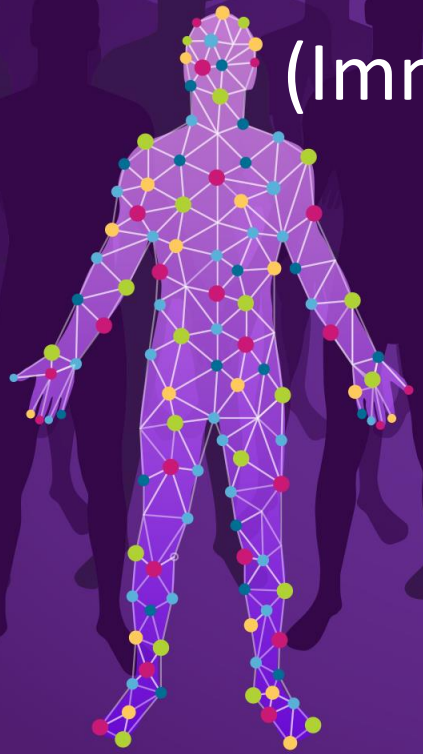
AST | AMERICAN SOCIETY OF TRANSPLANTATION

Donor Specific Antibodies - Different (Immunosuppressive) Strokes for Different Folks



Deborah Jo Levine
University of Texas Health Science Center

CEOT 2019

CEOT CUTTING EDGE of TRANSPLANTATION

TRANSPLANT SUMMIT 2019

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

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

Disclosures

- Will mention the off label therapy directed at DSA

Mrs. K. 56 yo

5 mo post transplant for IPF

- PFTs: Progressively improving since transplantation
- Clinical: stable, active
- Pneumonia at 3 mo Resolved.

ACR: A2B0 at 3 months. Resolved at next biopsy.

AMR: Path and C4d Negative

DSA: No pre-formed DSA. De Novo DSA at 3 month : DQ5 2900 MFI, DQ 6 4200

Mrs. E. 60 yo

5 mo post transplant for IPF

- PFTs: 18% decline FEV1 last month
- Clinical: Worsening exercise tolerance
- No infection
- **ACR:** Negative for 4 months.
- **AMR**: Negative C4d. Mild chronic interstitial thickening.

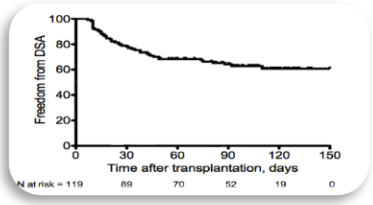
DSA: No pre-formed DSA. De Novo DSA at 3 month:DQ5 2400 MFI, DQ 6 3200

What therapeutic options do we have for these two patients?

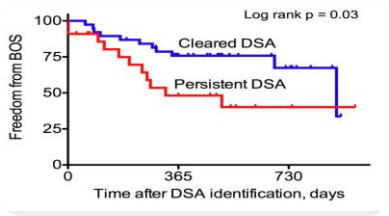
If the two therapeutic decisions are different, what were those decisions based on.

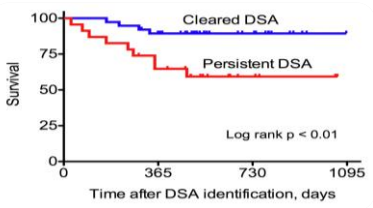
“HLA antibodies and Lung Transplantation”: Publications by year

These studies provide evidence establishing a relationship between DSA and outcomes post transplantation.

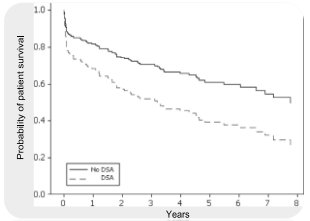


Hachem, AJT 2018; 18: 2285

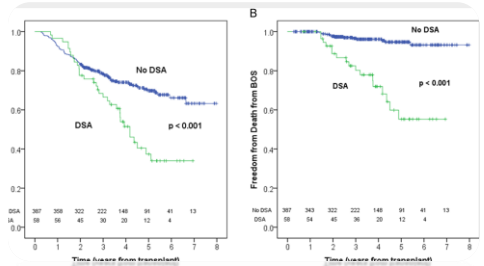




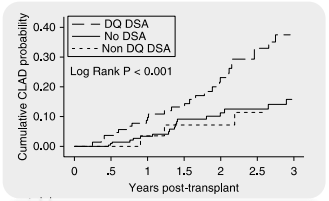
Hachem JHLT 2010; 29: 973



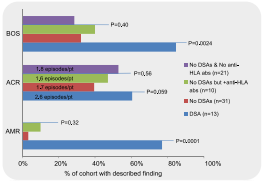
Safavi JHLT 2014;33:1273–1281



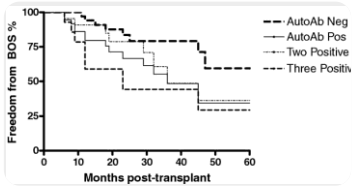
Morrel JHLT 33, No 12, December 2014



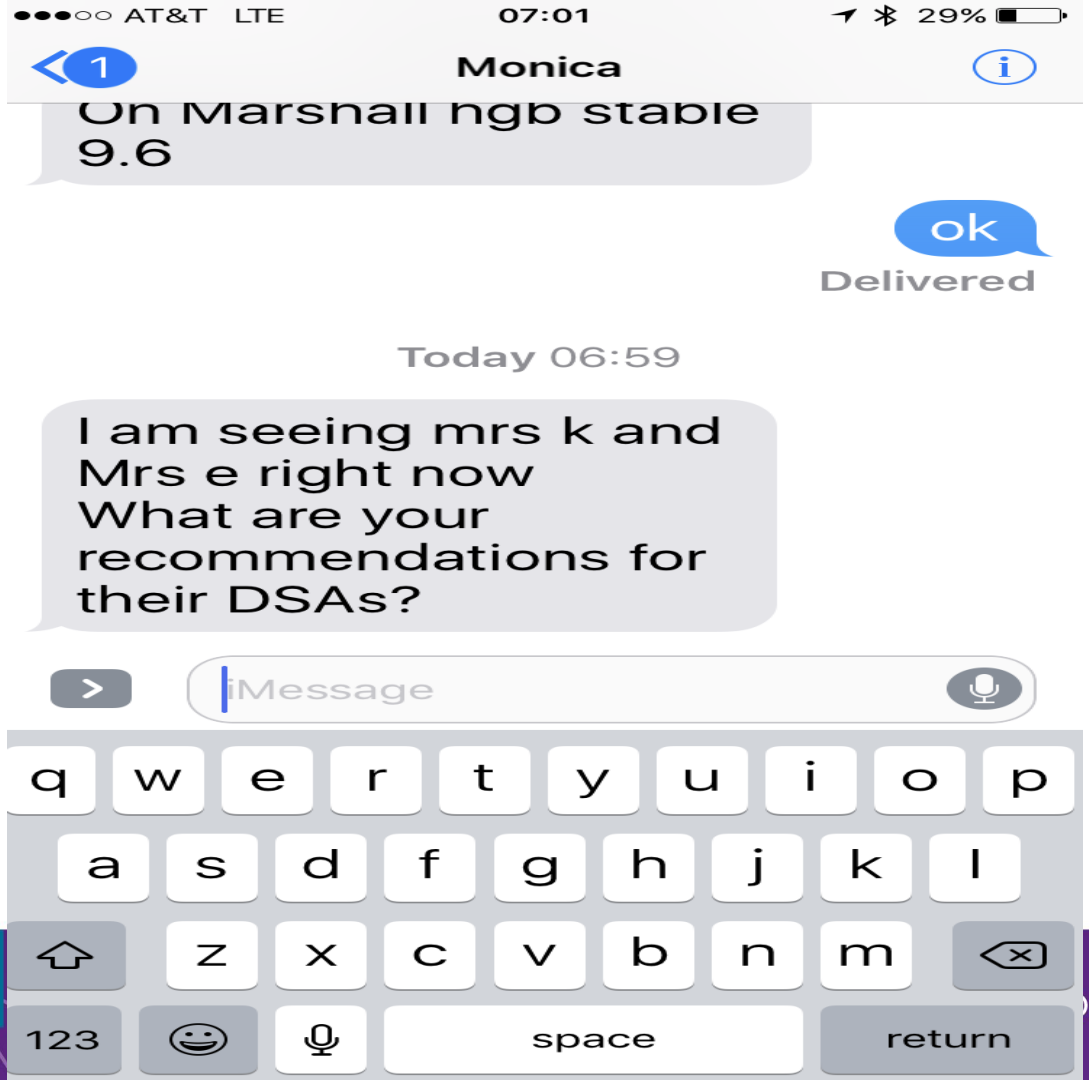
Tinkanen AJRCCM 2016 194L 5



Lobo 2013 JHLT 32: 70



Barhat Ann Thorac Surg 2010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Monica
On Marshall hgb stable 9.6
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Today 06:59
I am seeing mrs k and Mrs e right now What are your recommendations for their DSAs?
iMessage
q w e r t y u i o p
a s d f g h j k l
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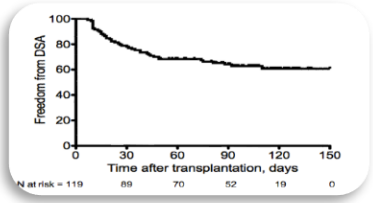
These studies provide evidence establishing a relationship between DSA and outcomes post transplantation.



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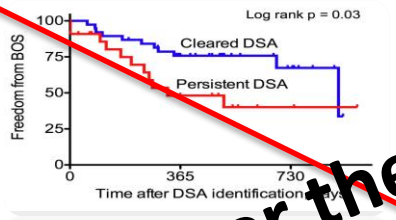

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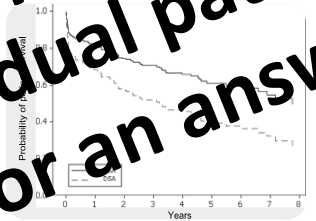
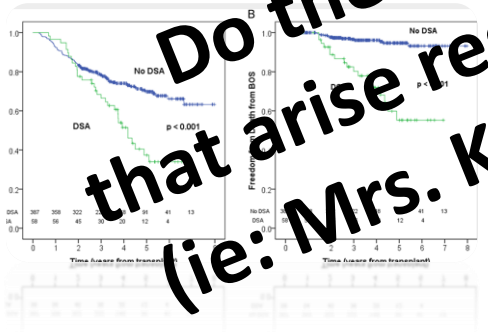
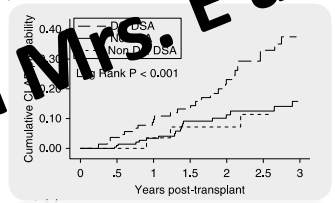


Safavi JHLT 2014;33:1273–1281

Do these answer the daily clinical questions that arise regarding DSA in our individual patients? (ie: Mrs. K and Mrs. E are waiting for an answer)





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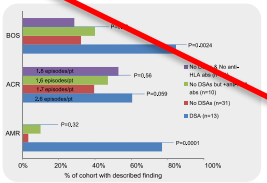

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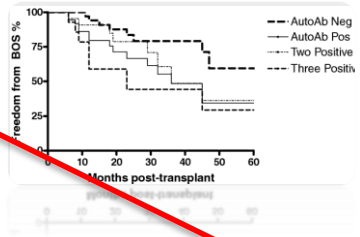
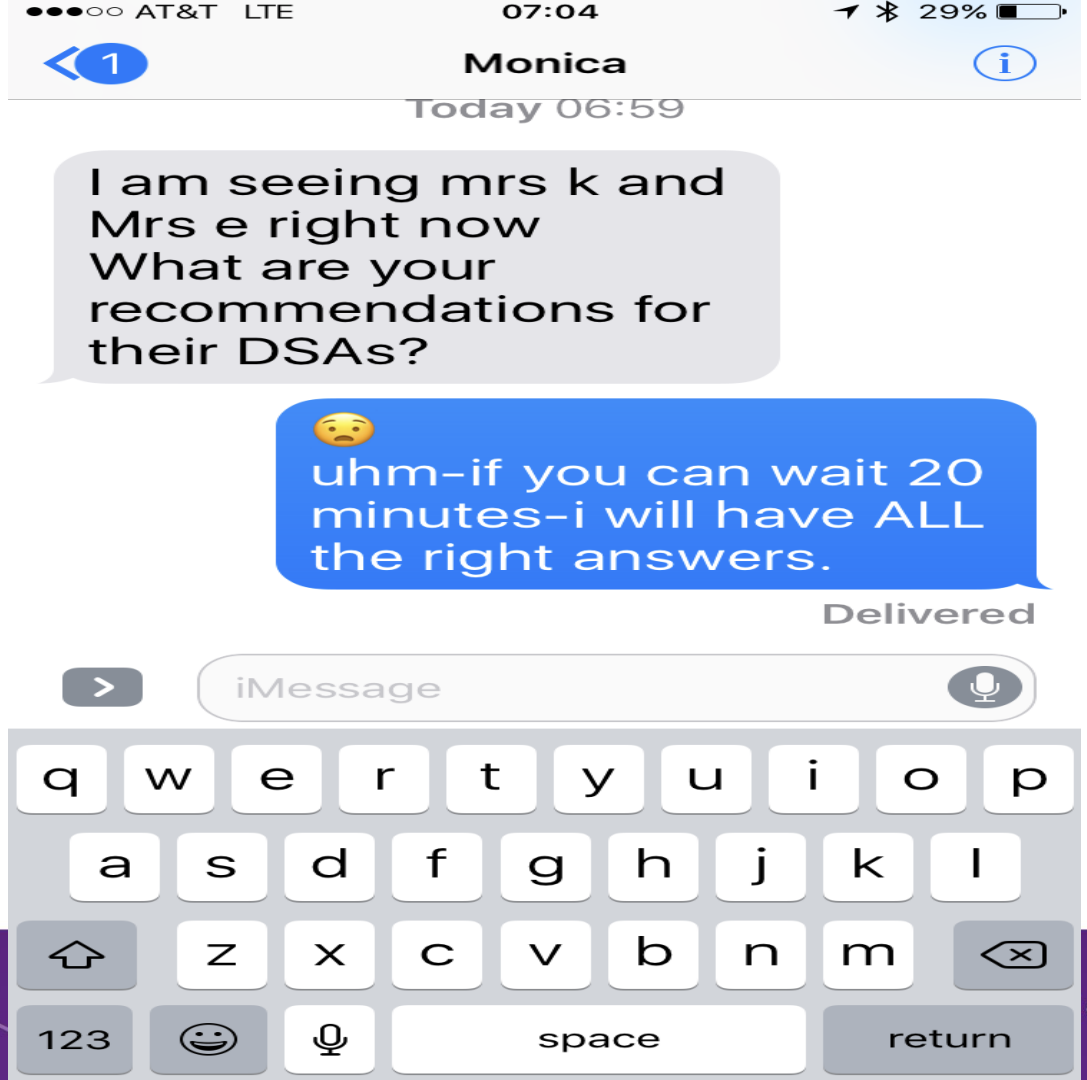


Morrel JHLT 33, No 12, December 2014

Barhat Ann Thorac Surg 2010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Monica
Today 06:59
I am seeing mrs k and Mrs e right now What are your recommendations for their DSAs?
uhm-if you can wait 20 minutes-i will have ALL the right answers.
Delivered
iMessage
q w e r t y u i o p
a s d f g h j k l
z x c v b n m
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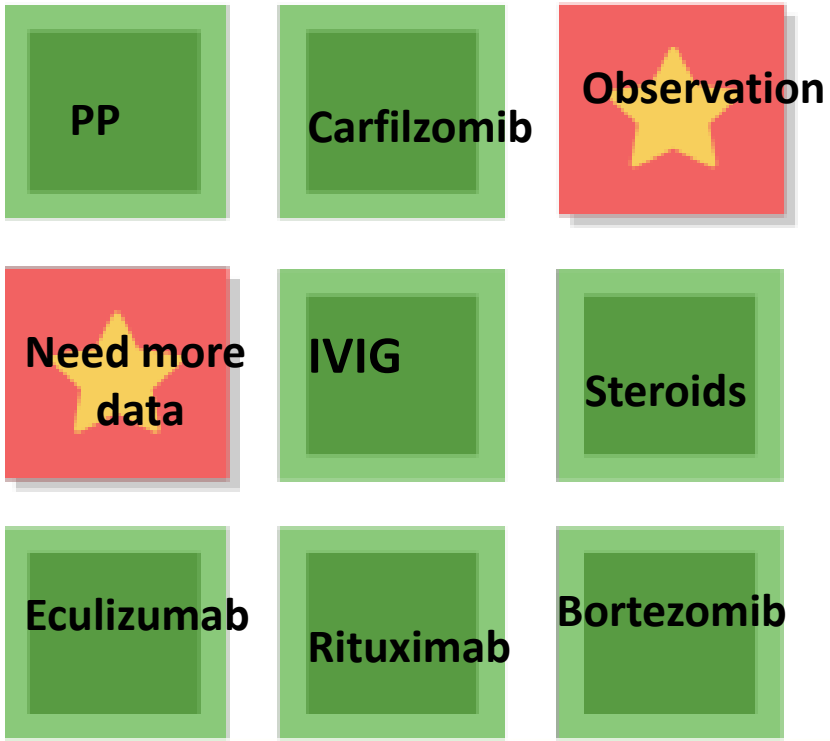
return

In 20 minutes, you *will not* have all the right answers for when to use which of these therapies for DSA and on whom…



Or what to definitively use for each DSA scenario you come across…

DSA is Class I versus Class II?

DSA is De Novo?

DSA is persistent

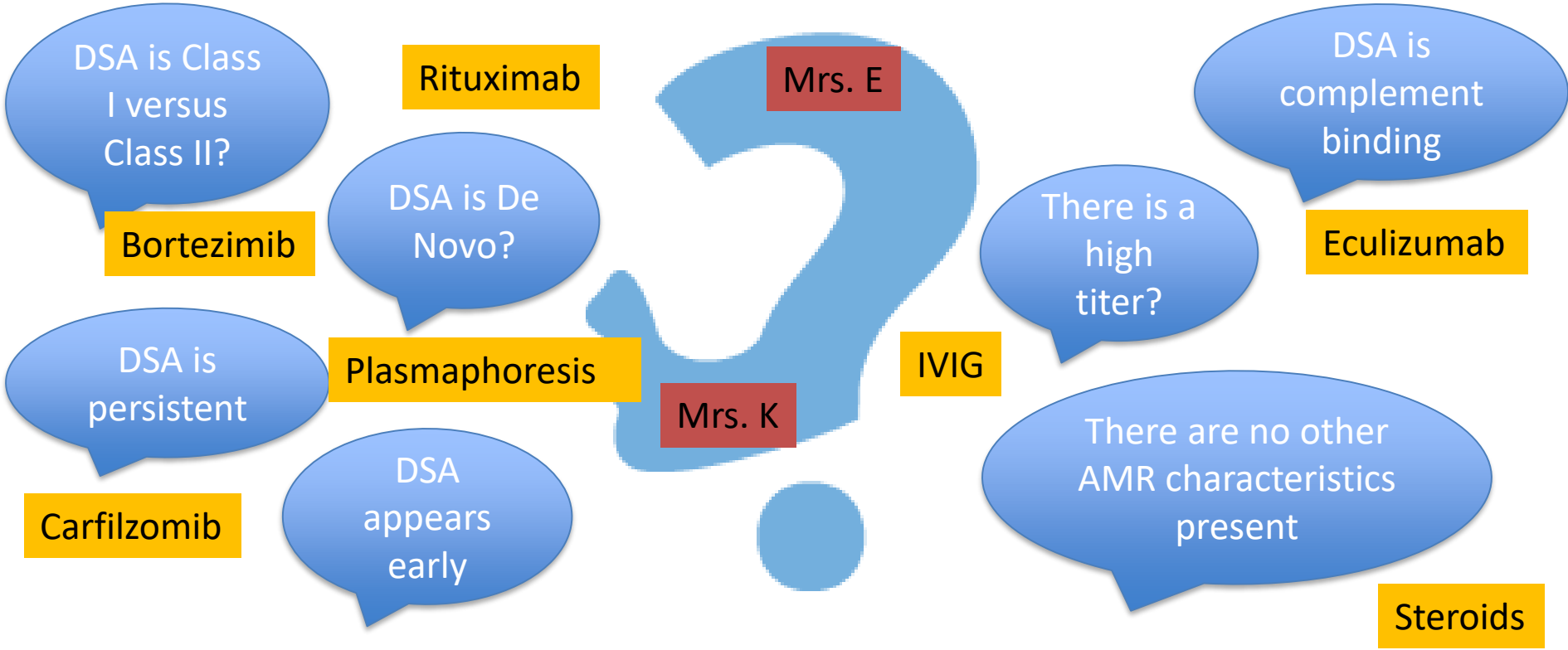
DSA appears early

DSA is complement binding

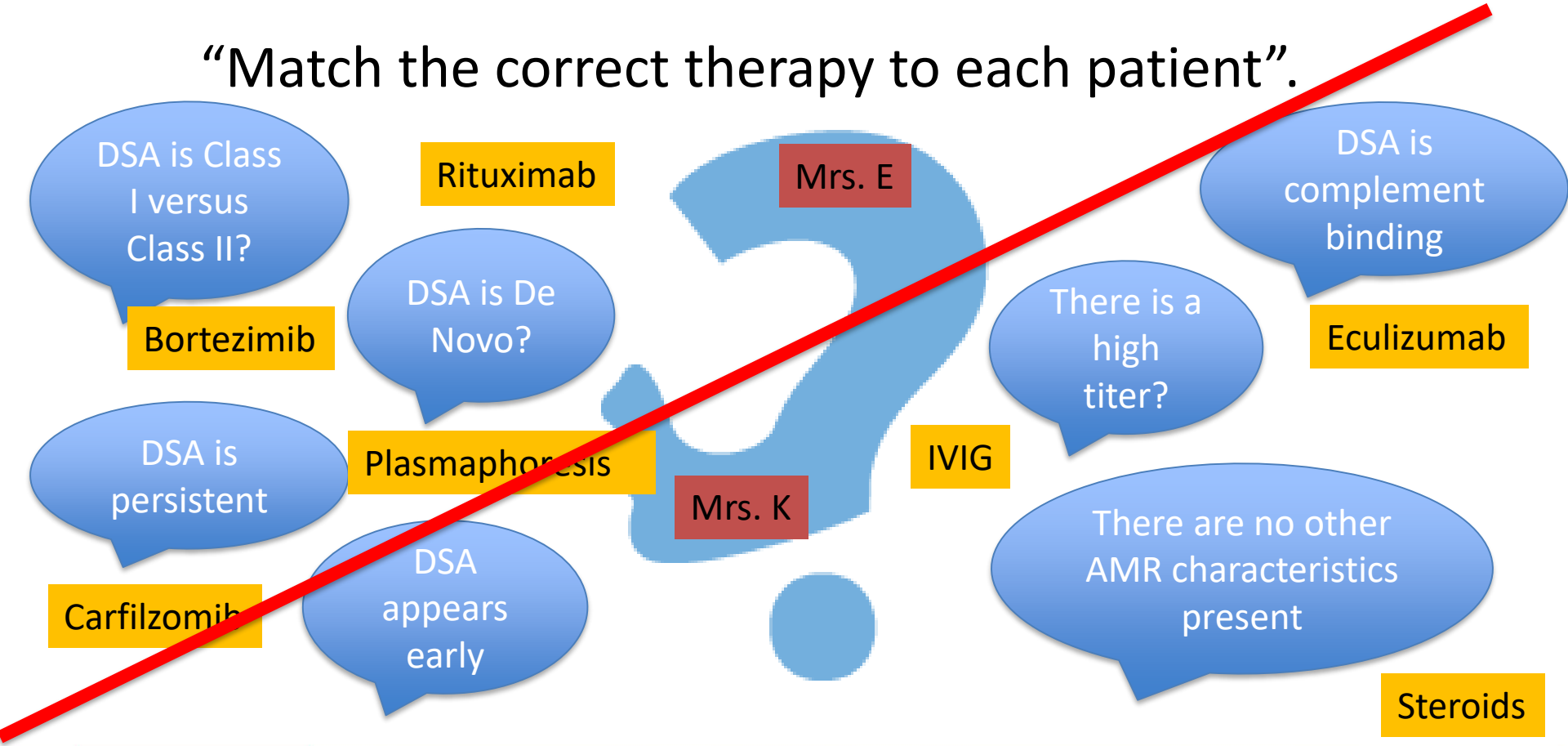
There is a high titer?

There are no other AMR characteristics present

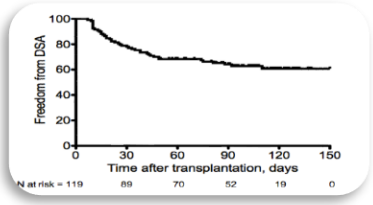
“Match the correct therapy to each patient”.



“Match the correct therapy to each patient”.



These results show us that DSA's can lead to graft dysfunction, AMR, CLAD and decreased survival… but what they *don't* show...



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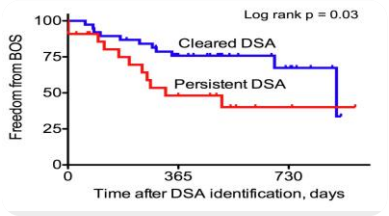

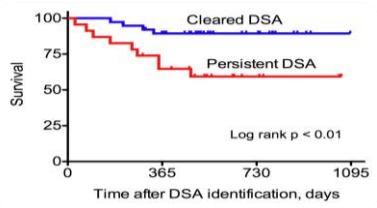

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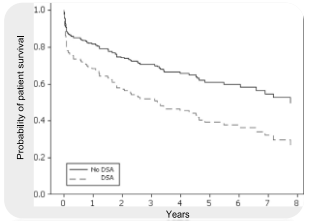

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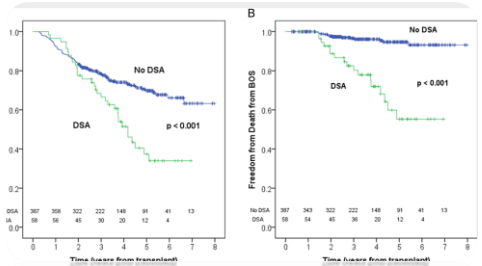

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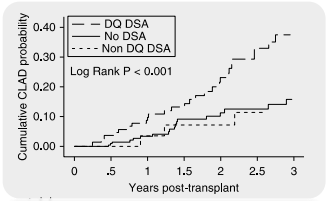
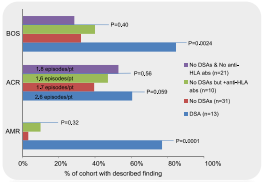


Tinkanen AJRCCM 2016 194L 5



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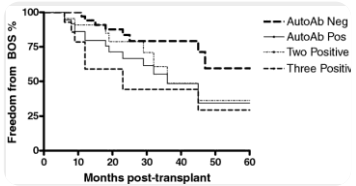
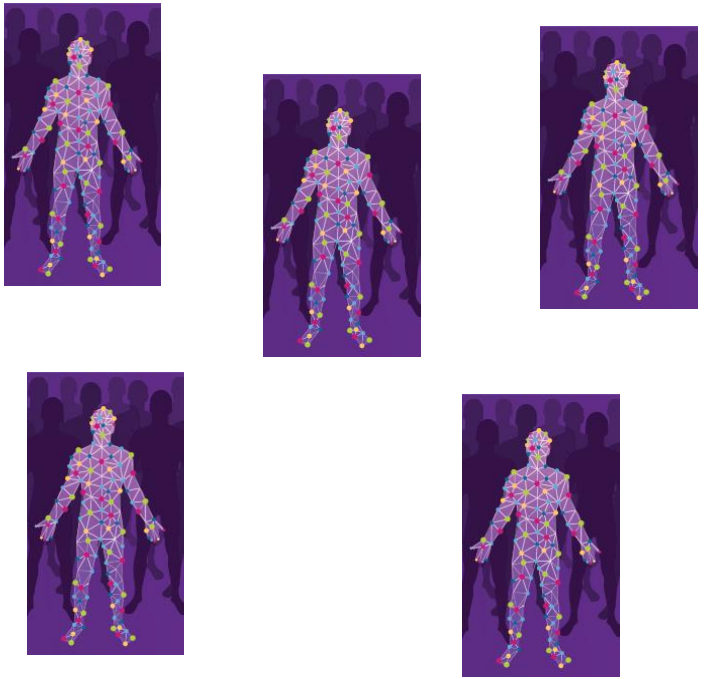


Barhat Ann Thorac Surg 2010

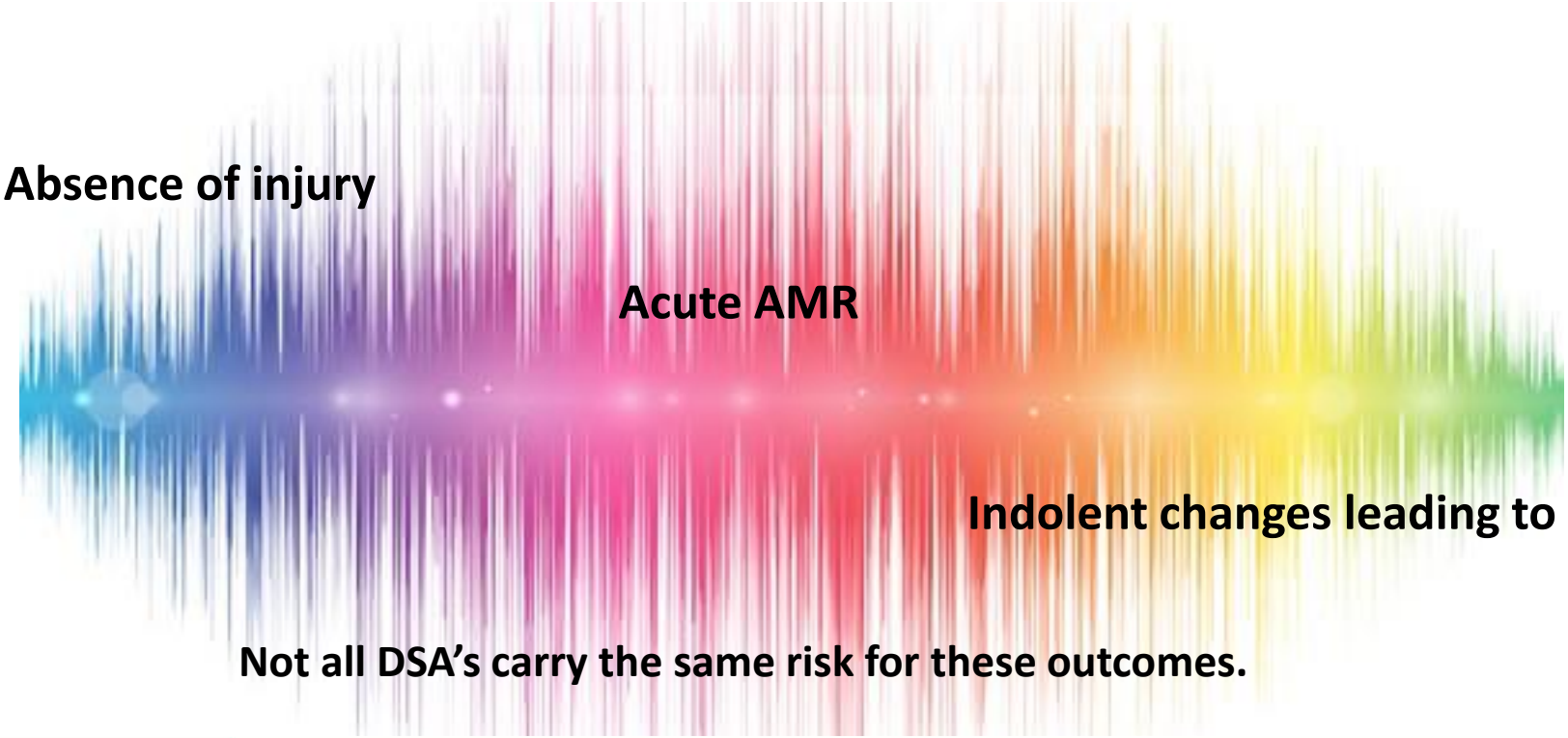
… is which patient with a specific DSA will benefit from a particular therapy

One-size fits all



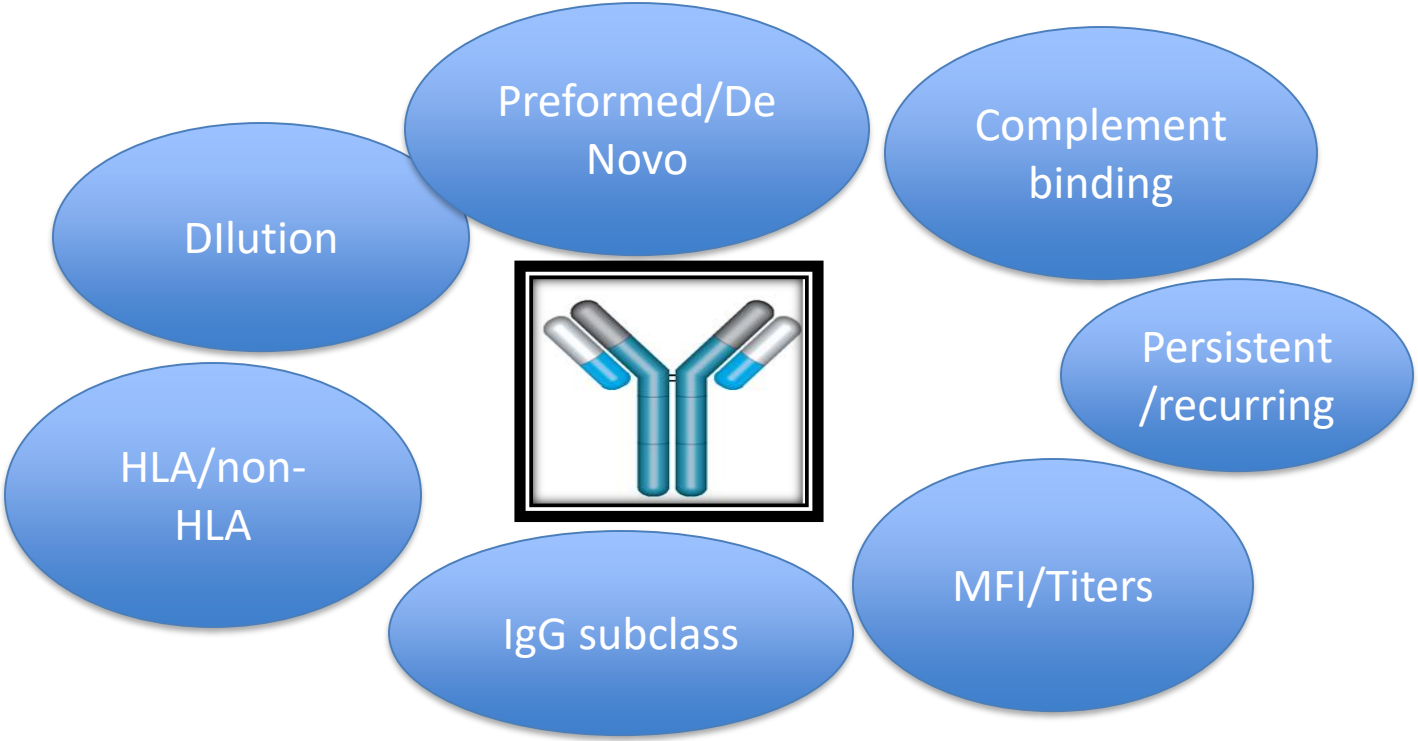
Personalized therapies tailored to individual characteristics

DSA associated with a wide spectrum of effects on allograft.



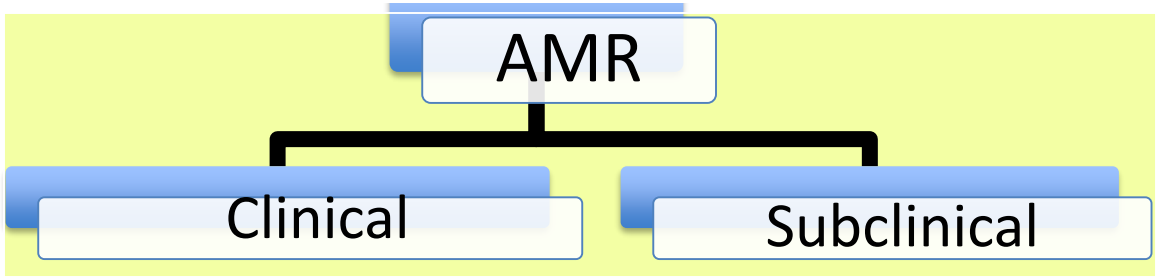
Not all DSA's carry the same risk for these outcomes.

What characteristics of DSA's should we look for when evaluating for treatment? Do these studies provide this?



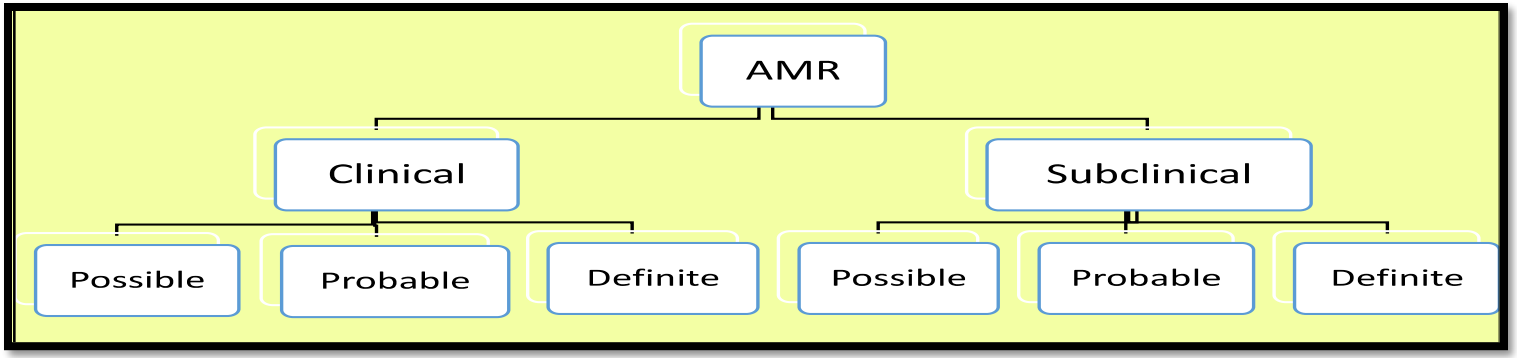
2016 ISHLT consensus focuses on DSA as an integral characteristic when defining AMR…

Measurable graft dysfunction

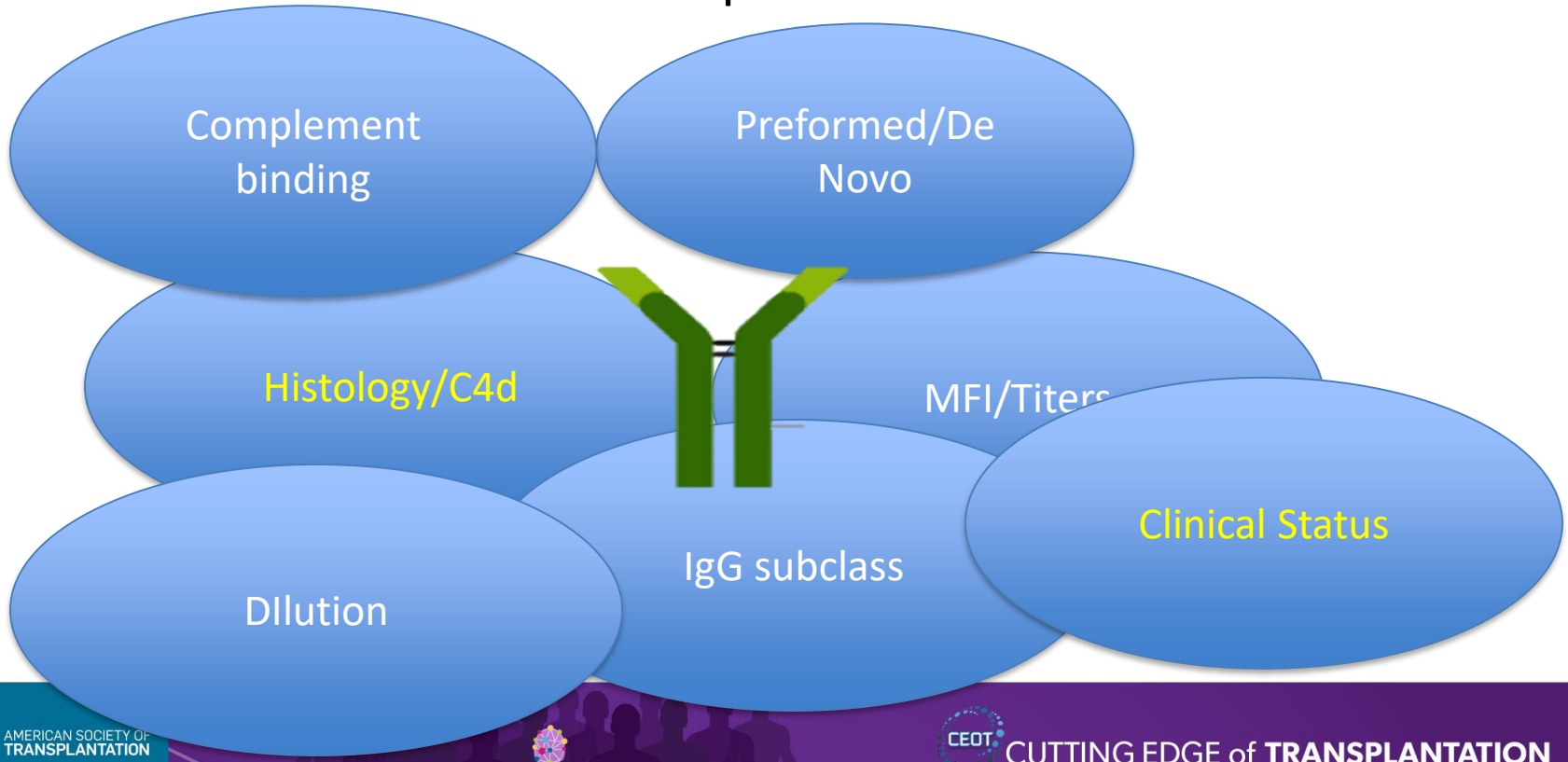


No graft dysfunction

Degree of Certainty

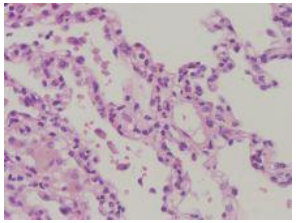


Each DSA is unique, each patient is unique, each situation is unique



Do we have the tools we need to identify individual patients with DSA who may be at higher risk for AMR, CLAD and decreased survival?

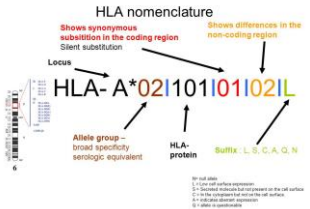
Patient



Pathology

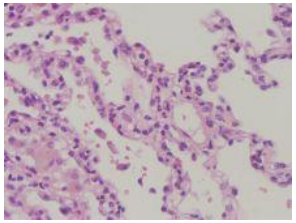
What we use now:
Useful clinical tools

HLA lab



Pulmonary function

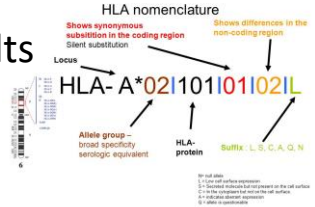
Low sensitivity
Low specificity



Sampling error
Poor reproducibility
Inter-observer variability
Experience dependent

All of these diagnostic tools have inherent issues

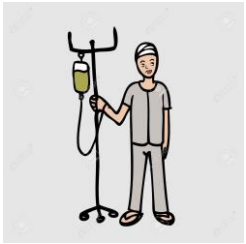
False positive
False negative
Discordant results
Specificity



HLA lab

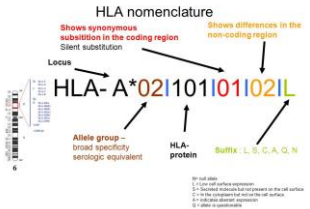
No definite thresholds
Variability
Low prognostic capacity
Other etiologic factors

Patient



Sometimes, elements of the work up is missing.

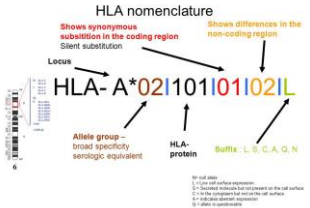
HLA lab



Pulmonary Function

Patient

HLA lab



Sometimes, only the DSA is positive.

	Histology	C4D	DSA
Definite	+	+	+
Probable	+	-	+
Probable	-	+	+
Probable	+	+	-
Possible	+	-	-
Possible	-	+	-
Possible	-	-	+

Challenges in DSA lab assessment

Challenges	Interpretations
False positive result	Clinically irrelevant HLA-ab to denatured antigens Nonspecific binding of IgG (ie: following therapy with IVIg)
False low MFI or negative results	Inhibition of SAB assay due to intrinsic and extrinsic factors Lack of donor antigen in the Luminex bead assay
Discordant results between SAB-MFI and reactivity using cellular targets	False low MFI: DSA to a shared target present on multiple beads
Assessment of DSA specificity	Incorrect assignment when donor allele is missing
AMR features without serum HLA DSA	Presence of non-IgG DSA of non-HLA Ab of DSA against a non-typed HLA gene or DSA against an HLA allele not represtned in the SAB assay

Roux Am J Transplant. 2018;1–11.

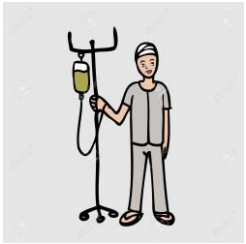
Limitations of our current knowledge may lead to opportunity…

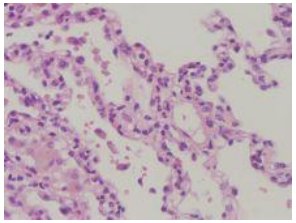
- Reflect the need for additional diagnostics then is provided by our conventional histologic, serologic and functional work up. (ie: be addressed by newer techniques)

- Reflect the need for better use of our current techniques (ie: closer and more standardized monitoring, increasing the sensitivity and specificity of our present analyses).

- May be a combination of both…. (ie: molecular profiling added to new histologic findings or cfDNA added during close monitoring of pulmonary function).

Patient

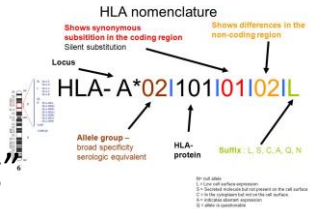




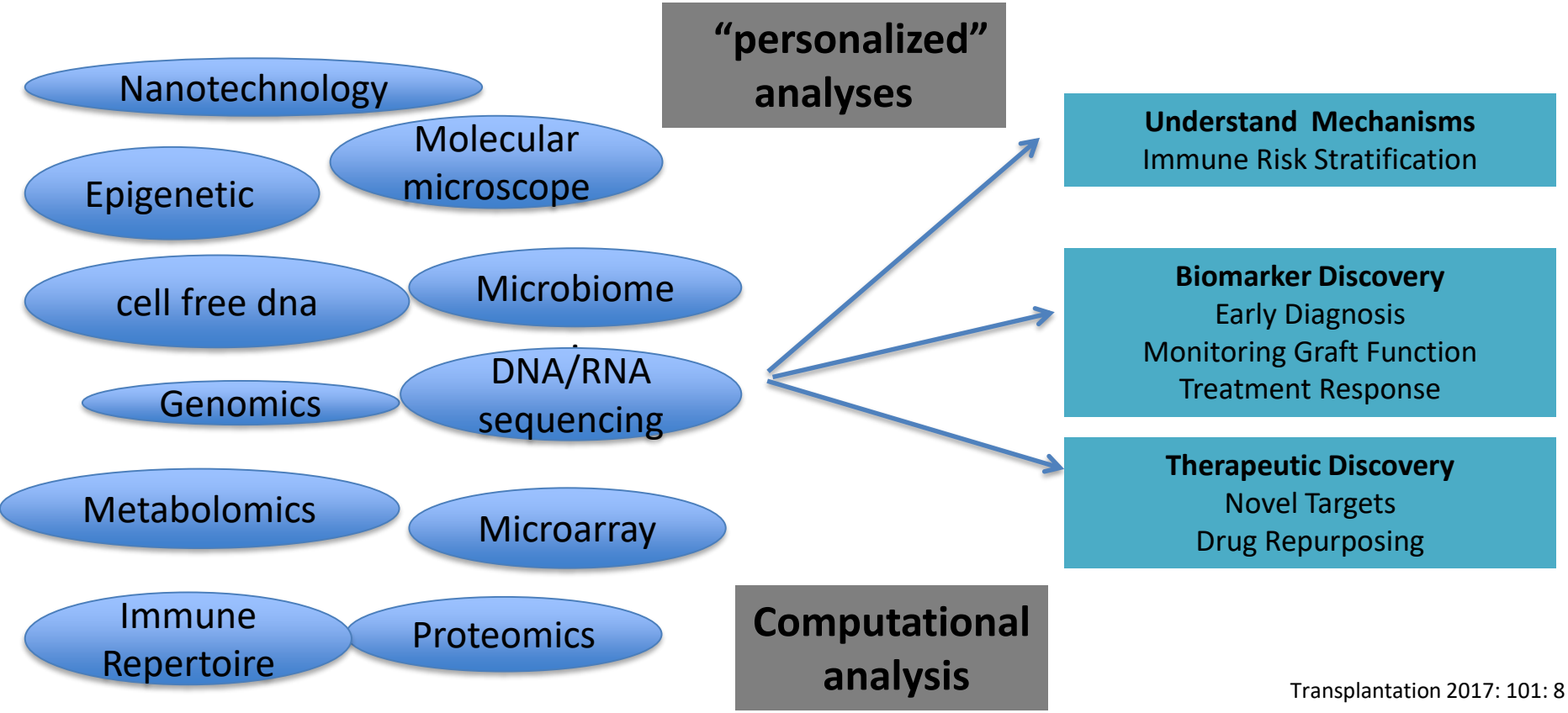
Pathology
“alveolar septal widening”

Tools we use now
How we use them
May not be enough to guide individualized therapy

HLA lab
“eplet
Matching”



Pulmonary function



Transplantation 2017: 101: 8

Maybe with these combinations we could *objectively* and *confidently* assess the risks of each patient with DSA.

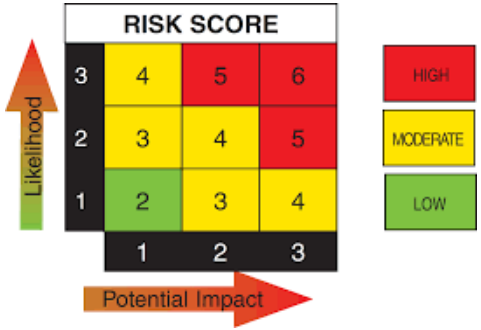
Treat those who would benefit from therapy and hold on therapy on those who would not.

How do we get there?

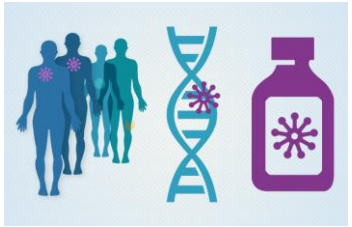
Data, lots of data

Database

Risk analysis



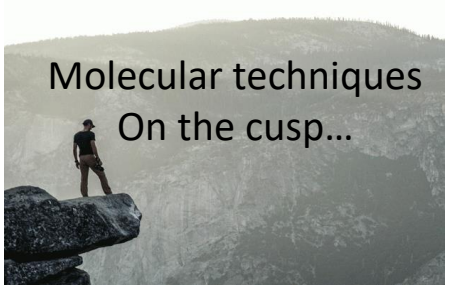
Individualized therapy



Implementation of a large-scale diagnostic registry is crucial to identify and develop risk characteristics and eventually lead to successful precision therapy..

1. Data collection

- Current and novel data points.
- Amalgamation of clinical, historical, behavioral, functional and genetic data important in risk stratification.
- Prospective data collection with *serial* measurements.



180 - Molecular Diagnosis of Rejection Phenotypes in Lung Transplant Biopsies: Initial Findings of the INTERLUNG Study

Clin Transplant 2016: 30: 295–305 DOI: 10.1111/ctr.12689

Clinical Transplantation

Multiplexed color-coded probe-based gene expression assessment for clinical molecular diagnostics in formalin-fixed paraffin-embedded human renal allograft tissue

ARTICLE IN PRESS

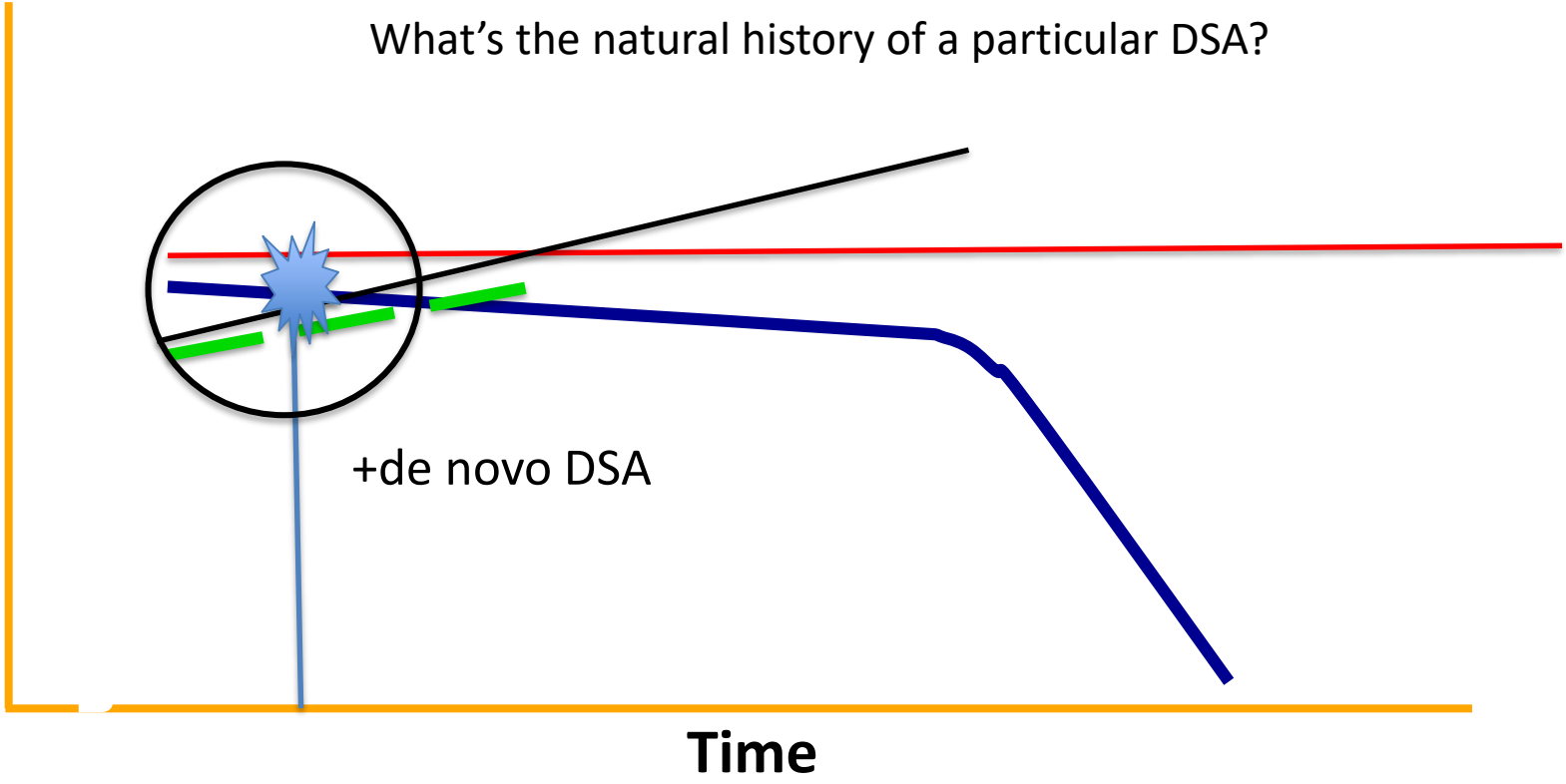
ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

ORIGINAL PRE-CLINICAL SCIENCE

Late manifestation of alloantibody-associated injury and clinical pulmonary antibody-mediated rejection: Evidence from cell-free DNA analysis

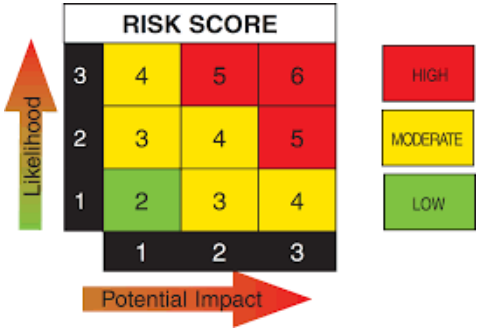
What's the natural history of a particular DSA?



Centralized multi-center registry

- Agree on a standardized diagnostic schedule for monitoring:
  - Frequency
  - Types of tests
  - Patients to test
  - Cost-benefit
  - Outcomes required to follow
- Determine the outcomes in a consistent manner
- ***Define DSA attributes that correlate with risk***
- ***Consider therapeutic options and post therapy follow up***

2. Risk Assessment is a continuous endeavor.



3. Individualized “precision” therapy: Not just h*ow* to treat but *who* to treat and when?

- **Who do we treat?**
  - Specific patients?
  - Specific antibodies?
  - Specific titers?
- **When do we treat?**
  - Asymptomatic or wait for symptoms?
- **How do we treat?**
  - Do we treat all antibodies the same?
  - How many courses/cycles of treatment is appropriate

What outcomes do we expect after “Successful treatment” of De Novo DSA?

- Antibody clearance (what is the definition?)*
- Antibody reduction (what constitutes success?)
  - Reduction of what? (MFI? Titer?)
  - How much of a reduction is necessary?
- Prevention of graft dysfunction?
- Prevention of AMR, CLAD?
- Survival?

Mrs. K. 56 yo

5 mo post transplant for IPF

- PFTs: Progressively improving since transplantation
- Clinical: stable, active
- Pneumonia at 3 mo Resolved.

ACR: A2B0 at 3 months. Resolved at next biopsy.

AMR: Path and C4d Negative

DSA: No pre-formed DSA. De Novo DSA at 3 month : DQ5 2900 MFI, DQ 6 4200

Mrs. E. 60 yo

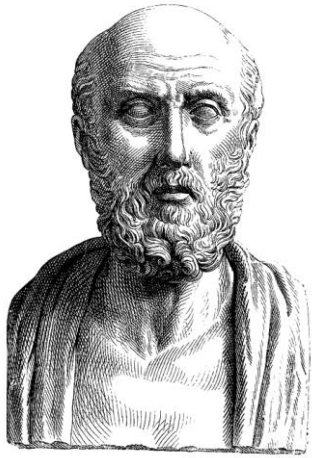
5 mo post transplant for IPF

- PFTs: 18% decline FEV1 last month
- Clinical: Worsening exercise tolerance
- No infection
- **ACR:** Negative for 4 months.
- **AMR**: Negative C4d. Mild chronic interstitial thickening.

DSA: No pre-formed DSA. De Novo DSA at 3 month:DQ5 2400 MFI, DQ 6 3200

"It is far more important to know what sort of person the disease has, than what sort of disease the person has."

Hippocrates



"It is far more important to know what sort of person the disease has, than what sort of disease the person has."

Thank you!
Any questions?

Email: Levinedj@uthscsa.edu

R.Y. Caine, *Tribute to the Organ Donor—The Real Hero of Transplantation*, 2000.