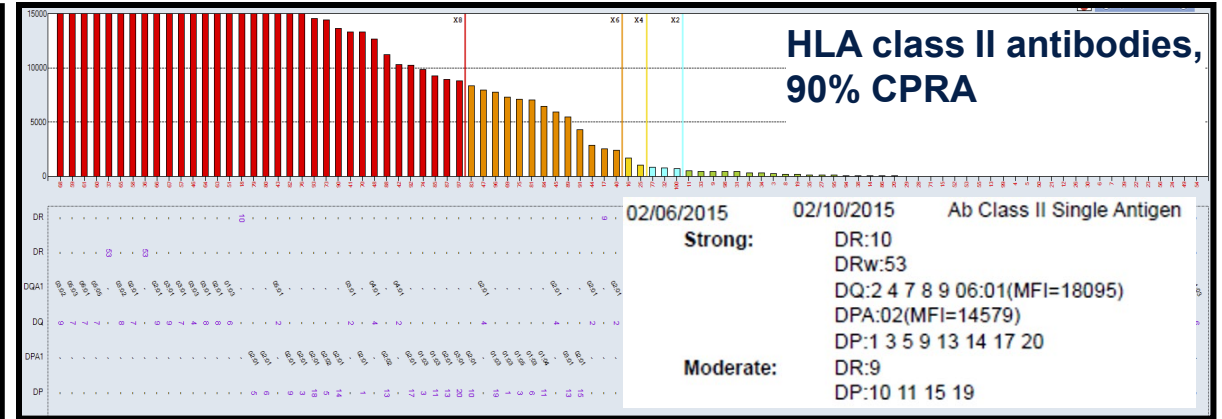
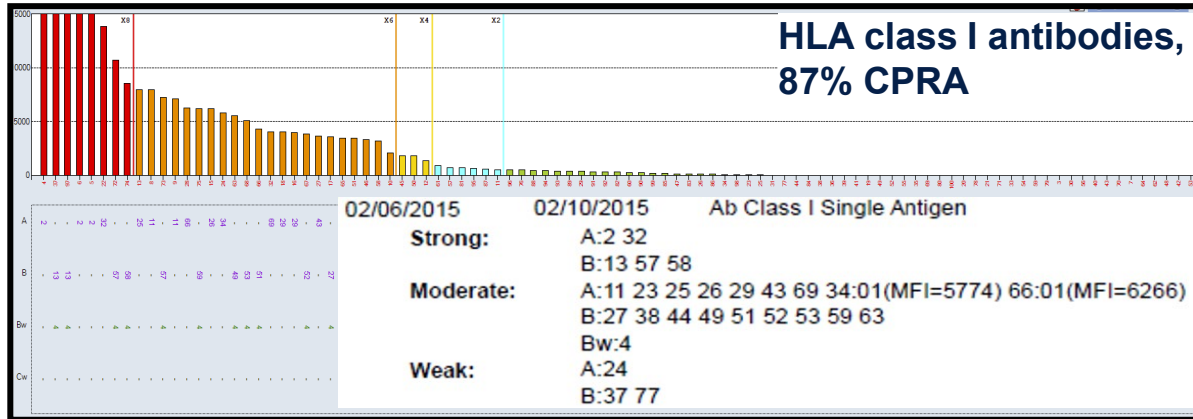


52% of waitlisted candidates with 100% CPRA have HLA-DP antibodies



Exploratory case transplanted with strong DP DSA (June 2015)

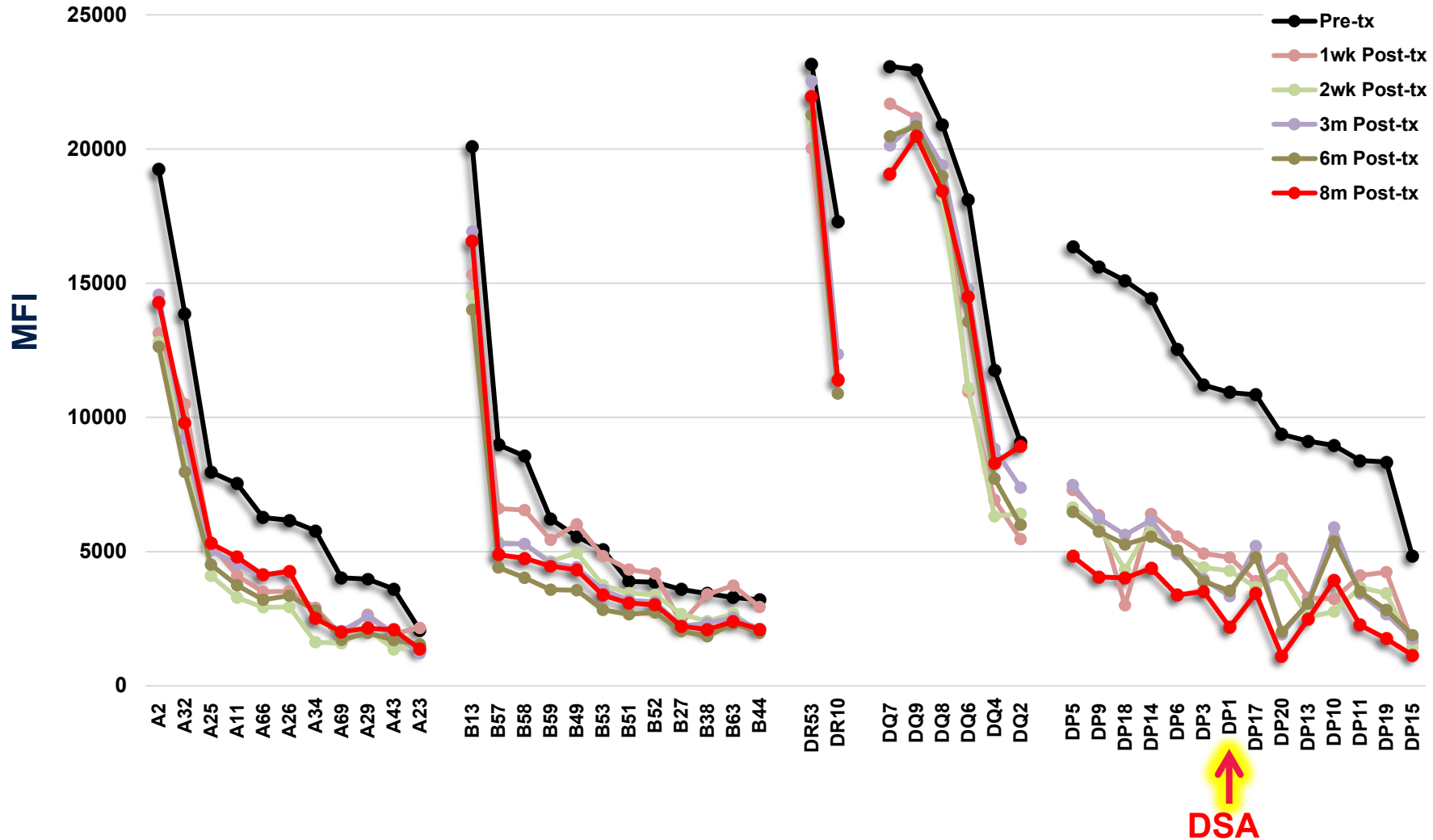
- 42 M; Received 1st KTx in 1990; Listed for 2nd KTx in 2014 (100% CPRA)



	A	B	Bw	Cw	DRB1	DRB3/4/5	DQB1	DQA1	DPB1	DPA1
Recipient	3, 68	7, 60	6, 6	7, 10	13, 15	51, 52	6, 6	01, 01	04:01, 04:02	01:03, 01:03
Donor	3, 68	7, 7	6, 6	7, 7	13, 15	51, 52	6, 6	01, 01	01:01 , 04:01	01:03, 02:01

- Donor-specific antibodies: DP1 (MFI=10,930)
- Pronase crossmatch: T cell negative (MCS=0/50), B cell border-line positive (MCS=125/120)
- Transplanted on: 6/26/2015
- Thymoglobulin induction.
- IVIG 2g/kg was given on POD 1. No additional desensitization therapy was used.
- Maintenance immunosuppression: Tac, MMF, and Prednisone.

Pre- and Post-tx HLA antibodies



Exceptional Case

Preformed donor-directed anti-HLA-DP antibodies may be an impediment to successful kidney transplantation

Simin Goral^{1,*}, Eline Luning Prak^{2,*}, Jane Kearns², Roy D. Bloom¹, Erin Pierce², Alden Doyle¹, Robert Grossman¹, Ali Najji³ and Malek Kamoun²

¹Renal Electrolyte and Hypertension Division, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA, ²Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA and ³Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA, USA



ELSEVIER

Contents lists available at ScienceDirect



journal homepage: www.elsevier.com/locate/humimm



Human Immunology 75 (2014) 703–708

Rapid Communication

Early acute antibody-mediated rejection of a negative flow crossmatch 3rd kidney transplant with exclusive disparity at HLA-DP



Beata Mierzejewska^a, Paul M. Schroder^b, Caitlin E. Baum^b, Annette Blair^c, Connie Smith^c, Rene J. Duquesnoy^d, Marilyn Marrari^d, Amira Gohara^e, Deepak Malhotra^e, Dinkar Kaw^e, Robert Liwski^f, Michael A. Rees^a, Stanislaw Stepkowski^{b,*}

^aDepartment of Urology, University of Toledo College of Medicine, Toledo, OH 43614, USA

^bDepartment of Microbiology and Immunology, University of Toledo College of Medicine, Toledo, OH 43614, USA

^cDepartment of Pathology, University of Toledo College of Medicine, Toledo, OH 43614, USA

^dDepartment of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA 15213, USA

^eDepartment of Internal Medicine, University of Toledo College of Medicine, Toledo, OH 43614, USA

^fHLA Typing Laboratory, Dalhousie University, Halifax, Nova Scotia, Canada



Clinical Case Report

Medicine®

Medicine (2016) 95:32(e4521) OPEN

Successful kidney transplantation after desensitization in a patient with positive flow crossmatching and donor-specific anti-HLA-DP antibody

A Case report

Seung Hwan Song, MD^a, Borae G. Park, MD^{b,*}, Juhan Lee, MD^a, Myoung Soo Kim, PhD^a, Yu Seun Kim, PhD^a, Hyon-Suk Kim, PhD^b

American Journal of Transplantation 2012; 12: 2845–2848
Wiley Periodicals Inc.

© Copyright 2012 The American Society of Transplantation and the American Society of Transplant Surgeons

doi: 10.1111/j.1600-6143.2012.04172.x

Case Report

Preformed Donor HLA-DP-Specific Antibodies Mediate Acute and Chronic Antibody-Mediated Rejection Following Renal Transplantation

E. C. Jolly^a, T. Key^b, H. Rasheed^a, H. Morgan^b, A. Butler^c, N. Pritchard^a, C. J. Taylor^b and M. R. Clatworthy^{a,*}

Background

Donor-specific HLA alloantibodies can cause hyperacute, acute and chronic antibody-mediated rejection (AMR) (1). However, not all HLA alloantibodies are considered pathogenic. Low expression of HLA-DP in renal endothelial cells (2) has led to the notion that DP-specific alloantibodies are of minimal significance, a concept supported by the observation that in a single study, HLA-DP antibody-positive renal transplant recipients did not have impaired allograft survival (3). However, HLA-DP mismatch is associated with reduced graft survival in retransplants (4,5), particularly in patients with high panel reactivity of lymphocytotoxic antibodies (4). More recently, a small number of reports have

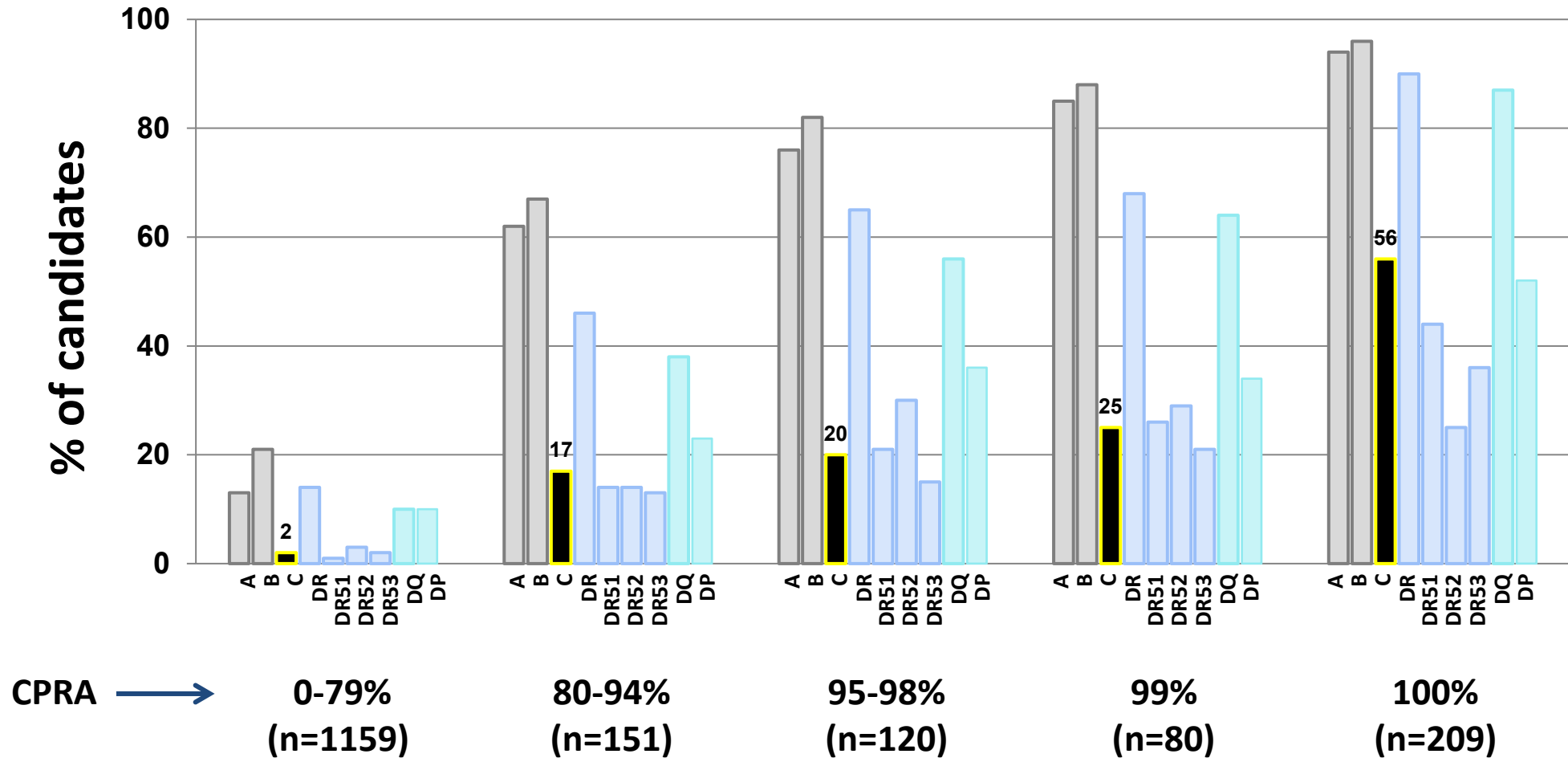
^aDivision of Renal Medicine, Department of Medicine, University of Cambridge, Cambridge, UK

^bTissue Typing Laboratory, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge, UK

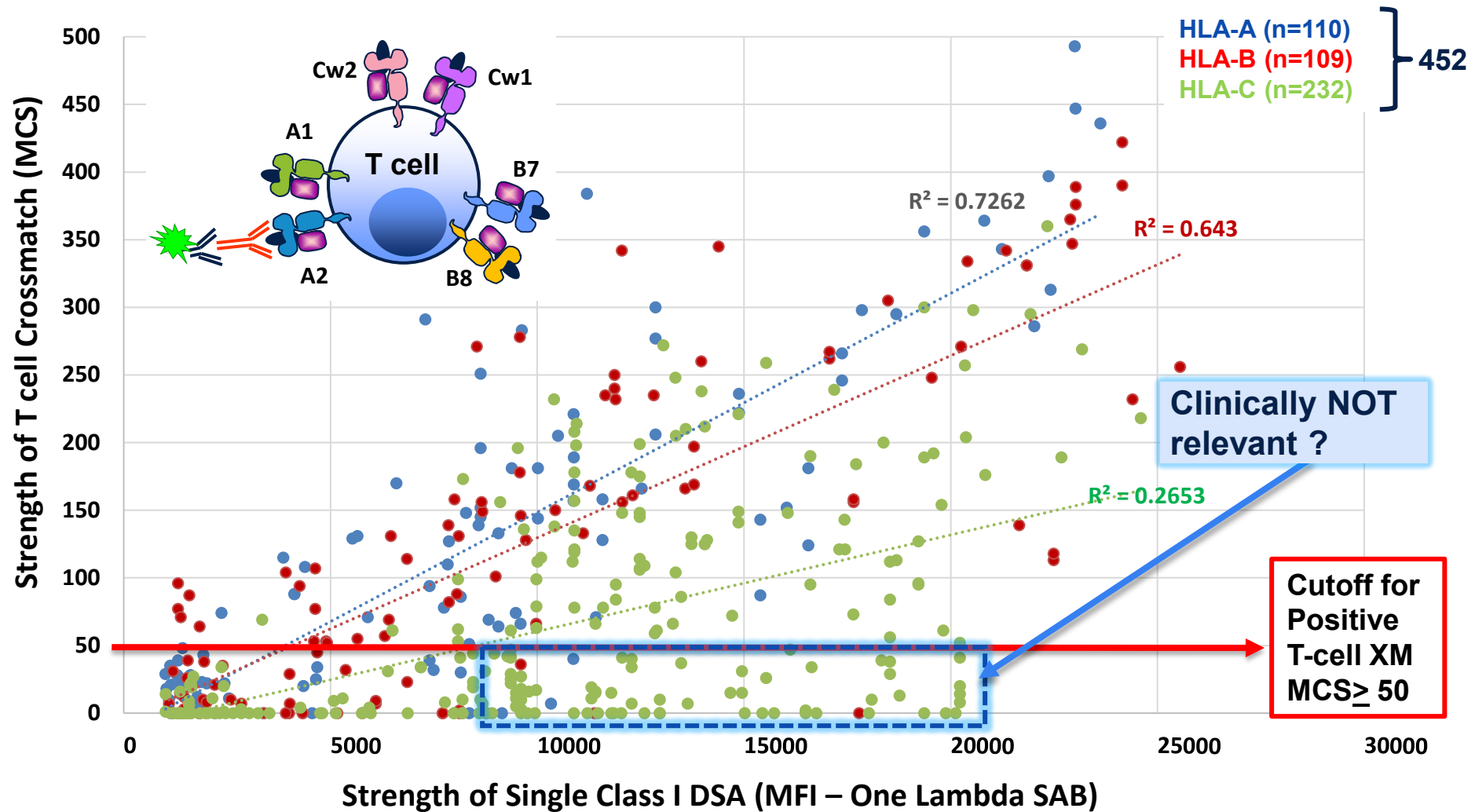
^cDepartment of Surgery, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Hills Road, Cambridge, UK

*Corresponding author: Menna R. Clatworthy, mrc38@cam.ac.uk

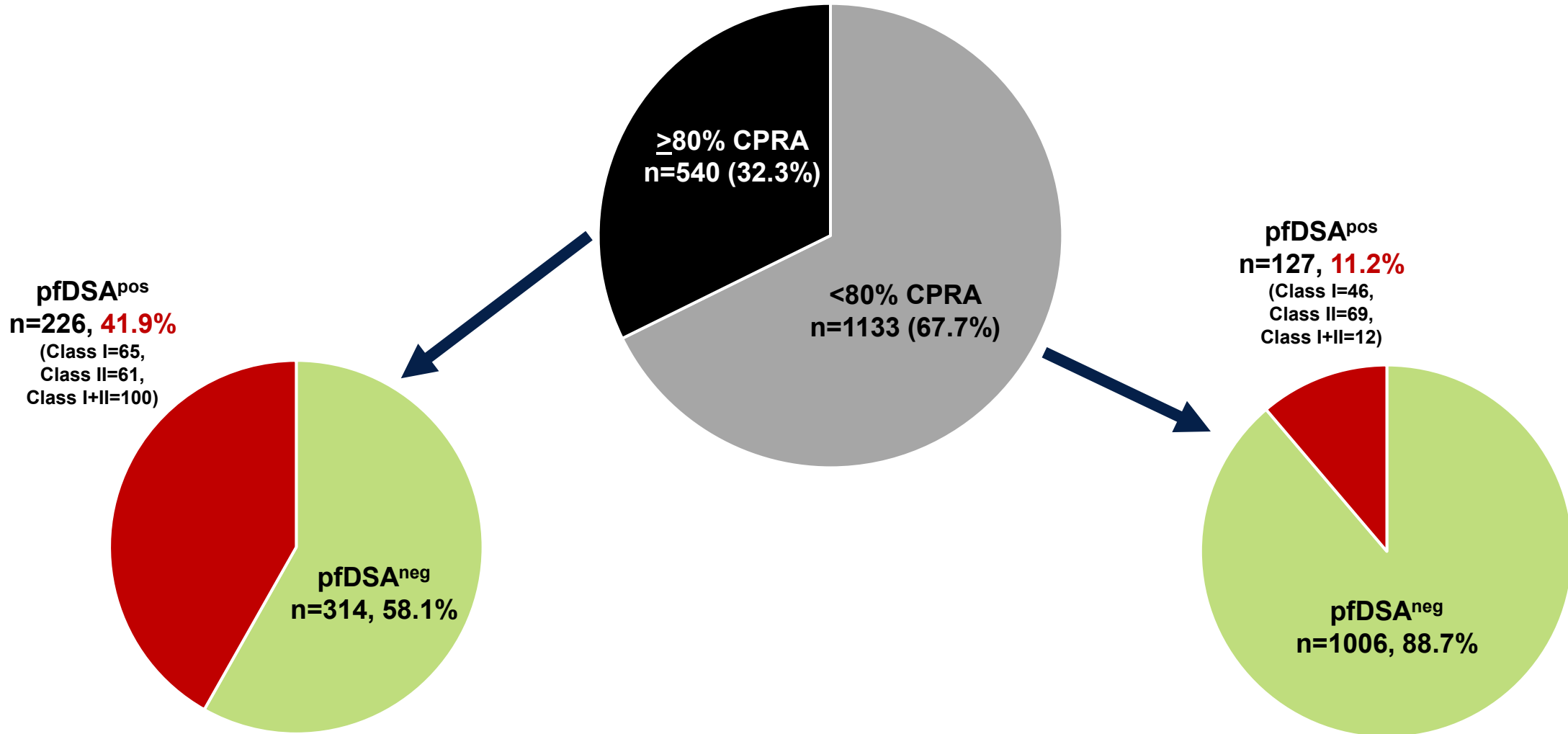
>56% of waitlisted candidates with 100% CPRA display HLA-C antibodies



Poor correlation between T cell XM and single HLA-C DSA

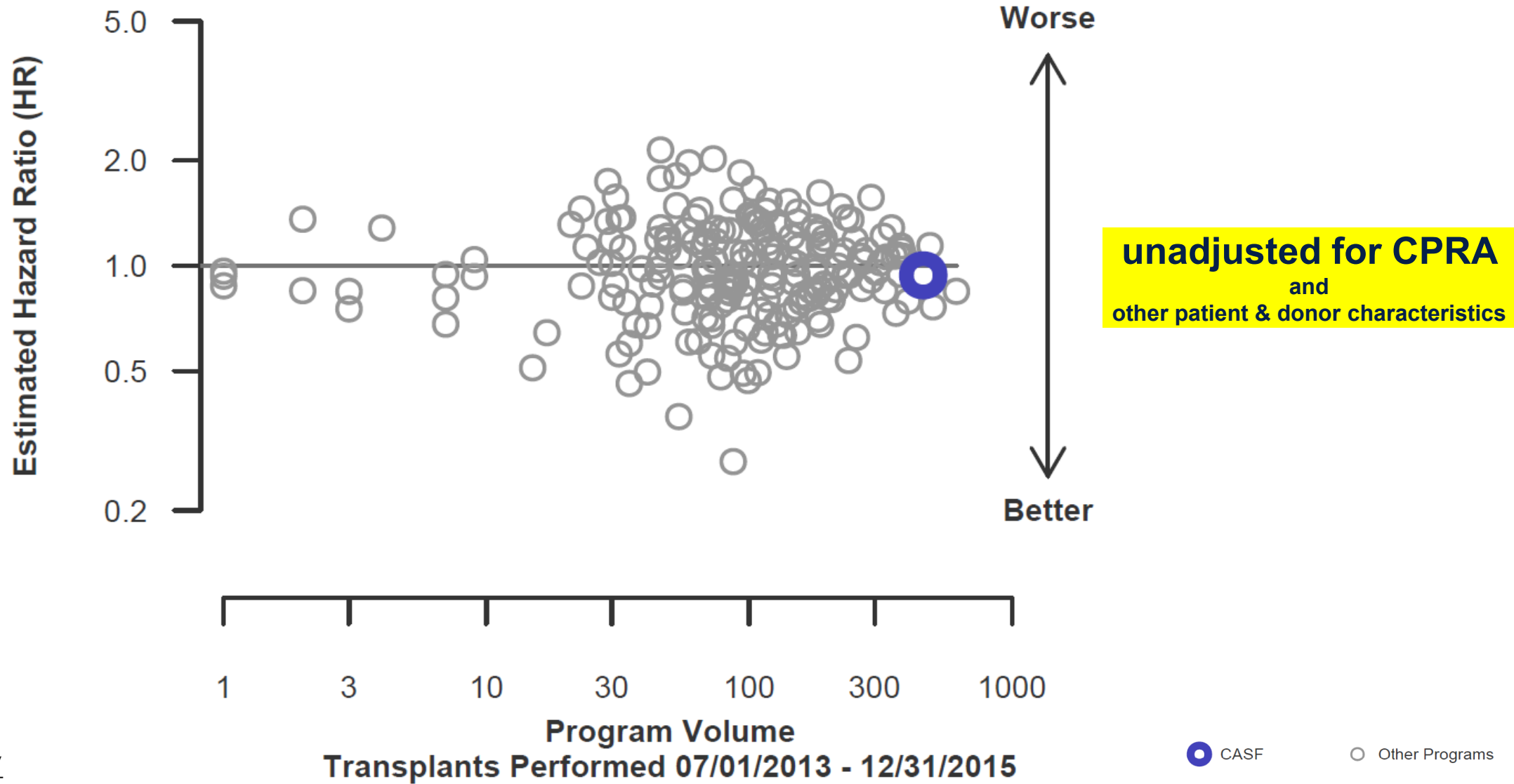


Deceased Donor kidney transplants (n=1673)



Adult (18+) 3-year deceased donor kidney graft failure Comparison: UCSF vs. other US centers

Deaths and retransplants are considered graft failures



<https://www.srtr.org/>

Summary

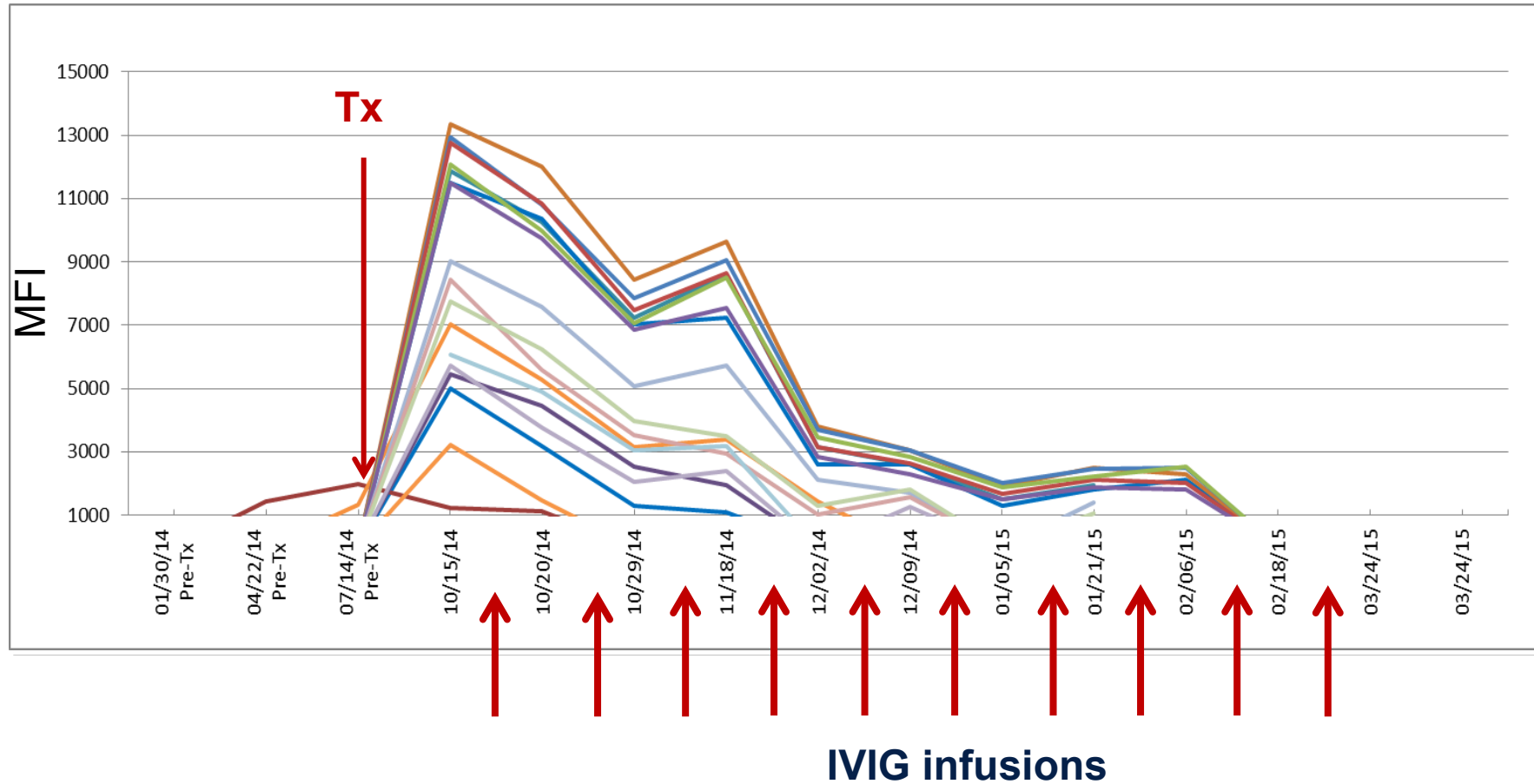
- **32.3% (n=540/1673) of the DD KTx were performed in highly sensitized patients with CPRA 80% and over.**
- **20.5% (n=343/1673) of the DD KTx were performed with preformed DSA.**
- **Despite crossing pfDSAs, the UCSF outcomes remains superior.**

Patients can be transplanted across **certain** preformed DSA, without aggressive desensitization, with no readily apparent effect on graft survival.

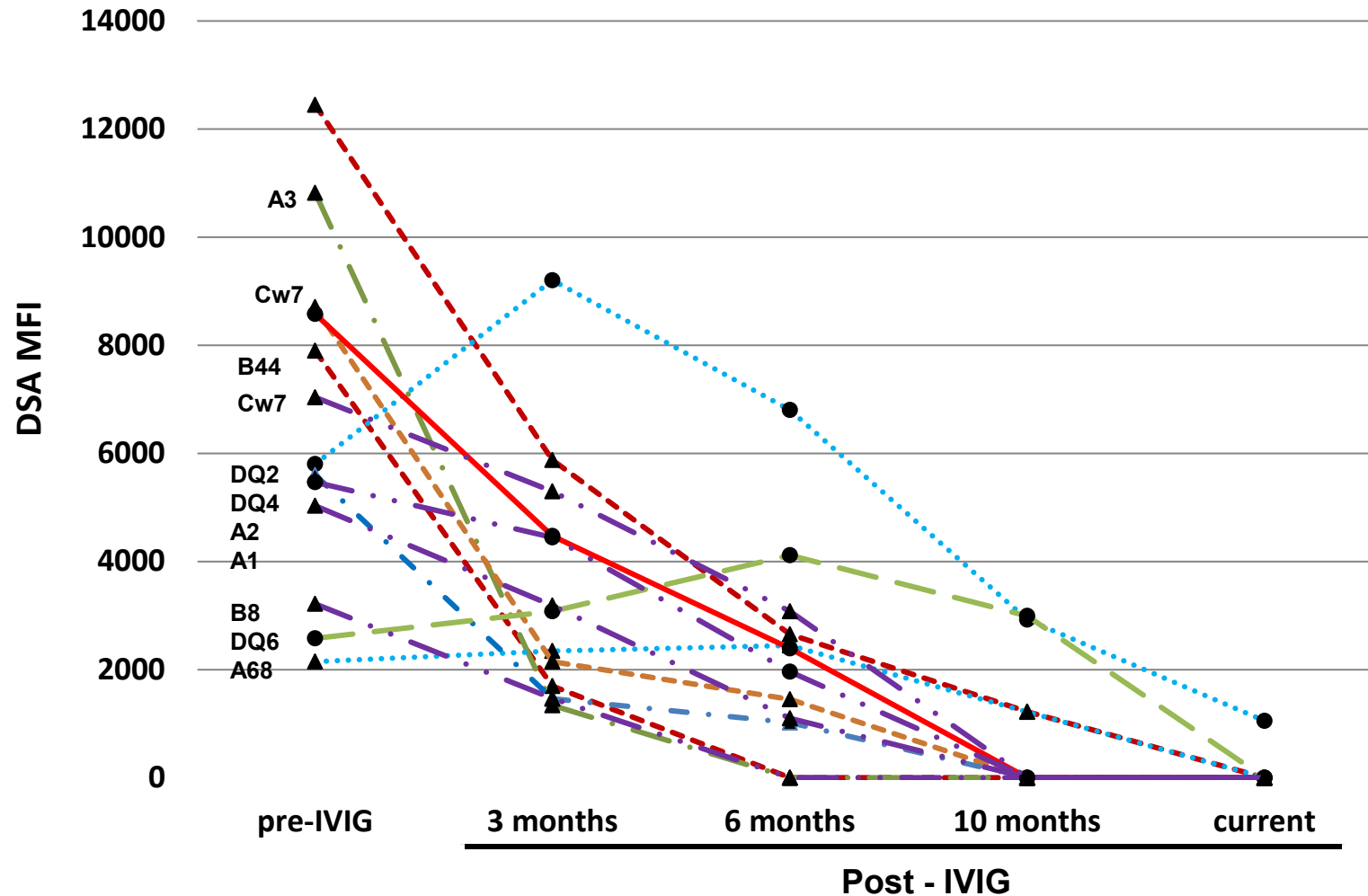


**IVIIG infusions deplete all HLA
antibodies in lung transplant recipients**

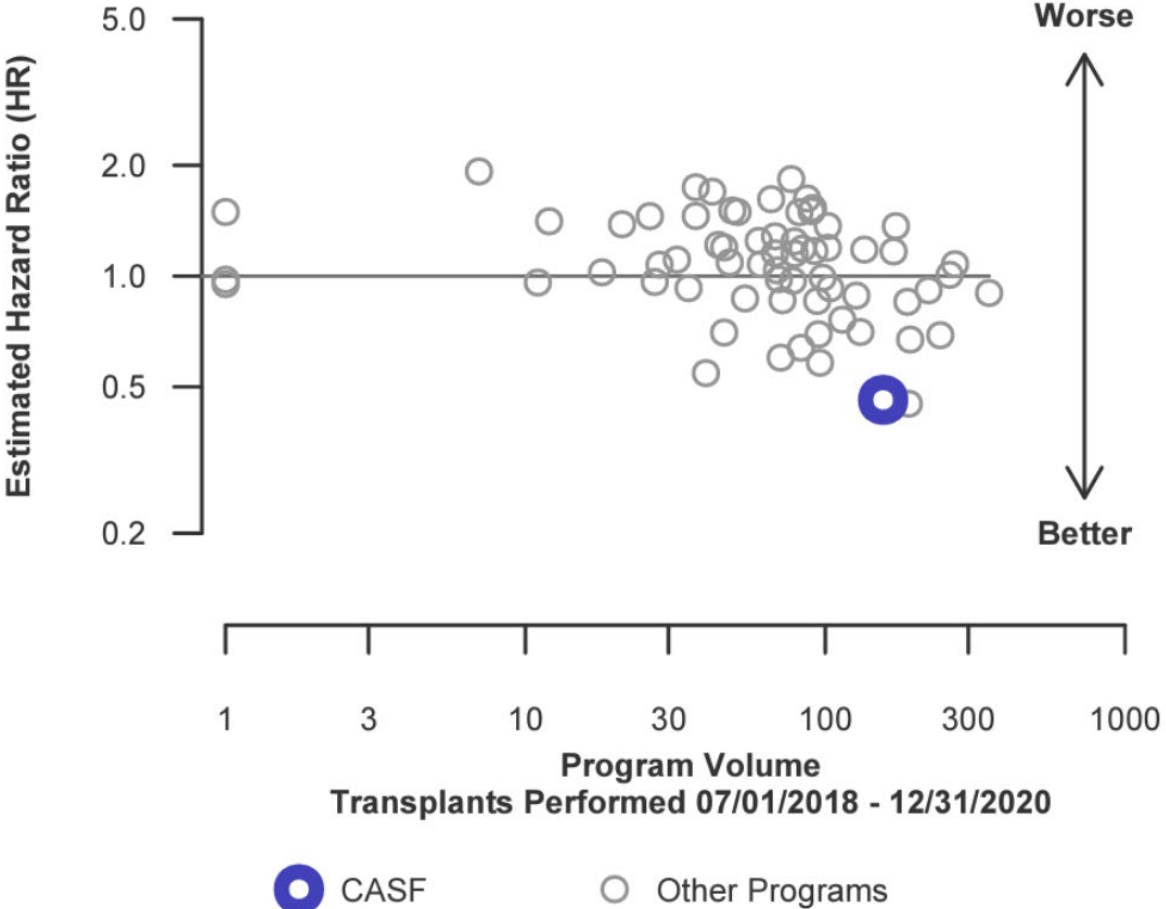
IVIg infusions deplete all HLA antibodies in lung transplant recipients



IVIg infusions deplete HLA DSAs in lung transplant recipients



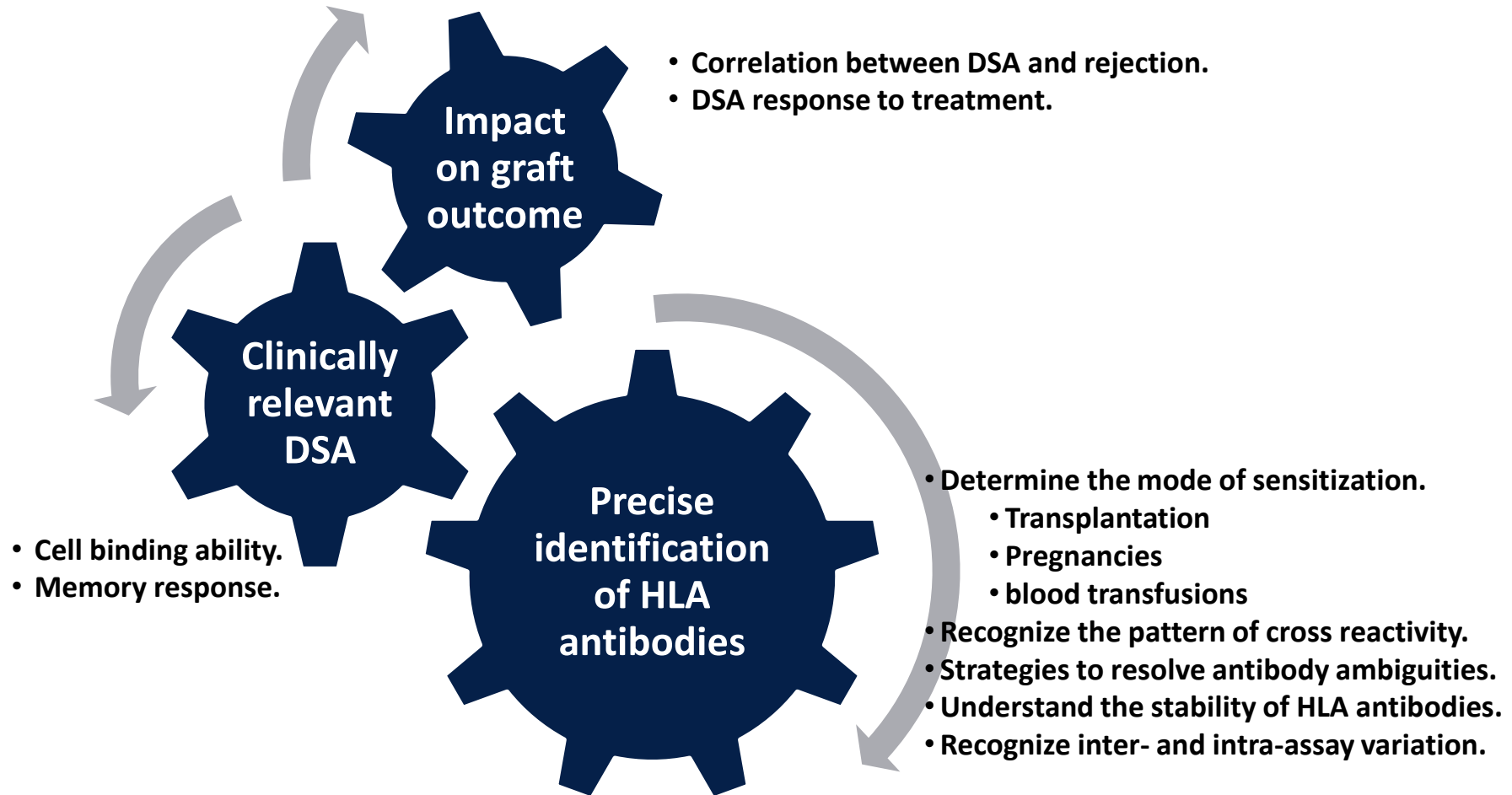
Adult 3-year deceased donor lung graft failure HR program comparison



**IVIIG infusions deplete all
HLA antibodies in lung
transplant recipients**



HLA antibodies in transplantation



Excellence from >250 yrs of combined experience in H&I



Thank You