TRANSPLANT DONOR SPECIFIC ANTIBODIES

BUT NO AMR…

What to do?

Joseph Spinner

Assistant Professor of Pediatrics – Baylor College of Medicine

Associate Medical Director of Heart Failure and Transplantation – Texas Children's Hospital

TRANSPLANT DONOR SPECIFIC ANTIBODIES

BUT NO AMR…

What to do?

Joseph Spinner

Assistant Professor of Pediatrics – Baylor College of Medicine

Associate Medical Director of Heart Failure and Transplantation – Texas Children's Hospital

DISCLOSURES

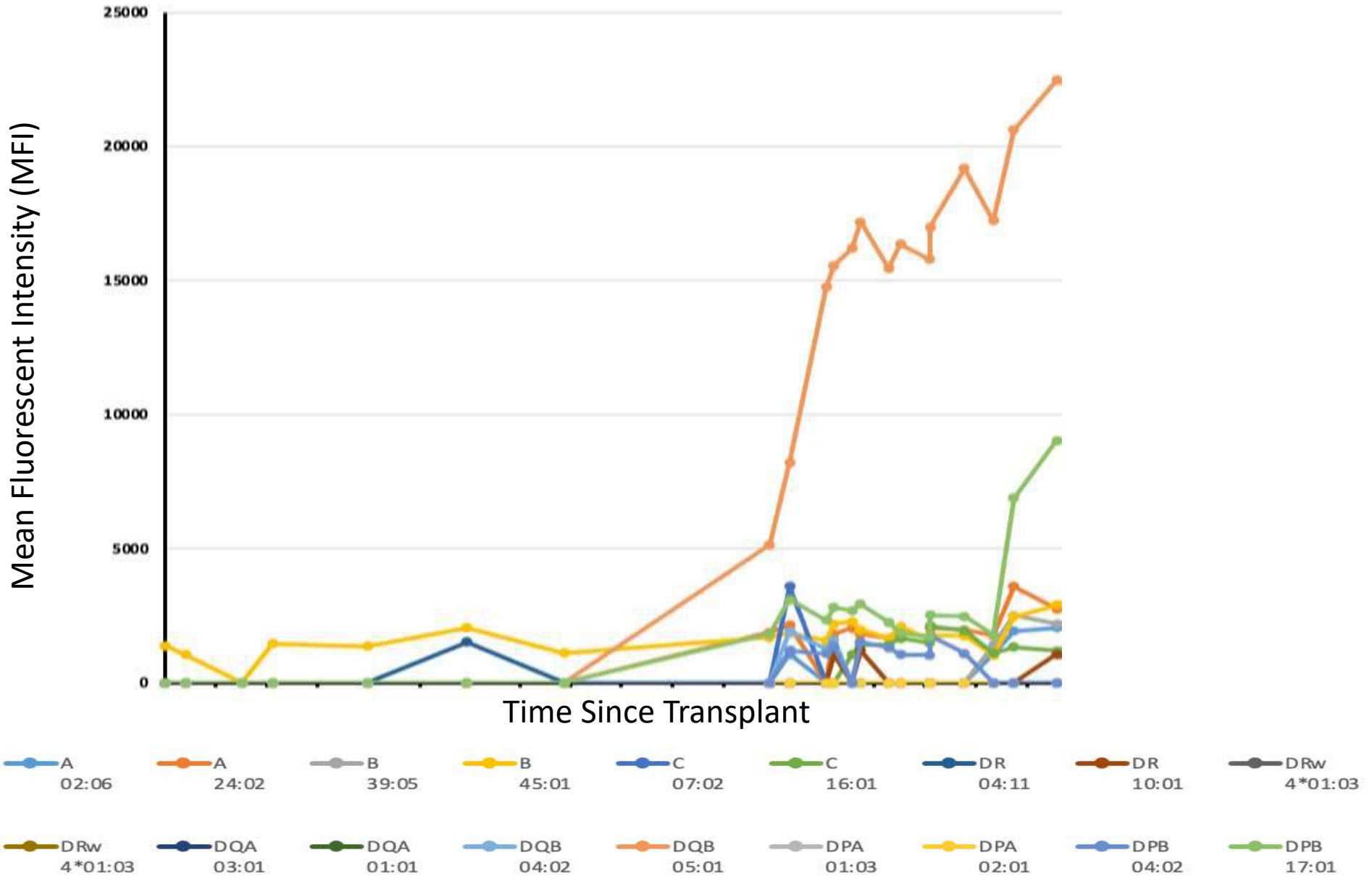
- I am not an immunologist but sometimes pretend to be
- I will discuss off-label uses of tests and medications

- *I don't own stock in spironolactone or SGLT-2 inhibitors even though it is going to sound like I do…*

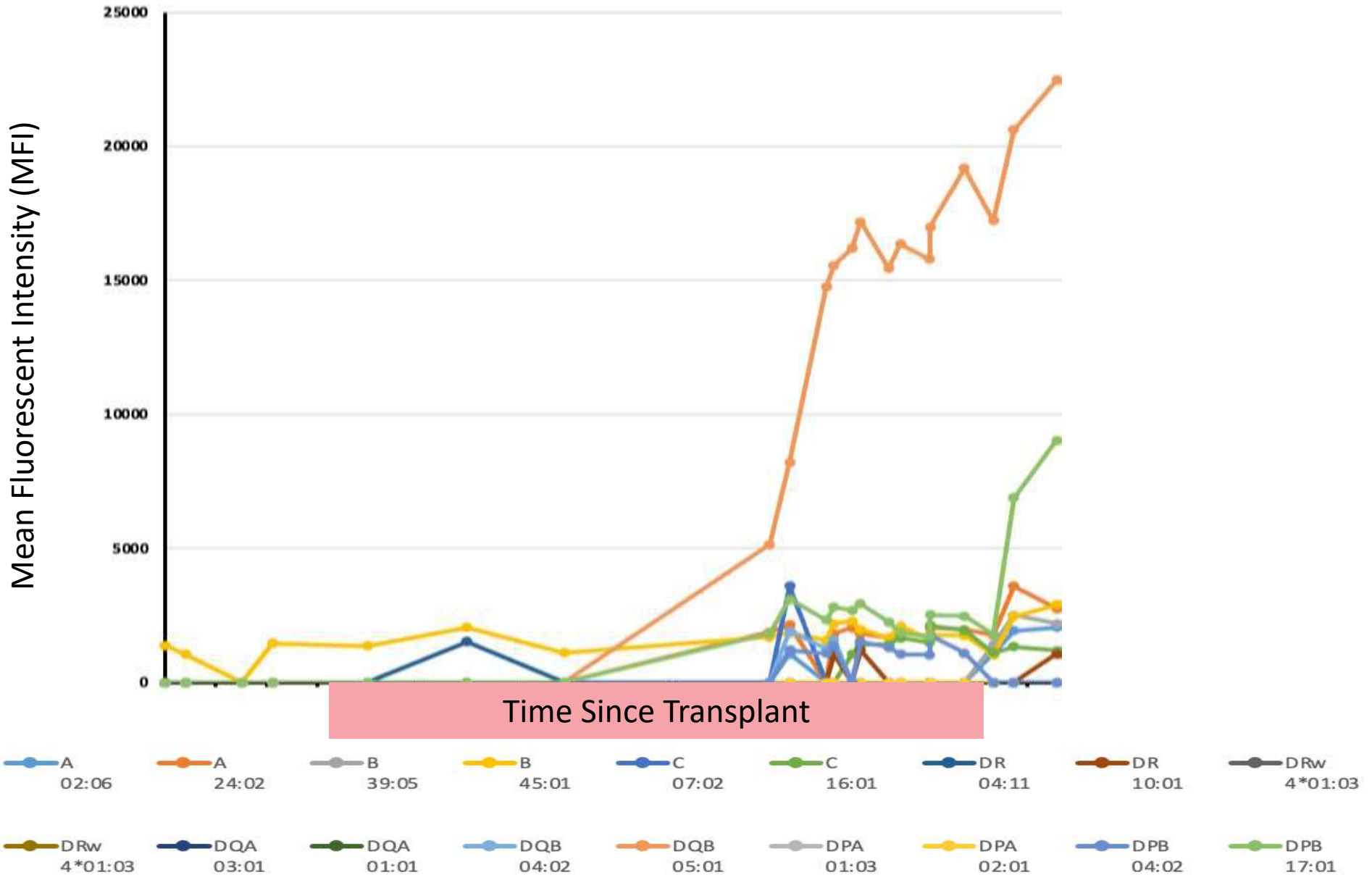
CLINICAL CASE

- 9 year old with familial arrhythmogenic cardiomyopathy
- Underwent heart transplant (HTx) in 2017
- Not sensitized (PRA 0/0) and crossmatch negative
- He was doing great ~ 5 years post-HTx
- No symptoms

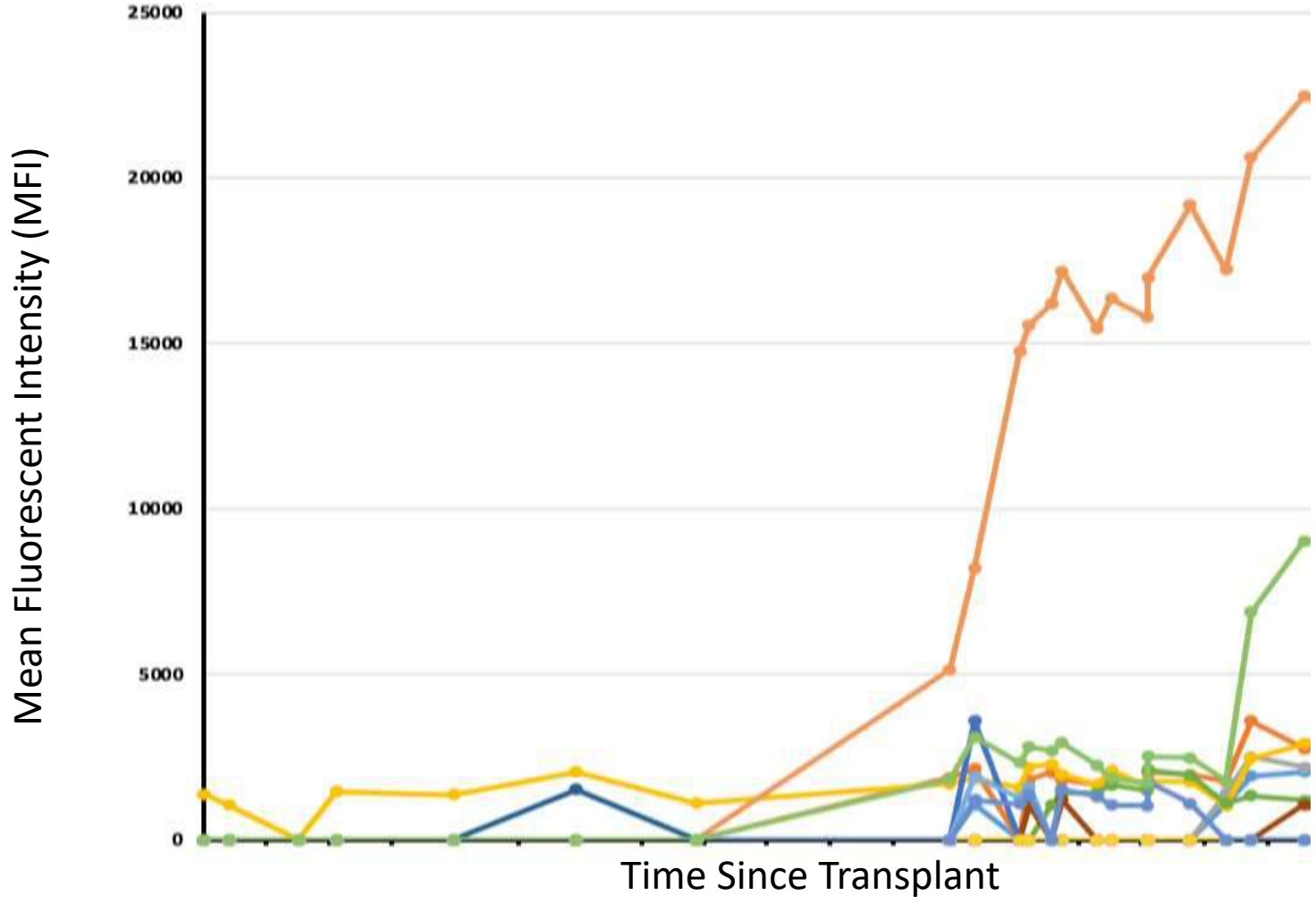
DEVELOPS DONOR SPECIFIC ANTIBODIES



DEVELOPS DONOR SPECIFIC ANTIBODIES

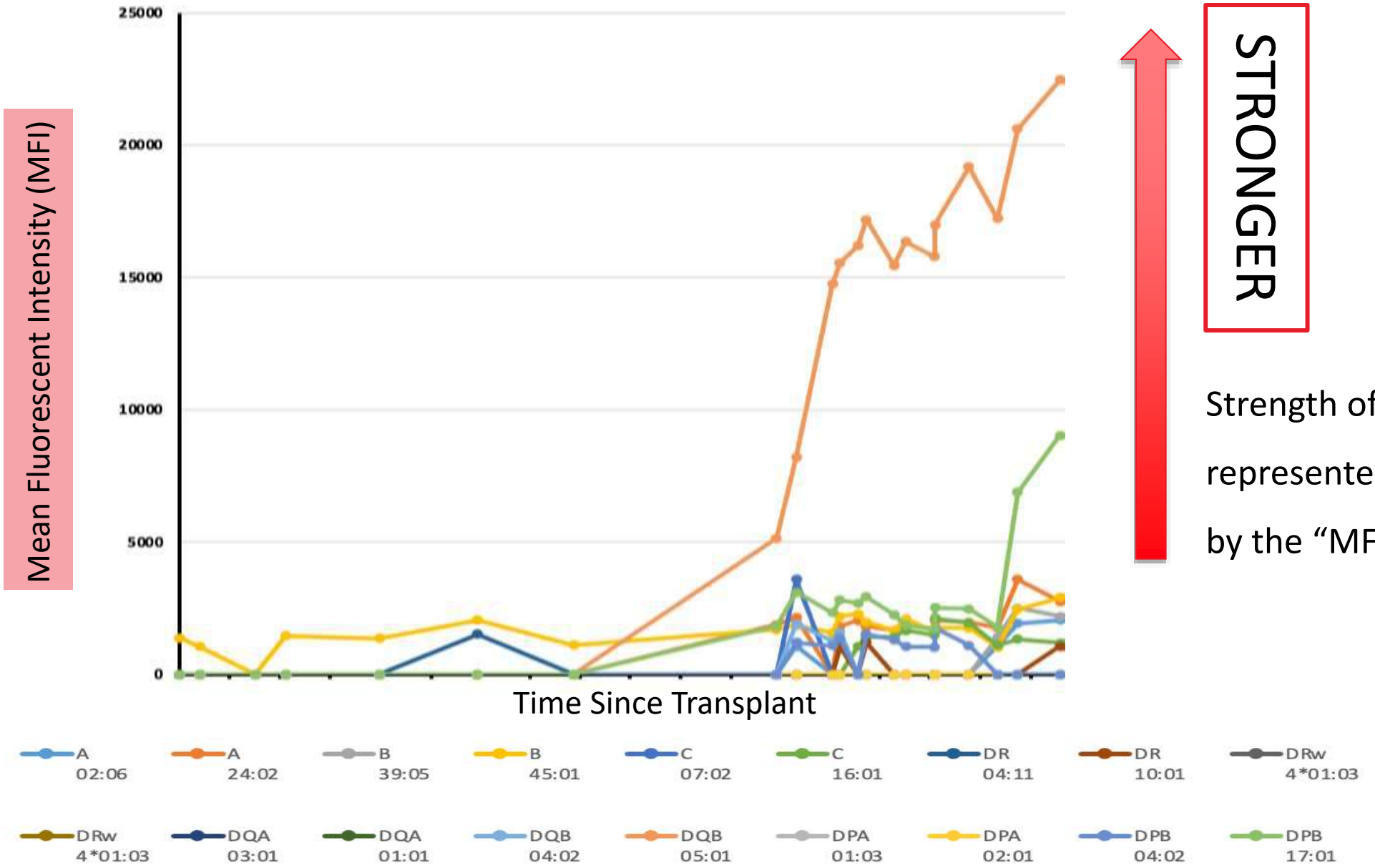


DEVELOPS DONOR SPECIFIC ANTIBODIES



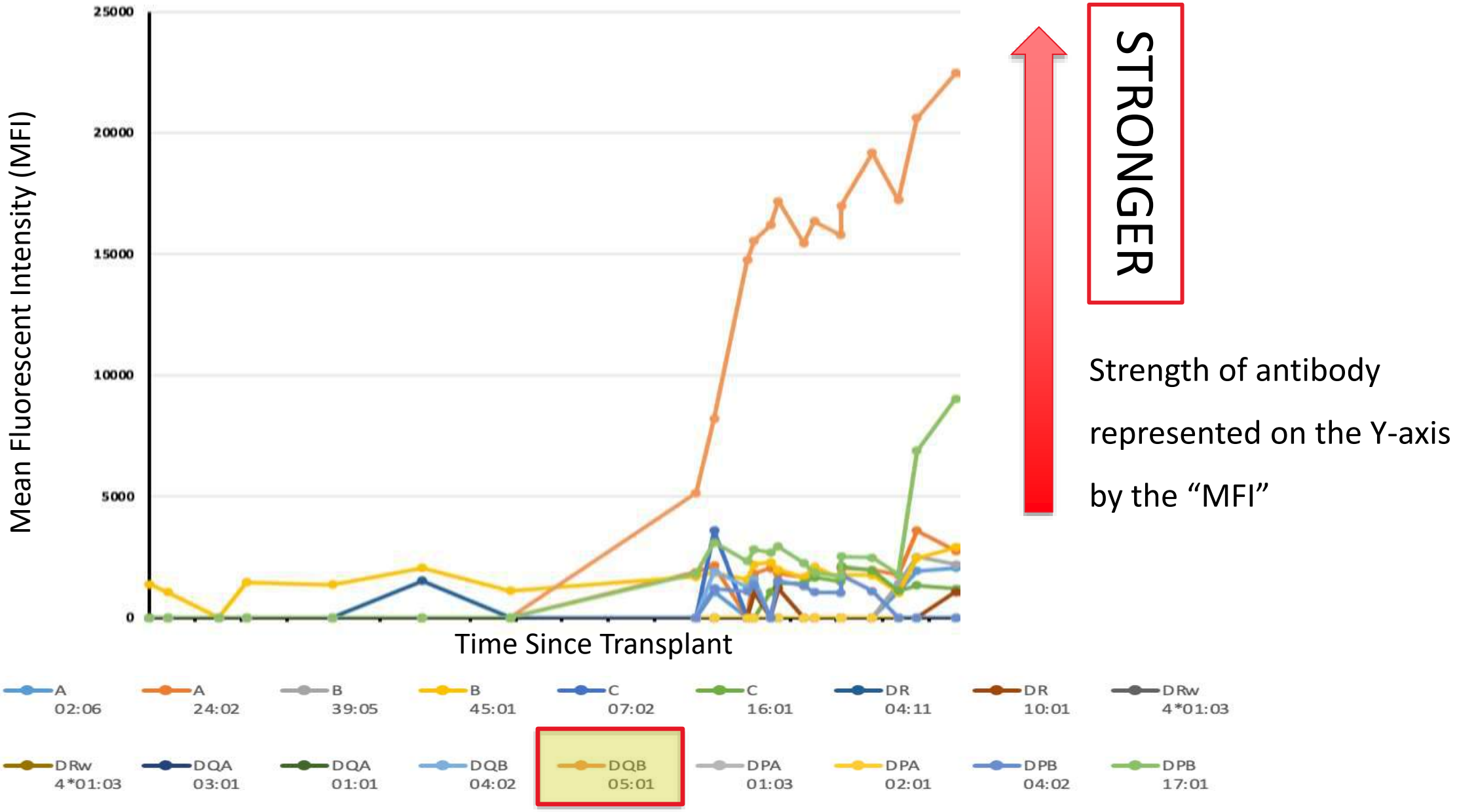
each color line is a different anti-HLA donor-specific antibody which recognizes the graft

DEVELOPS DONOR SPECIFIC ANTIBODIES



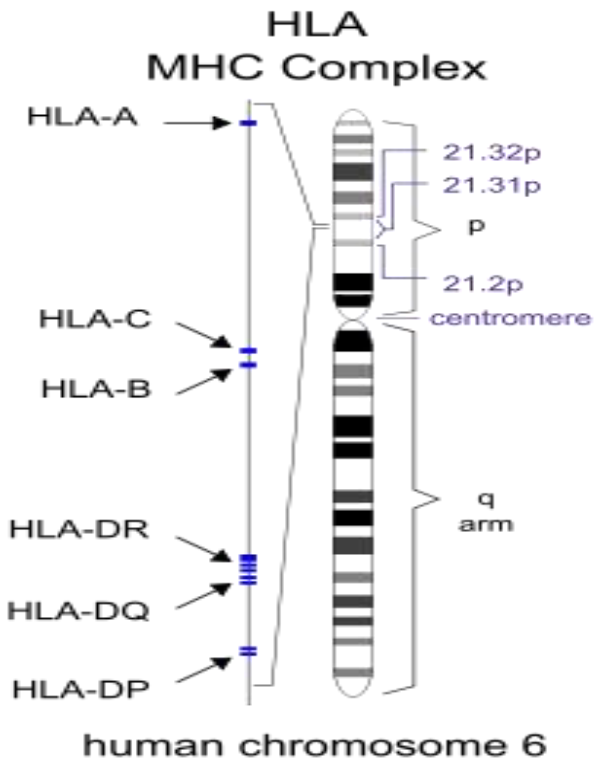
Strength of antibody represented on the Y-axis by the “MFI”

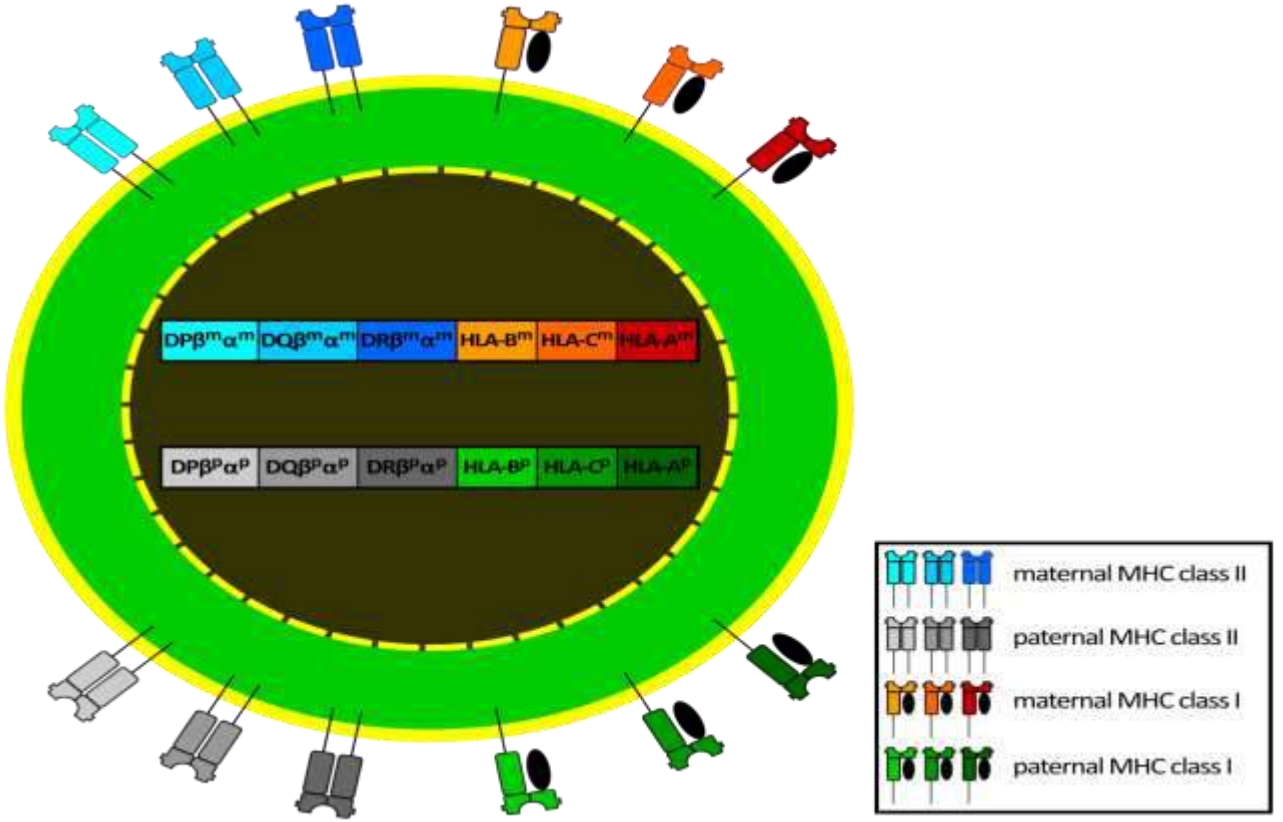
HE HAS SOME STRONG ANTIBODIES



WHAT ARE DONOR SPECIFIC ANTIBODIES (DSA)?

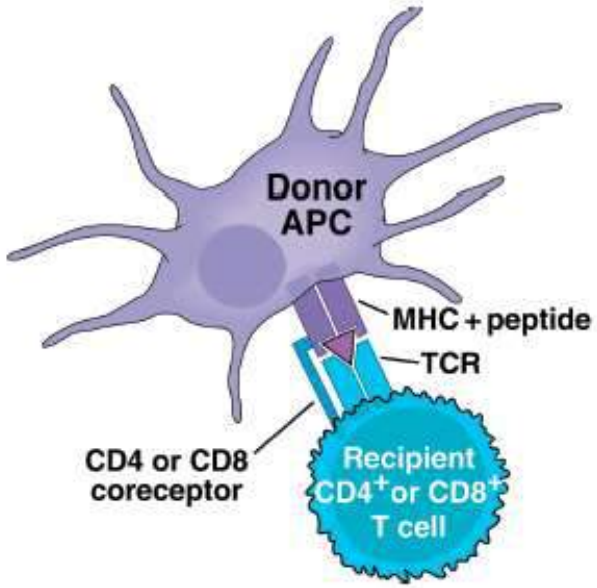
- The donor tissues express class I and class II “HLA” *antigens*

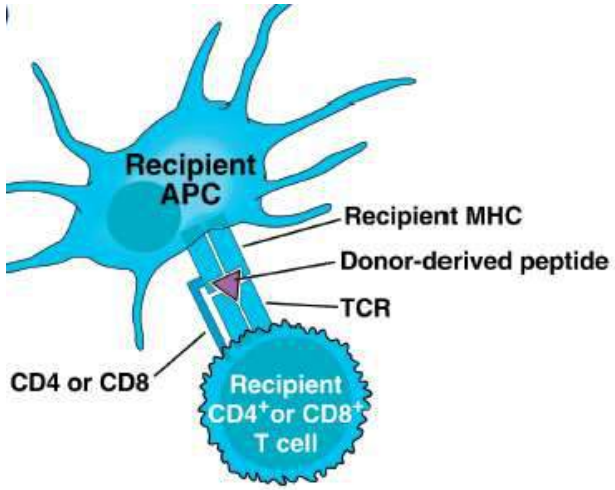


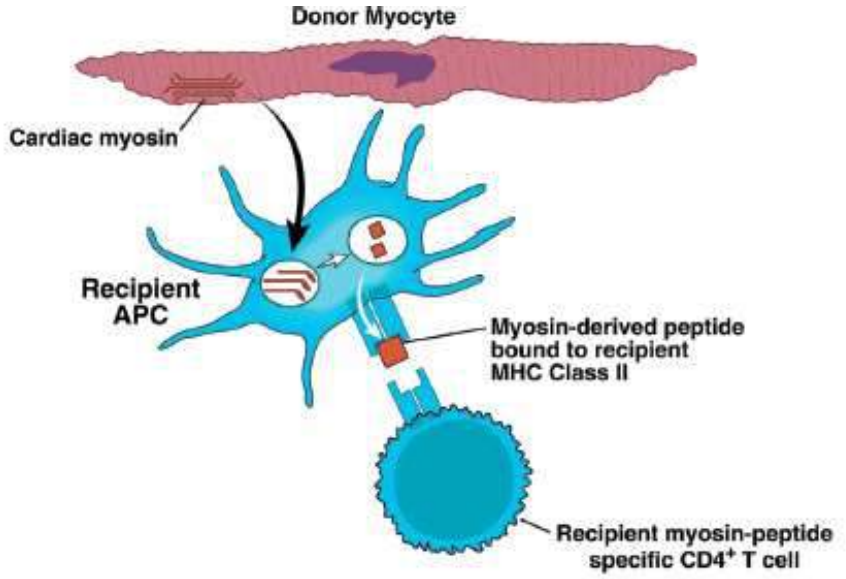


WHAT ARE DONOR SPECIFIC ANTIBODIES (DSA)?

- The donor tissues express class I and class II “HLA” antigens
- Donor *antigens* can be exposed to the recipient immune system

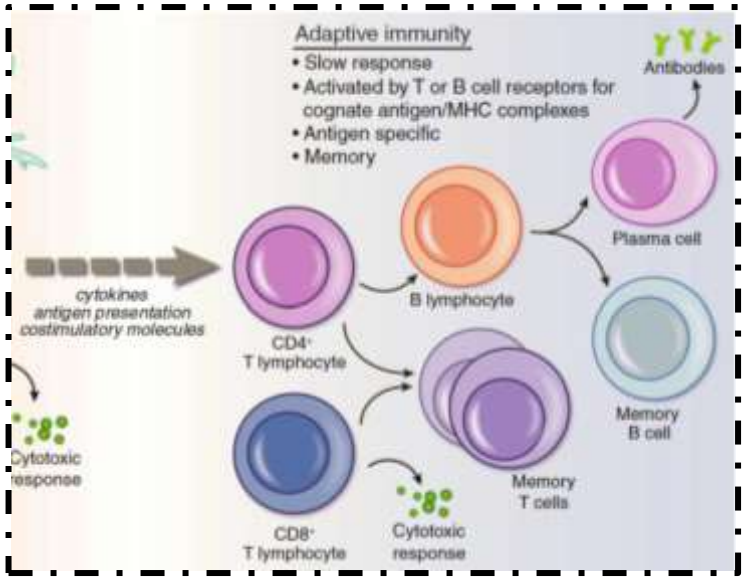






WHAT ARE DONOR SPECIFIC ANTIBODIES (DSA)?

- The donor tissues express class I and class II “HLA” antigens
- Donor antigens can be exposed to the recipient immune system
- The recipient can make anti-HLA donor specific ***antibodies (DSA)***



WHY DO DSA MATTER?

- DSA can bind to the donor graft

- DSA can **increase** the risks of developing:
  - **Antibody Mediated Rejection (AMR)**
  - **Coronary Allograft Vasculopathy (CAV)**

BACK TO THE PATIENT

- multiple biopsies
- no treatable ACR
- no AMR
- no *visually apparent* CAV

Cellular Score	AMR score	CAV
1R	pAMR0	No
1R	pAMR0	No
1R	pAMR0	No

ACR: acute cellular rejection
AMR: antibody mediated rejection
CAV: coronary allograft vasculopathy

QUESTION FOR THE GROUP

What should we do about DSA in absence of AMR?

QUESTION FOR THE GROUP

What should we do about DSA in absence of AMR?

QUESTION FOR THE GROUP

What should we do about DSA in absence of AMR?

What can help us decide?

QUESTION FOR THE GROUP

What should we do about DSA in absence of AMR?

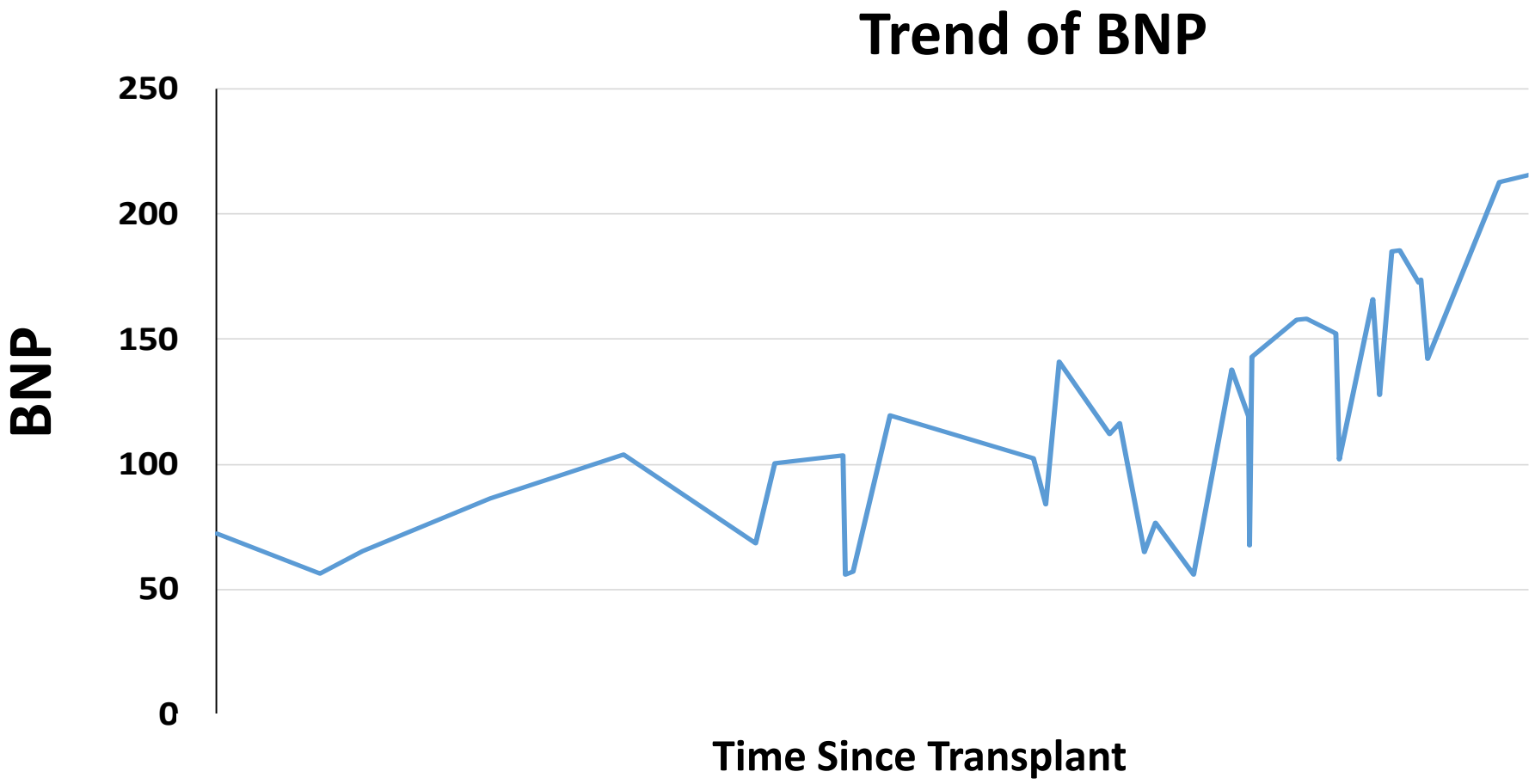
Does it matter which antibody?

SOME MORE INFORMATION

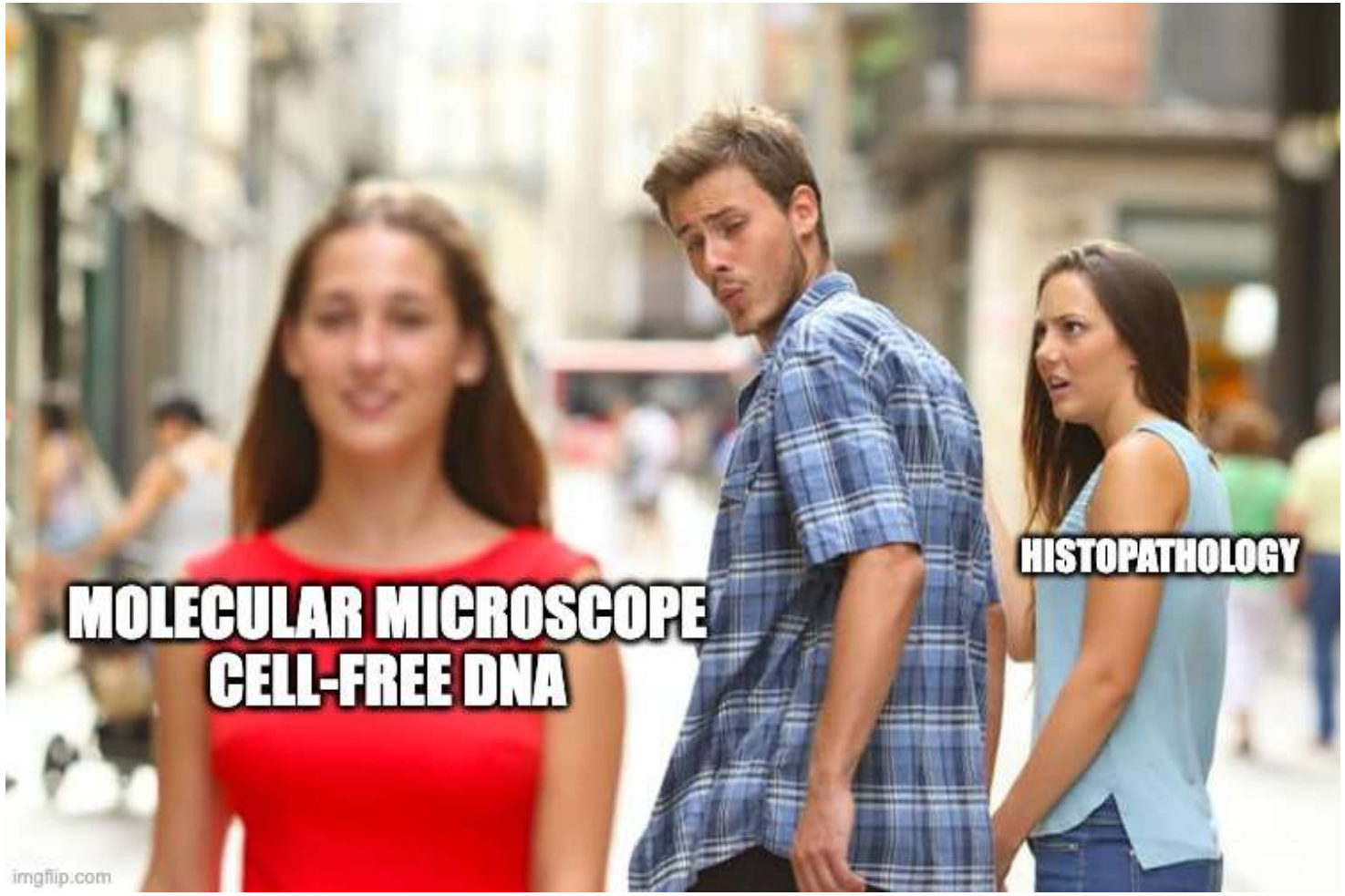
RAP	RVEDP	PAP	PCWP	Cellular Score	AMR score	CAV
8	8	17	12	1R	pAMR0	No
14	14	19	15	1R	pAMR0	No
16	16	22	21	1R	pAMR0	No

elevated and rising filling pressures

SOME MORE INFORMATION



WE HAVE NEW TOOLS WHICH *MAY* HELP



GOLD STANDARD: HISTOPATHOLOGY

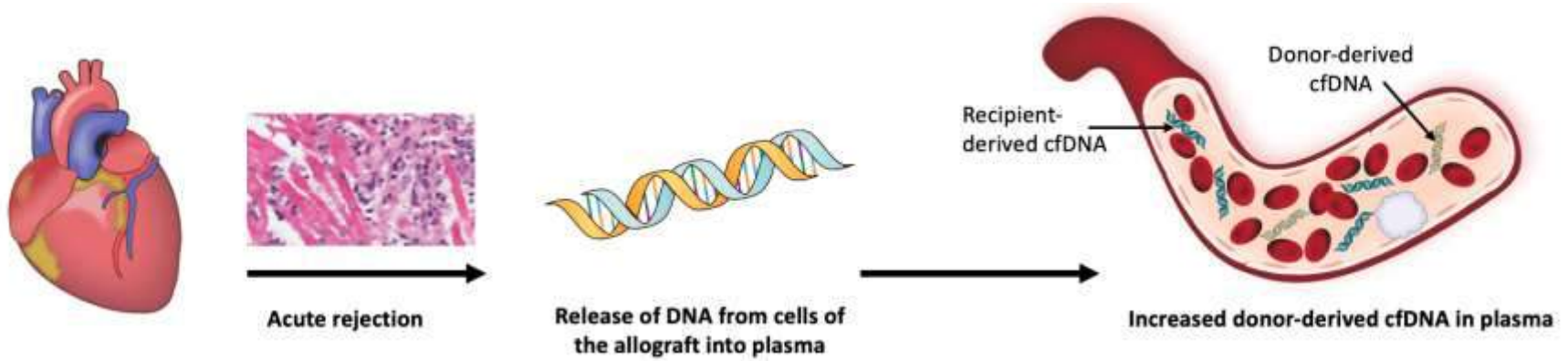
- Overall concordance among pathologists was 70%
- AND, this is mostly because of very good agreement on 0R
- For average pair of 2 pathologists, < 1/3 of biopsies assigned ≥ 2R had agreement

LET'S BE HONEST: IT'S NOT GOLD

- Overall concordance among pathologists was 70%
- AND, this is mostly because of very good agreement on 0R
- For average pair of 2 pathologists, < 1/3 of biopsies assigned ≥ 2R had agreement

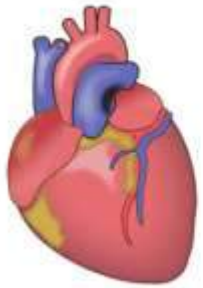
DONOR DERIVED CELL-FREE DNA

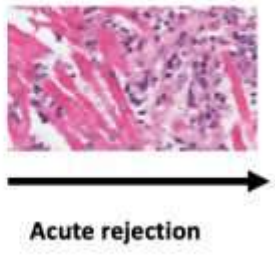
Donor Heart (with Donor DNA)



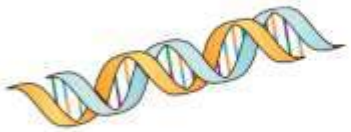
DONOR DERIVED CELL-FREE DNA

Donor Heart (with Donor DNA)

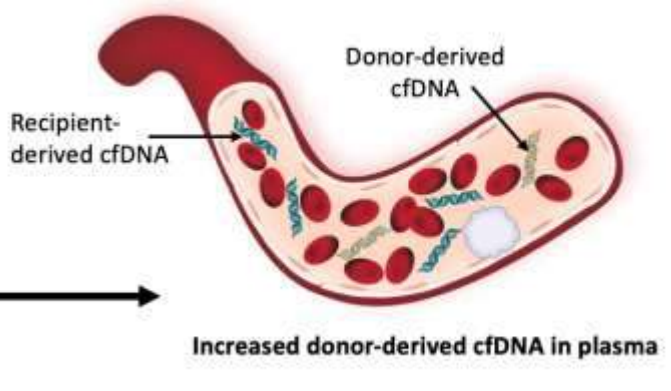




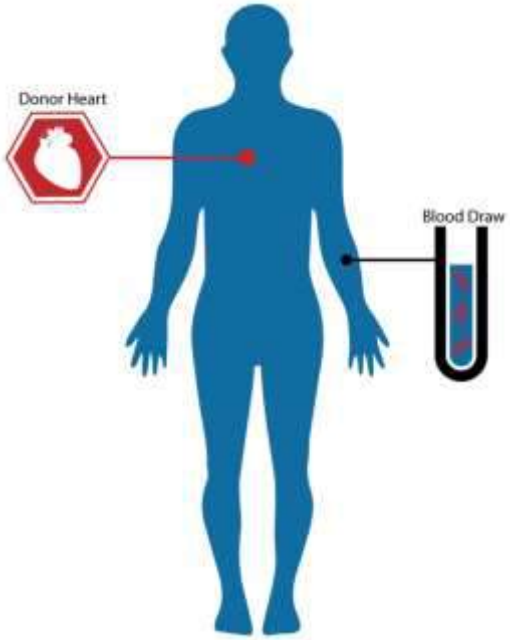
Acute rejection



Release of DNA from cells of the allograft into plasma

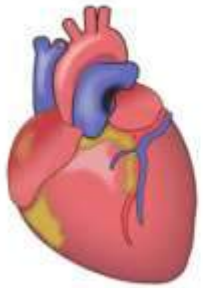


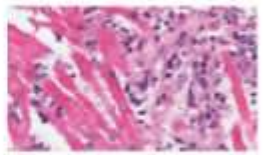
Increased donor-derived cfDNA in plasma



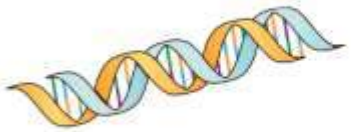
DONOR DERIVED CELL-FREE DNA

Donor Heart (with Donor DNA)

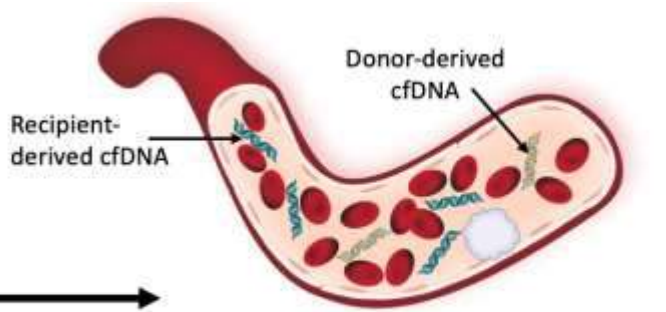




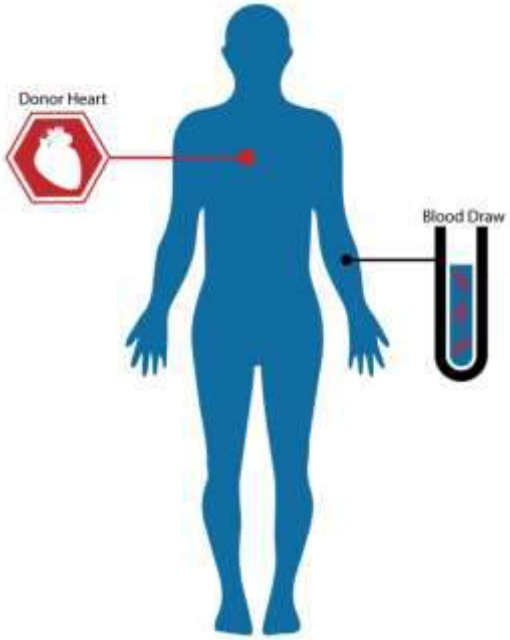
Acute rejection



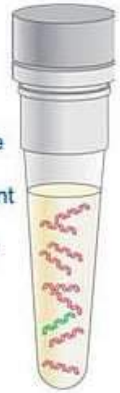
Release of DNA from cells of the allograft into plasma



Increased donor-derived cfDNA in plasma

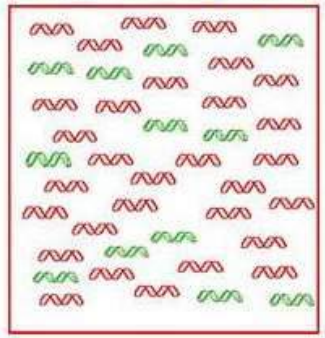


Plasma sample containing mixture of DNA from transplant recipient (red) and DNA from organ donor (green).

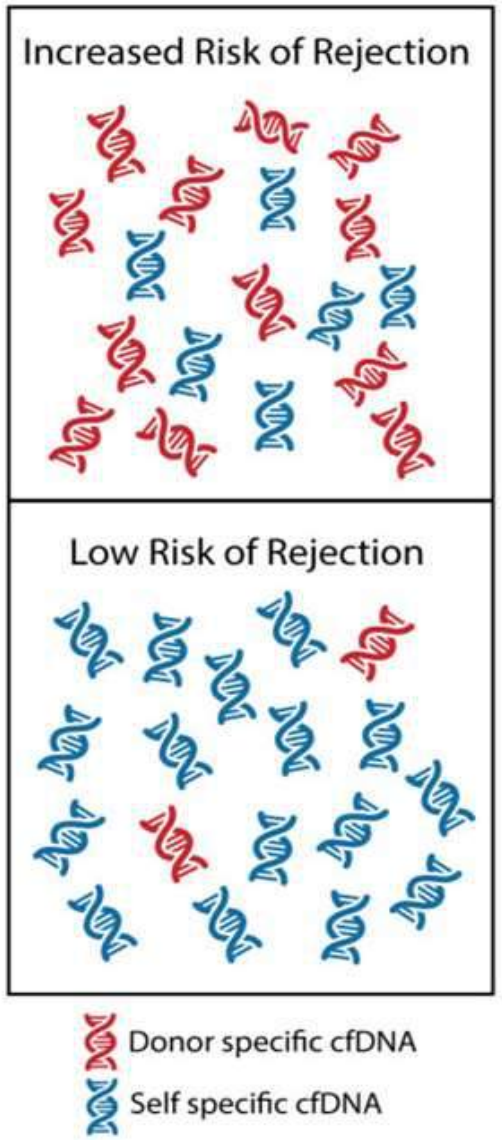


DNA sequencing

Computer analysis of DNA



DONOR DERIVED CELL-FREE DNA

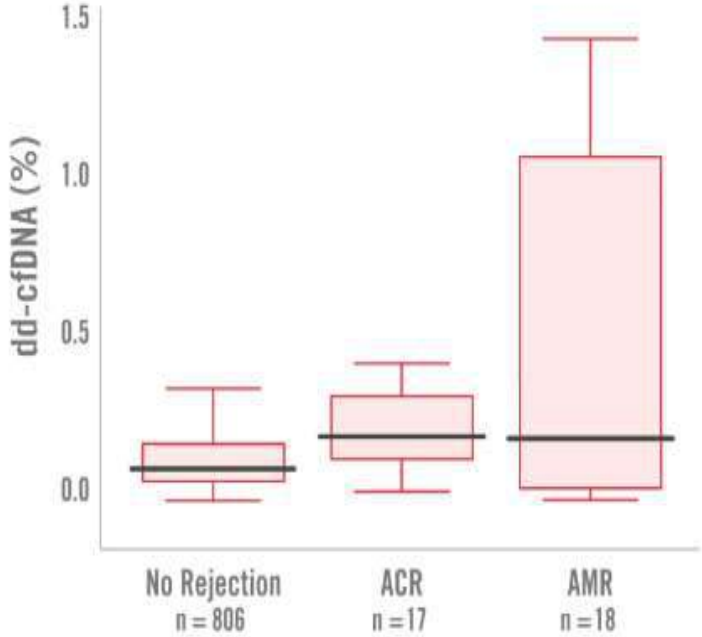


MORE donor derived cell-free DNA: BAD

- **A high value can rule-in rejection**

less donor derived cell-free DNA: GOOD

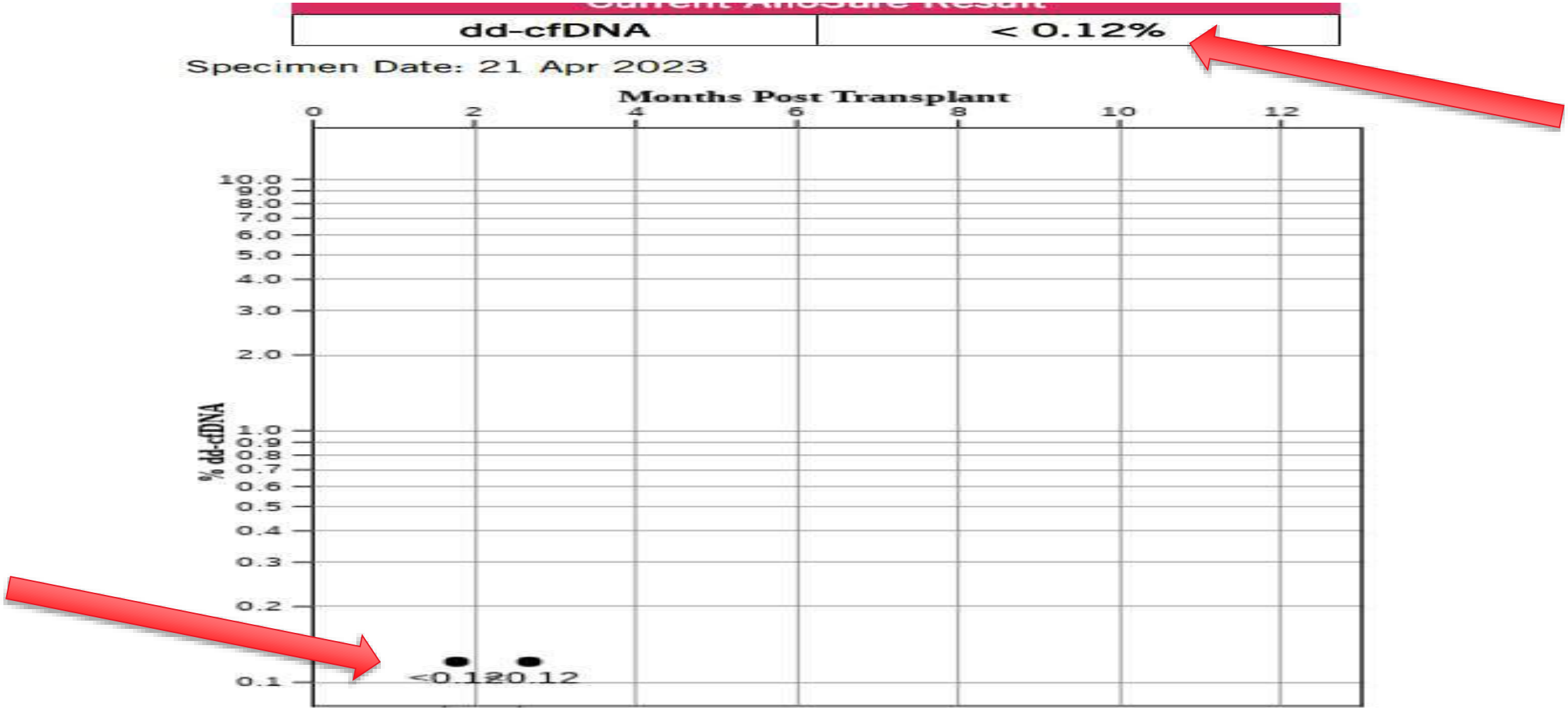
- **A low value rule-out rejection**



https://www.labmedica.com/pathology/articles/294780795/heart-transplant-monitoring-test-validated.html https://www.nih.gov/news-events/news-releases/blood-test-shows-promise-early-detection-severe-lung-transplant-rejection

THIS IS WHAT WE WANT IT TO LOOK LIKE

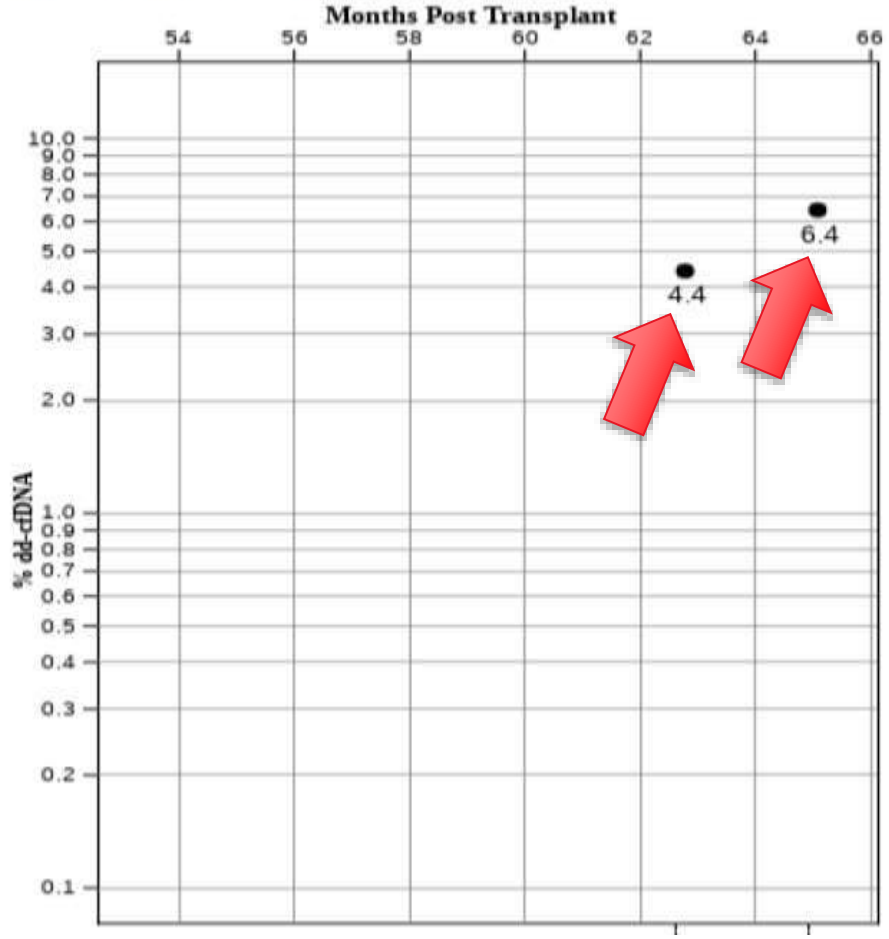
AlloSure®



AlloSure®

Current AlloSure Result	
dd-cfDNA	6.4%

Specimen Date: 12 Jan 2023



- Initial result: 4.4%
- Follow-up result: 6.4%
- “cut-off”: 0.12% - 0.2%

- These values are extremely high

MOLECULAR MICROSCOPE: MMDx®

- Certain genes are turned “on” when there is different types of rejection or injury to the heart muscle
- FROM the heart muscle, we can measure mRNA transcripts
- MMDx® can help us figure out WHAT is happening
- This *may* be help us decide HOW to treat

MMDx® ON BIOPSY TISSUE → WHICH GENES ARE "ON"

The MMDx process

ThermoFisher SCIENTIFIC

Collect biopsy
Place immediately in Invitrogen™ RNA*later*™ solution

Kidney core 3–5 mm
1–2 EMB bites
1–2 TBB bites
Liver 3–5 mm

Shipping/receiving at room temperature

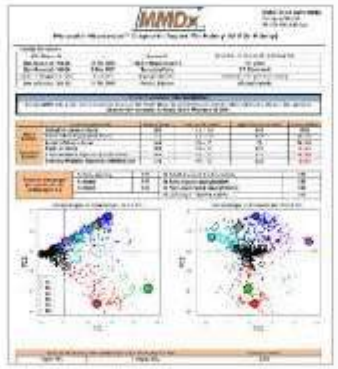
RNA extraction, cleanup, and quality control

RNA labeling

Hybridization

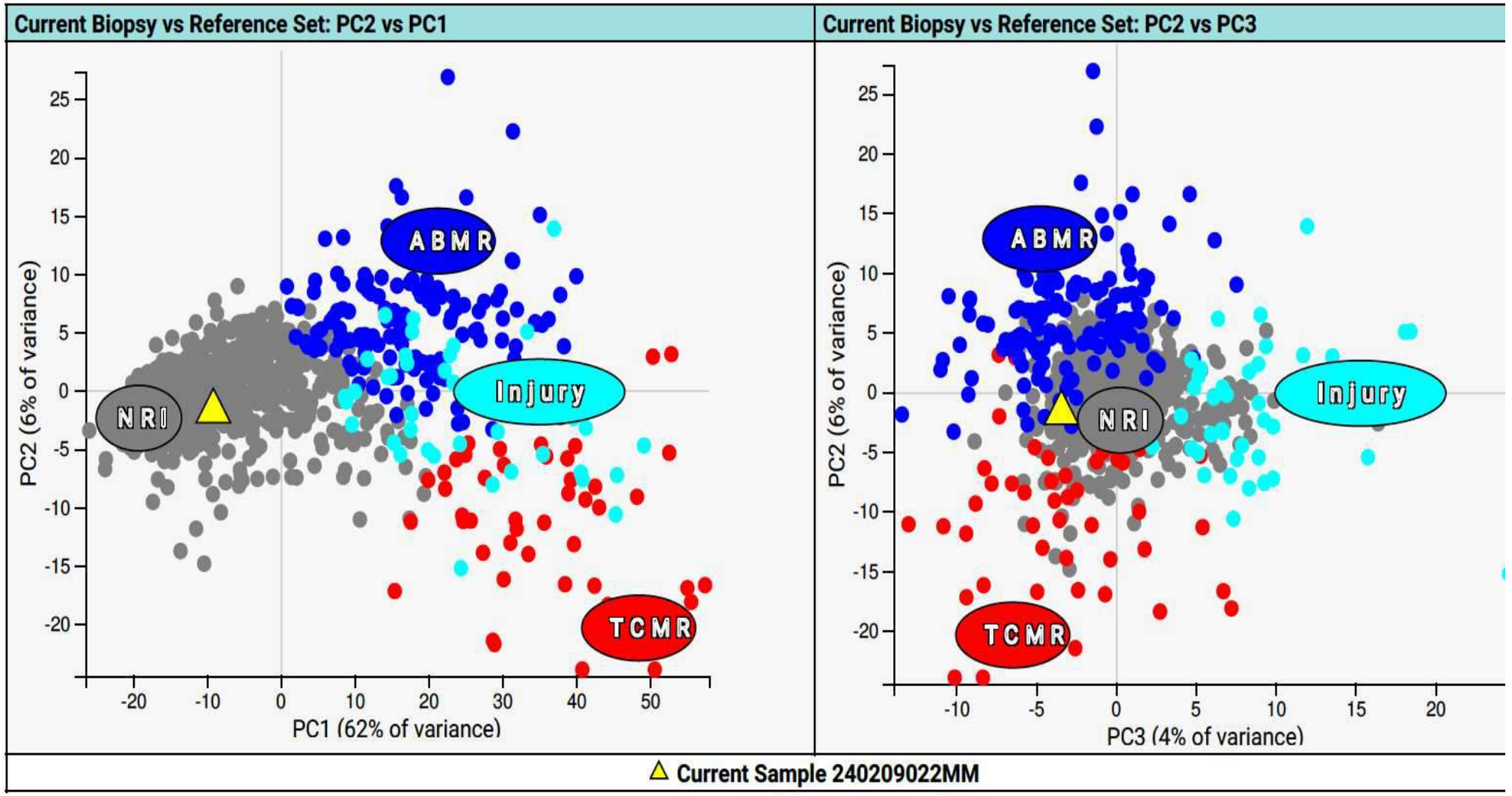
Wash and stain

Scan chips

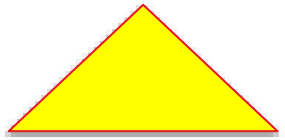


SLIDE PROVIDED BY THERMOFISHER SCIENTIFIC

Normal Biopsy



Look for Yellow Triangle = your patient



The test “compares” your patient to their Data Set

OUR PATIENT: AMR WITH INJURY

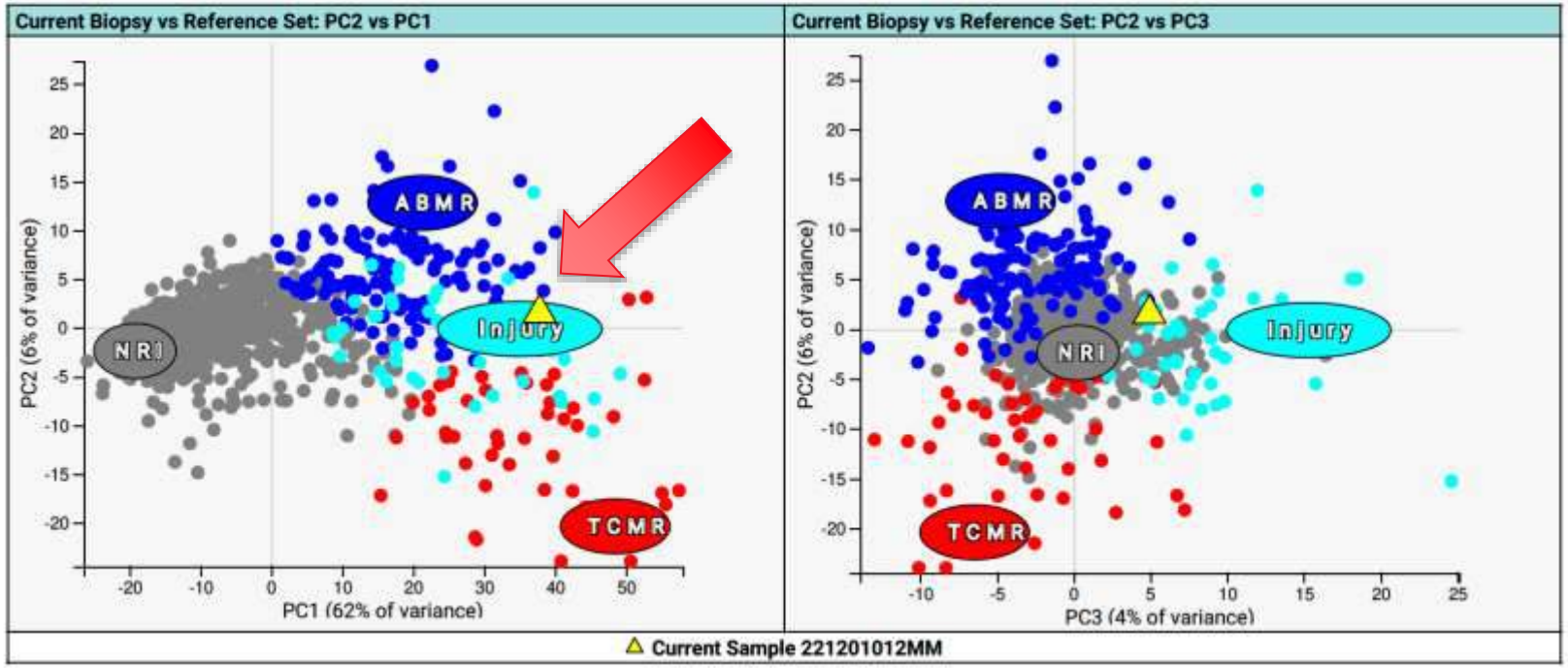
Result Details

Proportion Rejection and Injury*	Model 1	NRI	0.00	TCMR/Injury	0.52	ABMR/Injury	0.49		
	Model 2	NRI	0.00	TCMR	0.24	ABMR	0.26	Injury	0.51
Probable Rejection Diagnosis*	Using Model 1	NRI	0.00	TCMR/Injury	1.00	ABMR/Injury	0.94		
	Using Model 2	NRI	0.00	TCMR	0.14	ABMR	0.47		
Principal Component Scores				PC1	37.88	PC2	1.51	PC3	4.95

NRI (Normalness) = No Rejection or Injury.

Archetypal Analysis *(please see Archetypal Analysis Description on Page 2 for details)*

**Based on new algorithms accepted for presentation at the 2018 ISHLT meeting, April 11-14, Nice, France.*



Pure Molecular Interpretation (Results Summary)

Abnormal heart transplant biopsy with ABMR 5 years post-transplant. No TCMR. Extensive parenchymal injury (IRRATs, S4, and QCMATs abnormal) with some parenchymal dedifferentiation (HT1s abnormal).

QUESTION FOR THE GROUP: SO NOW WHAT?

- Extremely high (and rising) donor-derived cell-free DNA%
- Abnormal MMDx® with AMR and injury

QUESTION FOR THE GROUP: SO NOW WHAT?

- Extremely high (and rising) donor-derived cell-free DNA%
- Abnormal MMDx® with AMR and injury

- **Who would treat now?**
- **And with what?**

SO WE DID A LOT OF THINGS

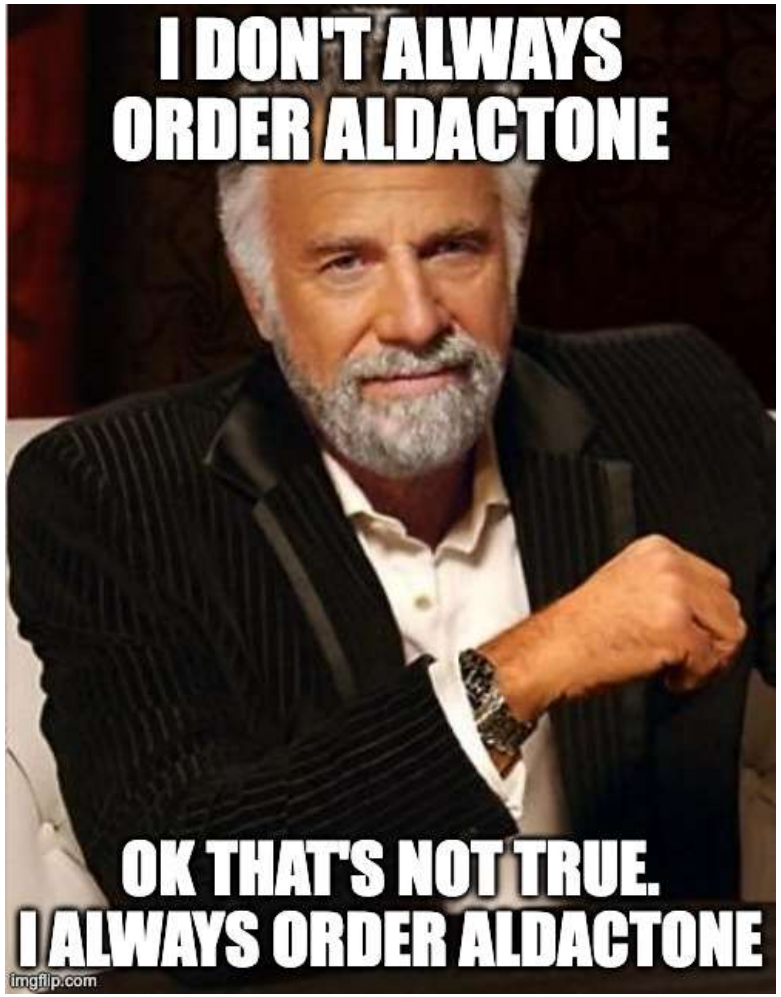
- Switched Tacrolimus/MMF → Tacrolimus/Sirolimus
- Gave rituximab (attacks memory B-cells)
- Gave bortezomib (attacks plasma cells)
- The goal of these therapies: reduce ***production*** of DSA

SO WE DID A LOT OF THINGS

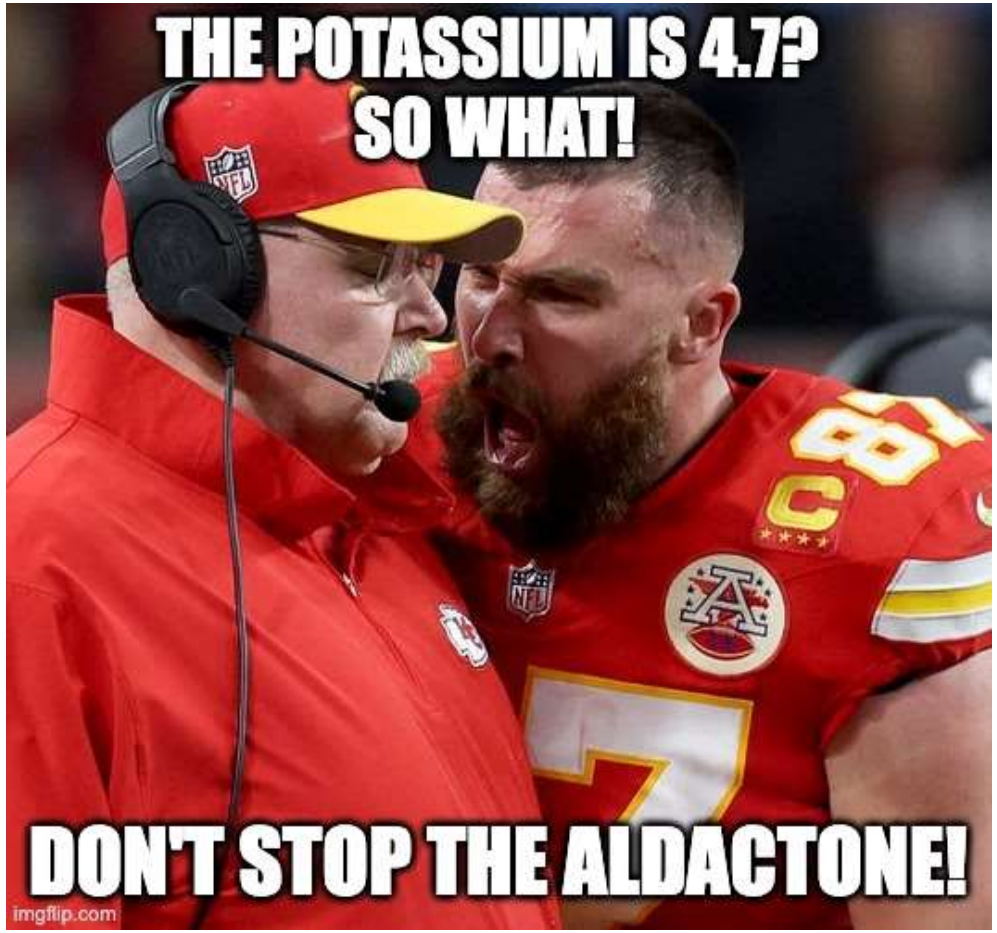
- Switched Tacrolimus/MMF → Tacrolimus/Sirolimus
- Gave rituximab (attacks memory B-cells)
- Gave bortezomib (attacks plasma cells)

- **And what about the impaired diastolic function?**

WHAT ABOUT THE IMPAIRED DIASTOLIC FUNCTION?

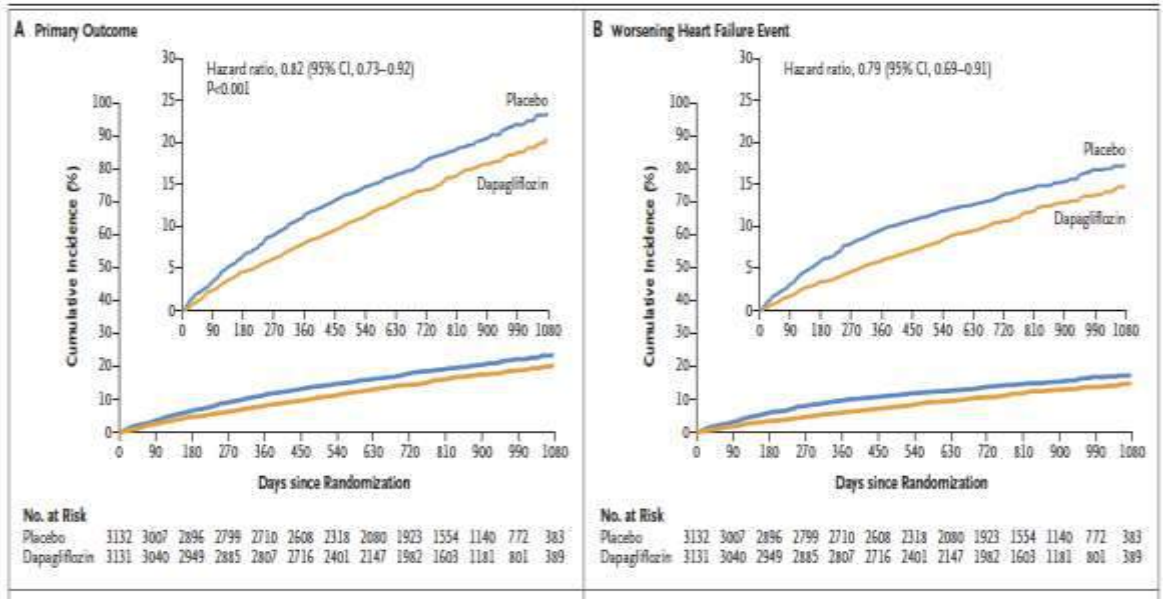


EVEN WHEN THE K^+ IS NOT LOW? YES!



WHAT'S THE DEAL WITH SGLT-2?

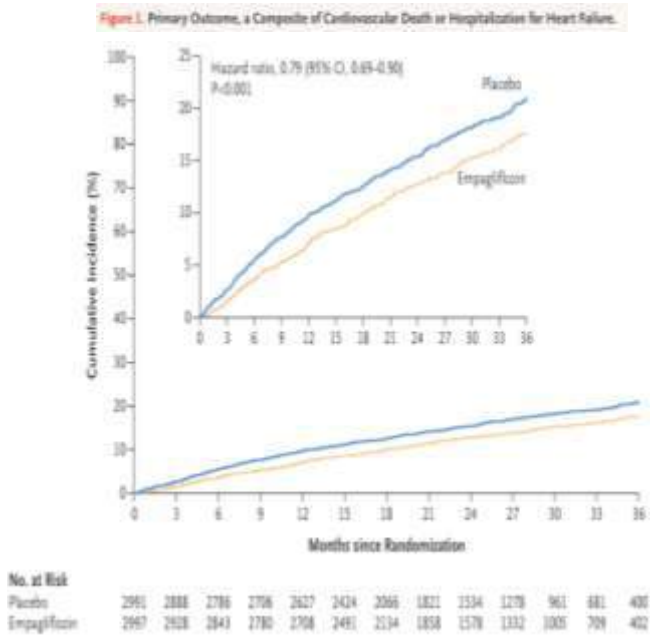
DELIVER (HFmEF or HFpEF)

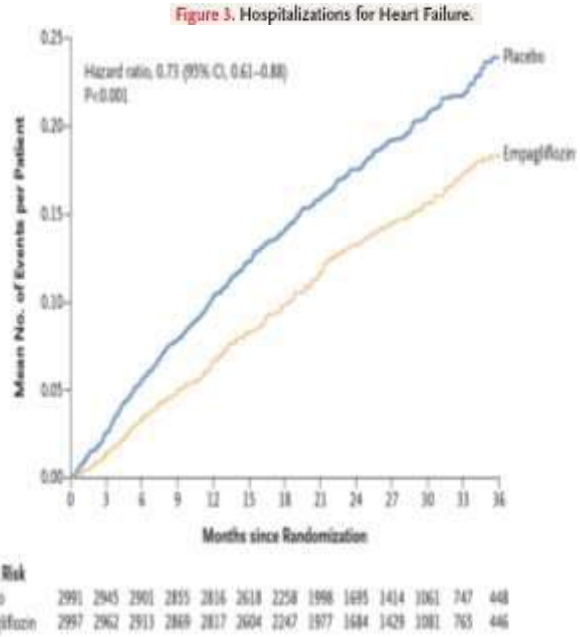


*** Results were similar among patients with LVEF < 60% vs LVEF > 60% ***

Solomon et al. NEJM 2022

EMPEROR-PRESERVED (HFpEF)

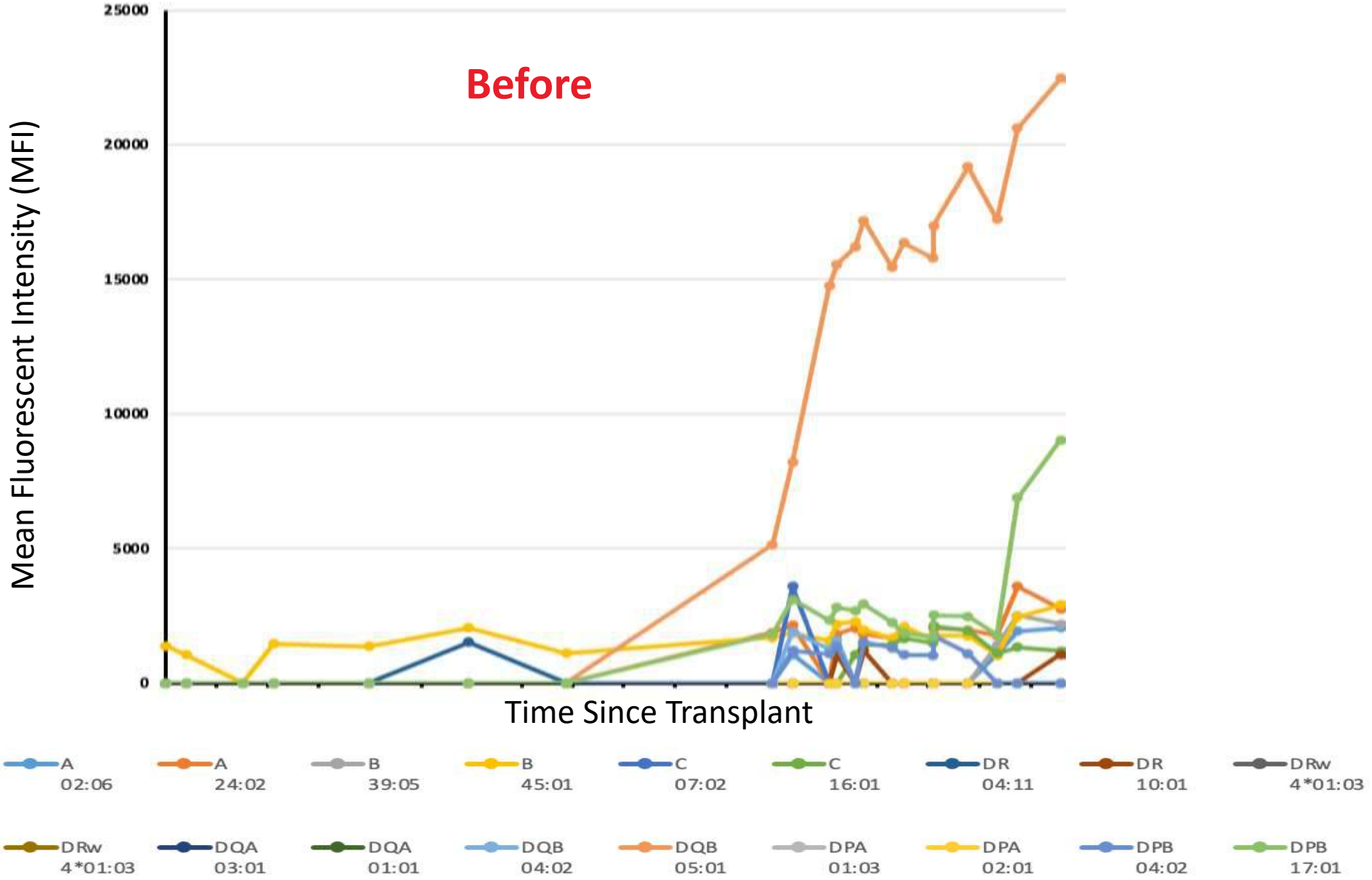




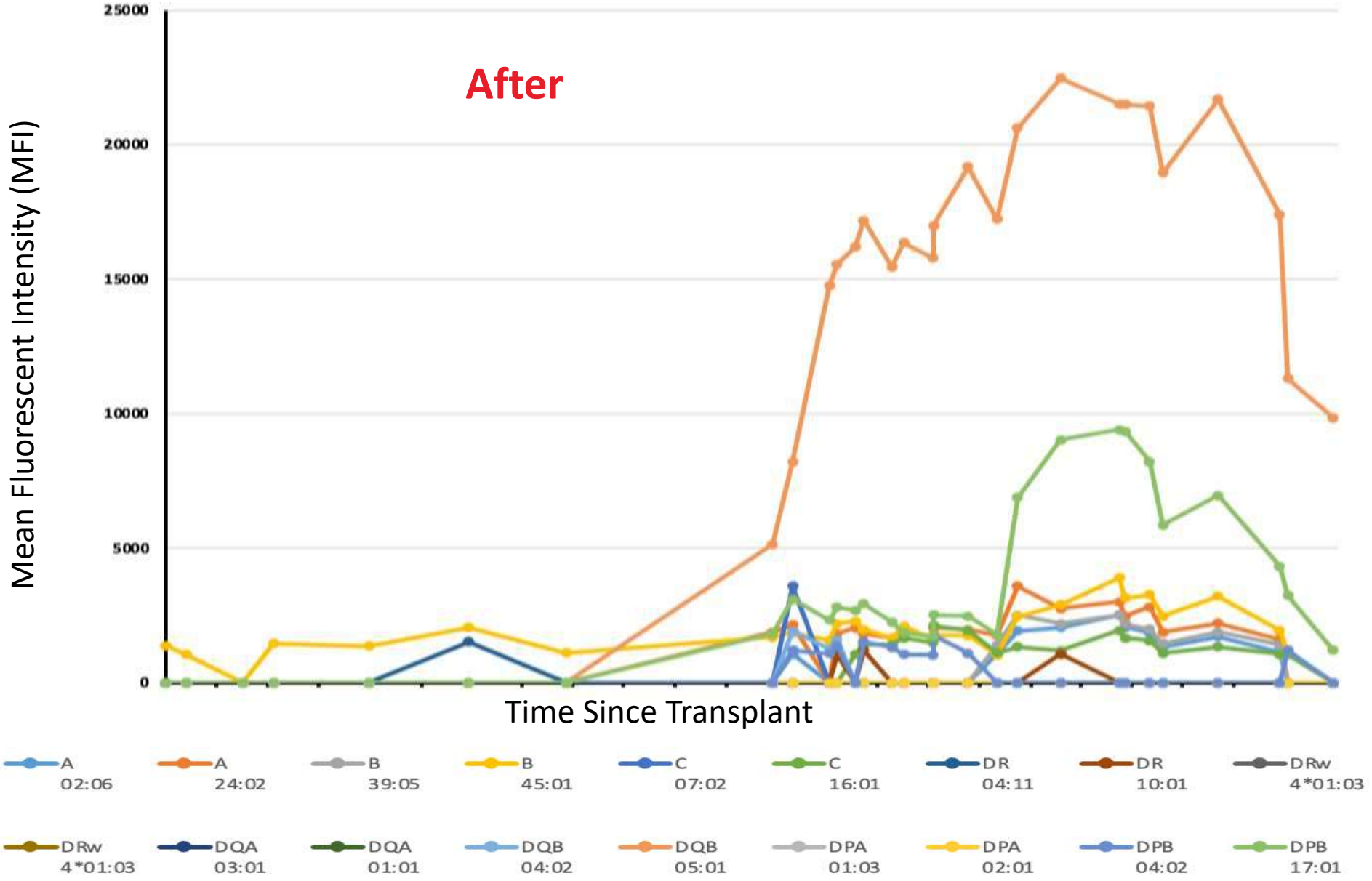
Anker et al. NEJM 2021


SO...WHAT HAPPENED?
imgflip.com

HOW IS HE DOING – DSA?

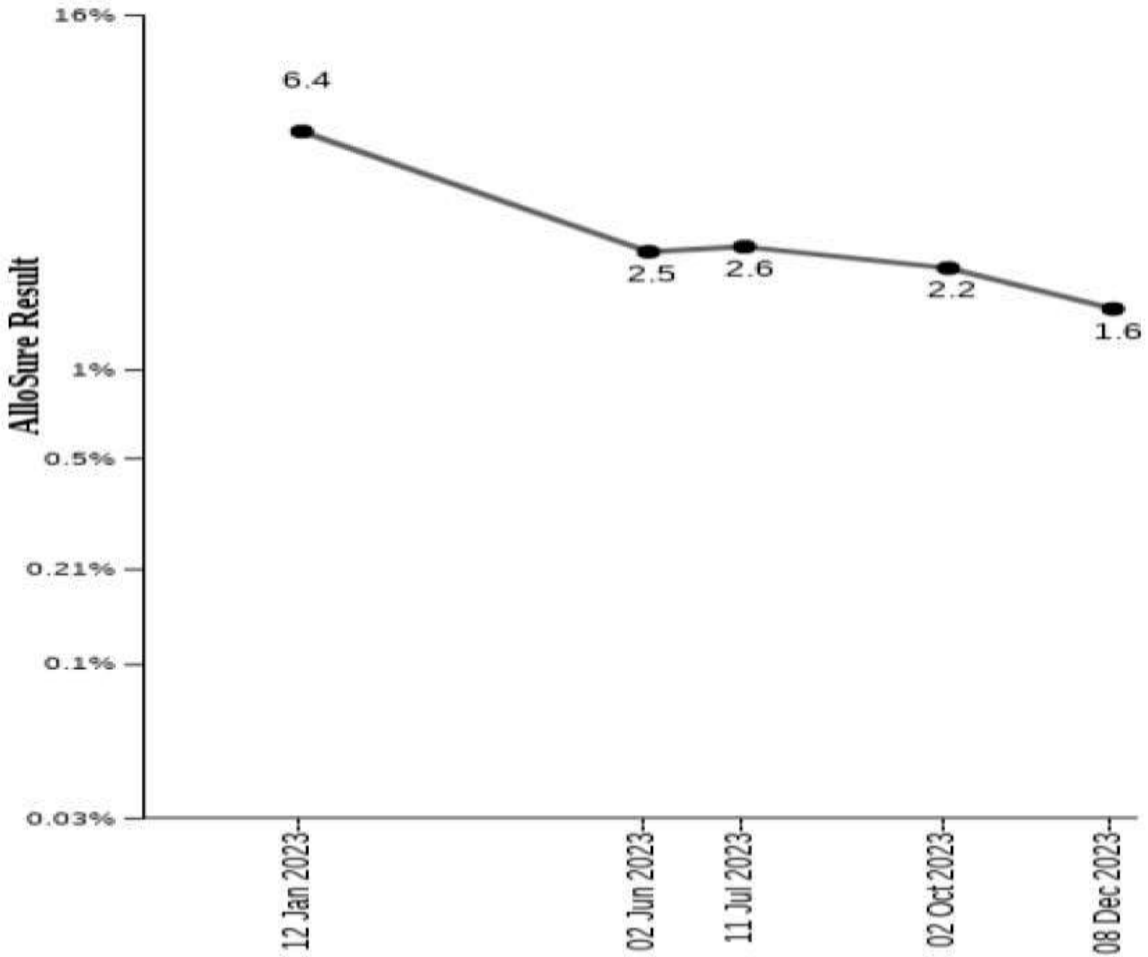


DSA ARE NOT GONE – BUT MUCH BETTER

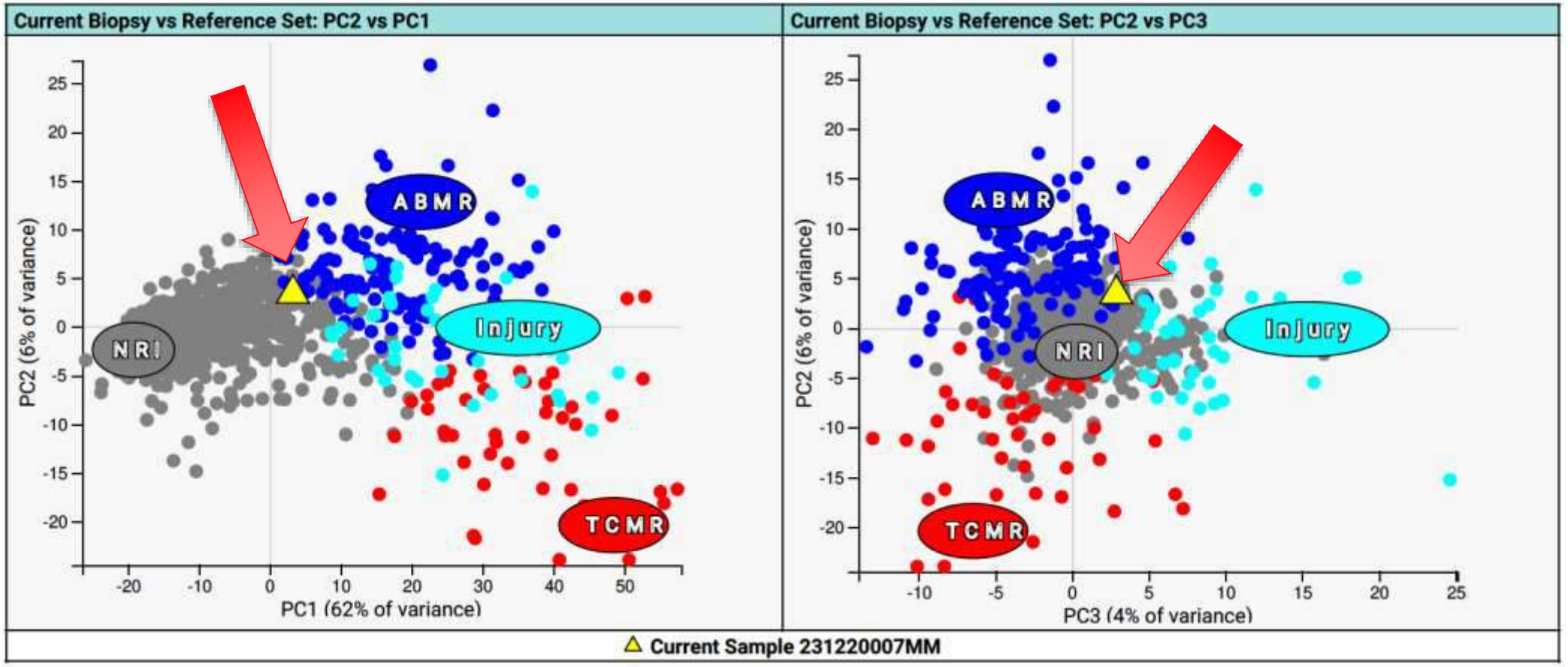


Allosure® cell-free DNA% trend

Current AlloSure Result	
dd-cfDNA	1.6%



Most Recent MMDx®



"Mild rejection-related inflammation (AMR-like) but **not meeting the threshold for rejection**. ***Mild*** parenchymal injury"

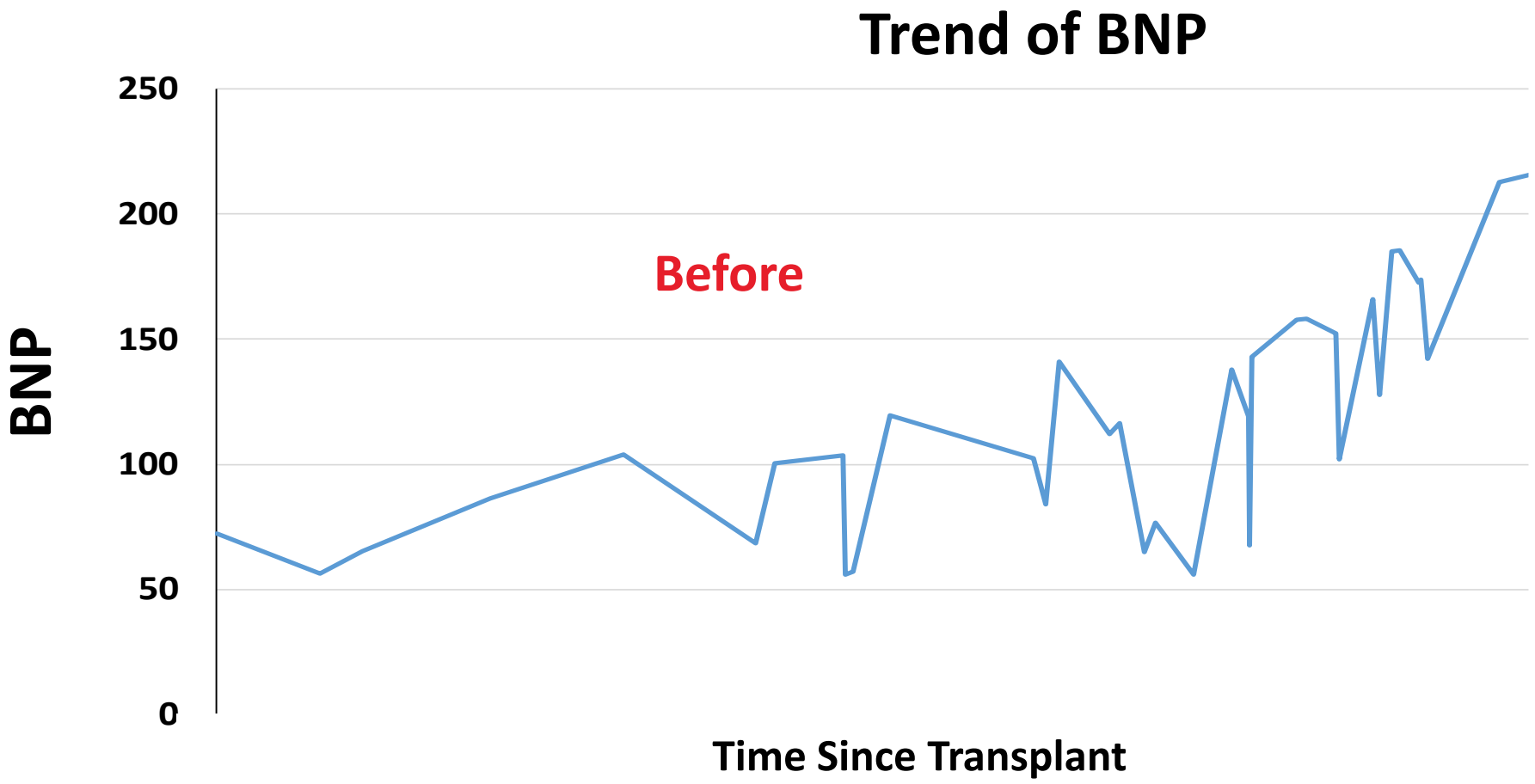
HOW IS HE DOING – HEMODYNAMICS?

RAP	RVEDP	PAP	PCWP	Cellular Score	AMR score	CAV
8	8	17	12	1R	pAMR0	No
14	14	19	15	1R	pAMR0	No
16	16	22	21	1R	pAMR0	No

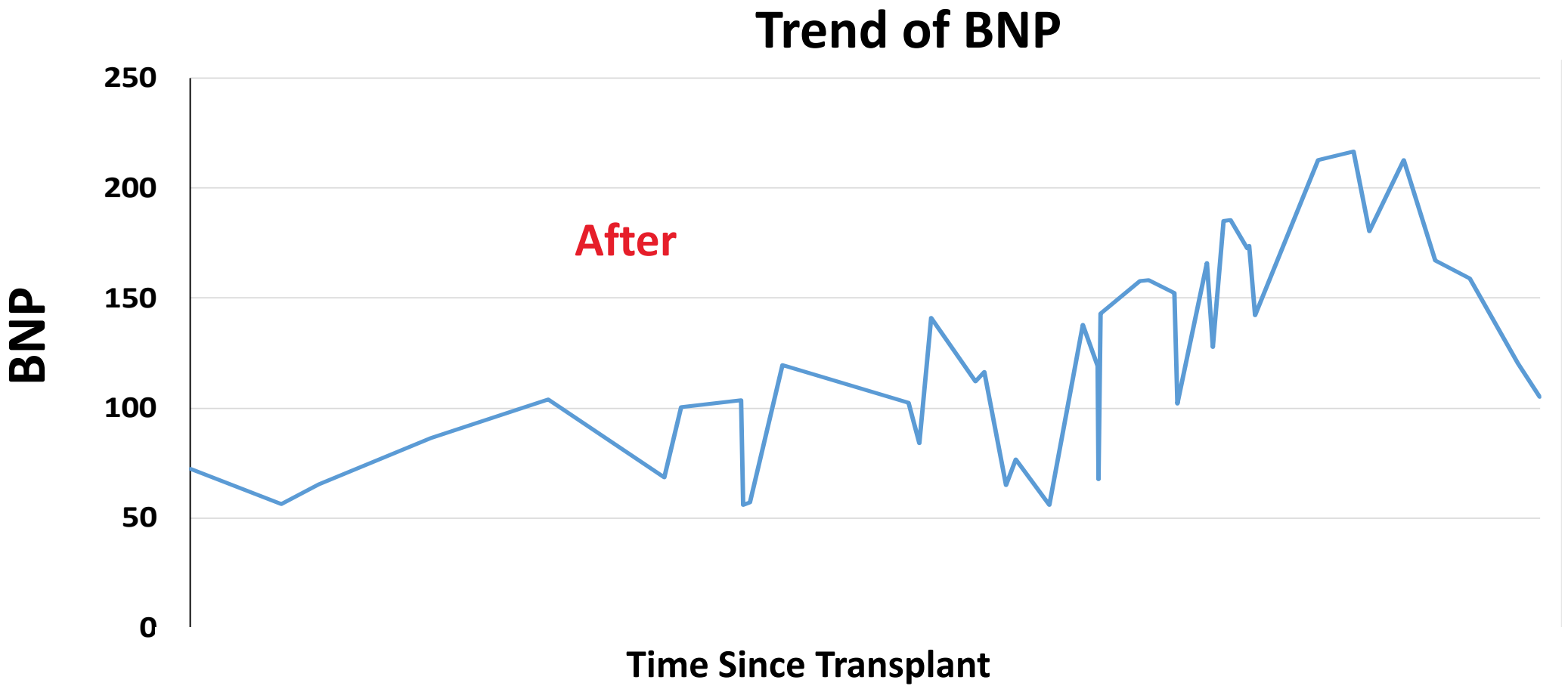
HOW IS HE DOING – PRESSURES ARE LOWER

RAP	RVEDP	PAP	PCWP	Cellular Score	AMR score	CAV
8	8	17	12	1R	pAMR0	No
14	14	19	15	1R	pAMR0	No
16	16	22	21	1R	pAMR0	No
10	10	19	16	1R	pAMR0	No
8	8	17	11	0R	pAMR0	No

HOW IS HE DOING – BNP?



HOW IS HE DOING – BNP IS LOWER



FINAL THOUGHTS

- There are new tools in our armamentarium to assess these pts
- What we do not know >>> than what we know!
- Have to weigh the benefits and risks of therapies
- *We need multi-center collaboration (ACTION, PHTS) to learn from one another in regards to new tests & therapies*

- I would love your feedback/questions! spinner@bcm.edu