Pre-transplant TCR Network Topology Predicts Kidney Allograft Rejection

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More Info at Poster #51 Session 1

Disclosures

Worked
- Santa Ana Bio
- Omniscope

Consulted
- Epana Bio
- Starling Bio
- Columbus Instruments

Stock
- Epana Bio

Sold Software
- Columbus Instruments

None related to the topics in this presentation

Solid Organ Transplantation

Definitive modality for care in end-stage organ failure (kidney, liver, heart, lung, pancreas).

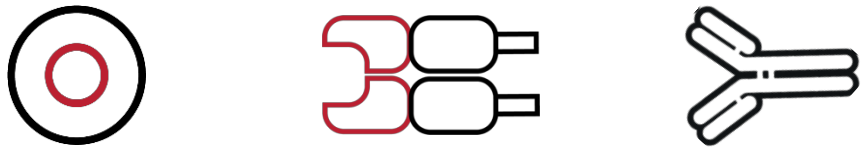
Cost of Immunosuppression $2-2.5 Billion

Incidence

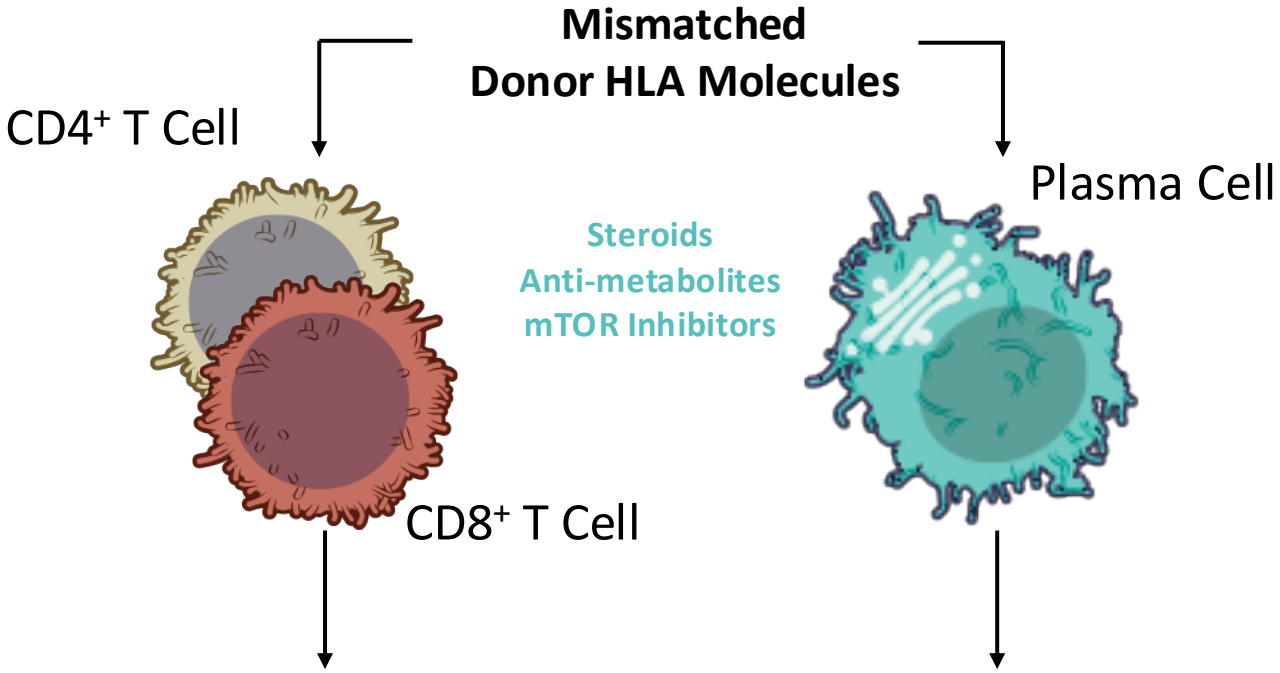
Globally	150,000
United States	50,000 (65% kidney)
WashU	350 Renal | 50 Liver | 50 Lung

What Does "Matching" Mean?

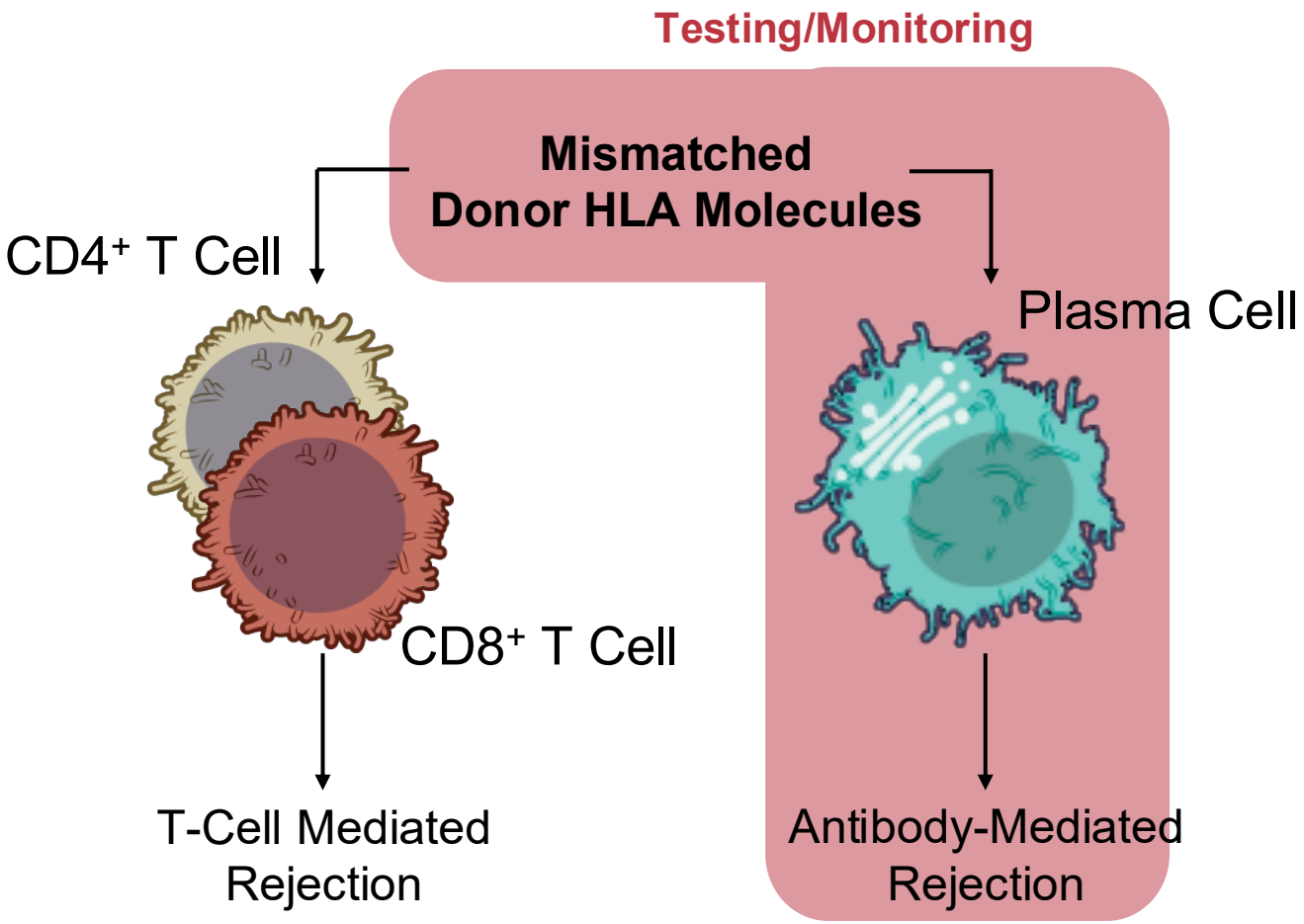
ABO compatibility **HLA typing** **Serological Reactivity**



Pretransplant Risk Stratification



The Clinical Blind Spot



10-15%

ACUTE REJECTION RATE

Rejection occurs in year one despite rigorous HLA matching.

0

ROUTINE T-CELL SCREENING

Routine pre-transplant T cell assessment in current practice

TCR Primer: Measuring the Immune Army

What are TCRs?

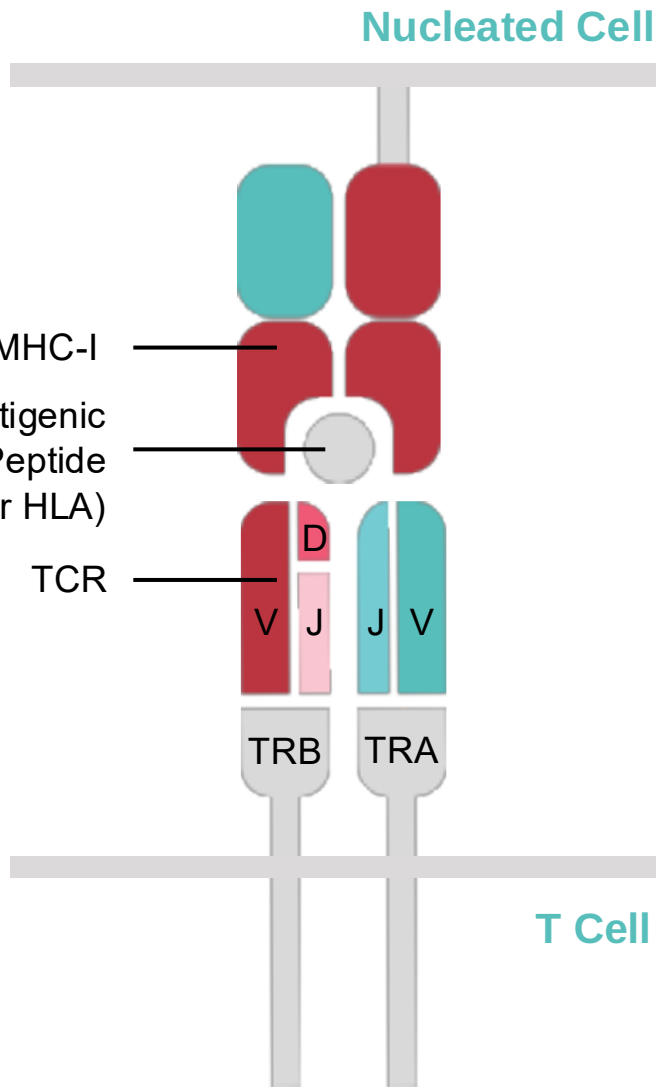
T-Cell Receptors (TCRs) are molecular keys on the surface of T-cells that recognize specific "targets" or antigens.

The Repertoire

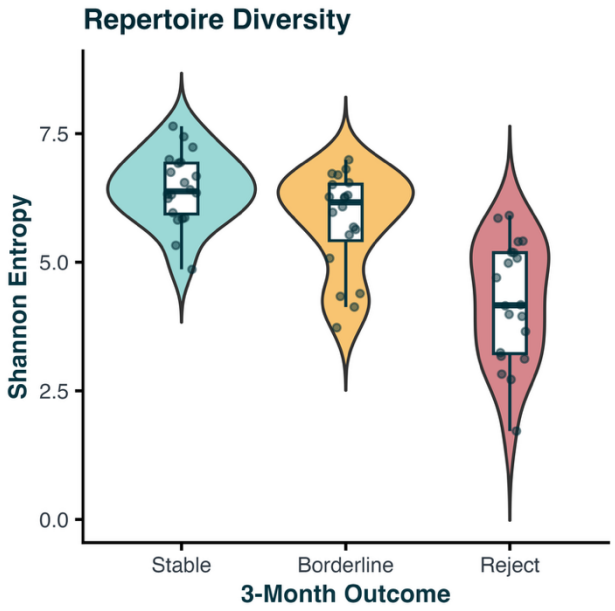
A "repertoire" is the massive collection of diverse T-cells in a patient. We can sequence these to get a fingerprint of the immune state.

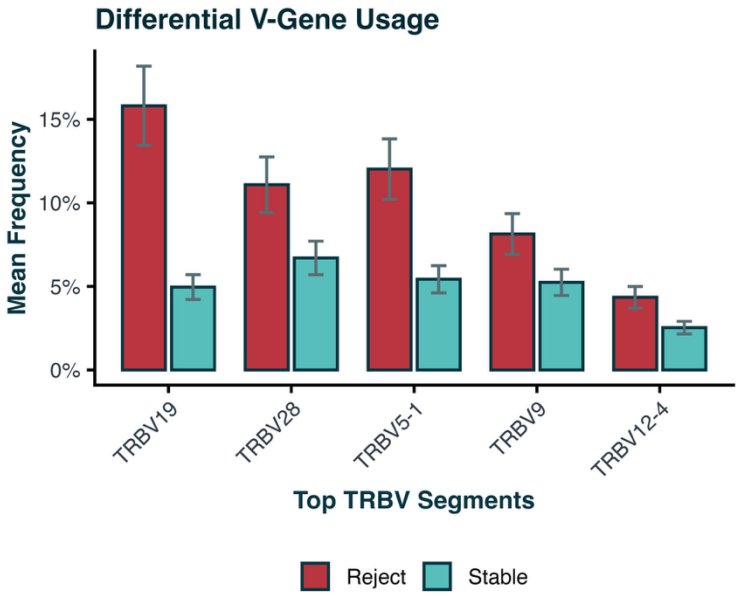
Hypothesis

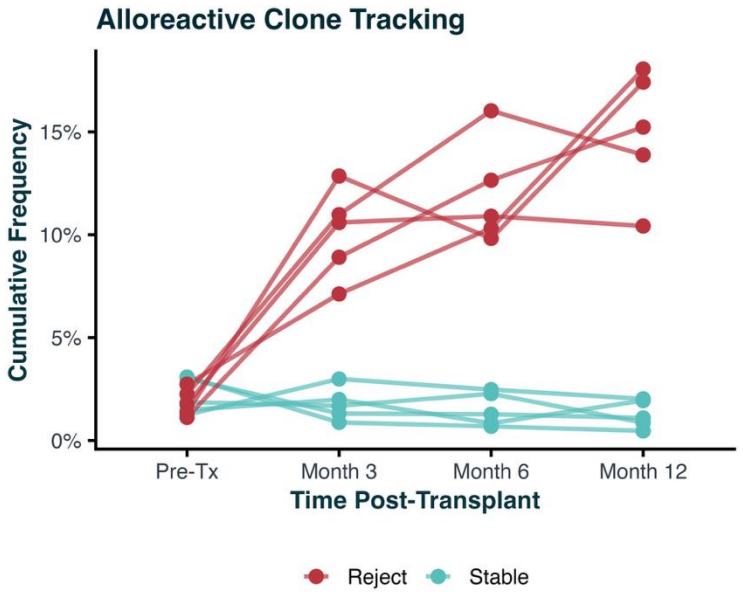
TCR repertoire architecture encodes functional risk of solid organ rejection.



Why Current Approaches Struggle





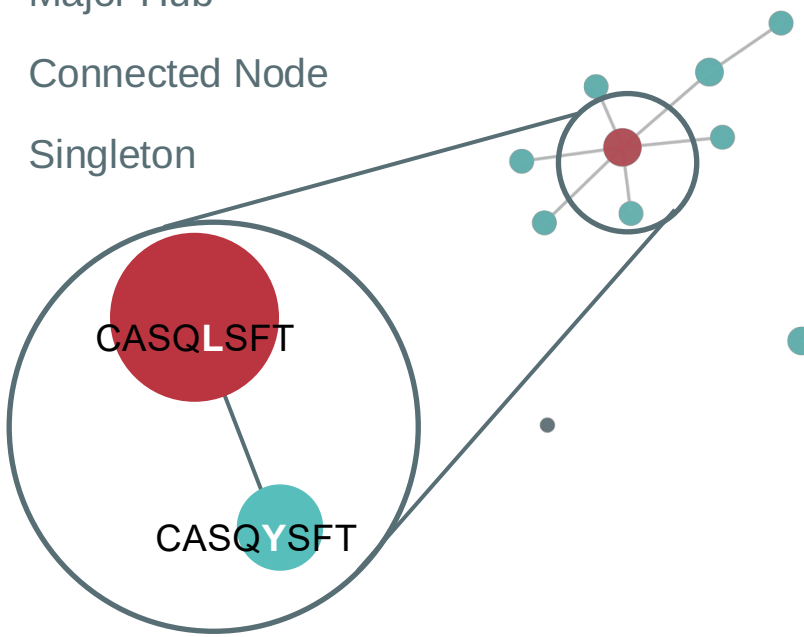


Measures	Total repertoire variety (clonality)	Frequency of gene segment usage	Individual alloreactive clones
Limitations	Compresses complex data into one number; ignores relationships.	Coarse signal; often vanishes post-transplant.	Requires multi-day culture; not scalable for pre-op clinics.

Repertoires as Social Networks

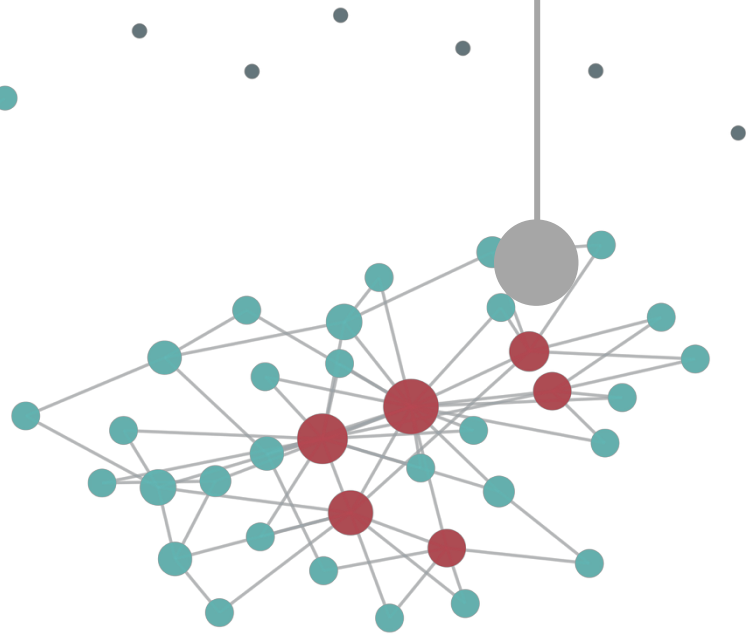
Nodes = Clone (TCR Amino Acid sequences).
Edges = Sequence similarity.

Major Hub
Connected Node
Singleton



Sequence Distance = 1

Extract Network Metrics



Degree = How many edges to a node

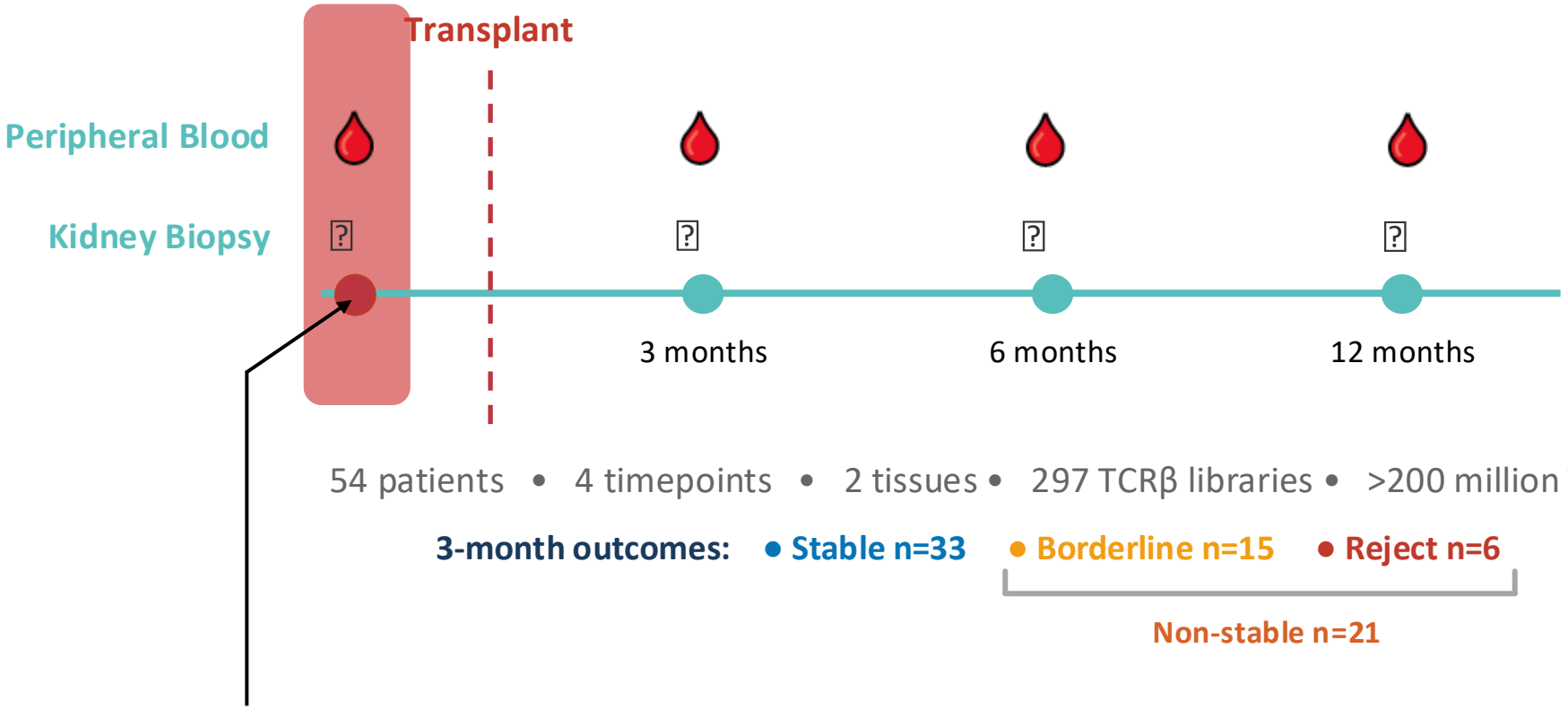
Strength = Sum of weights of all edges

Modularity = How easily a network can be divided into clusters

Degree Entropy = How random are the degrees across the network

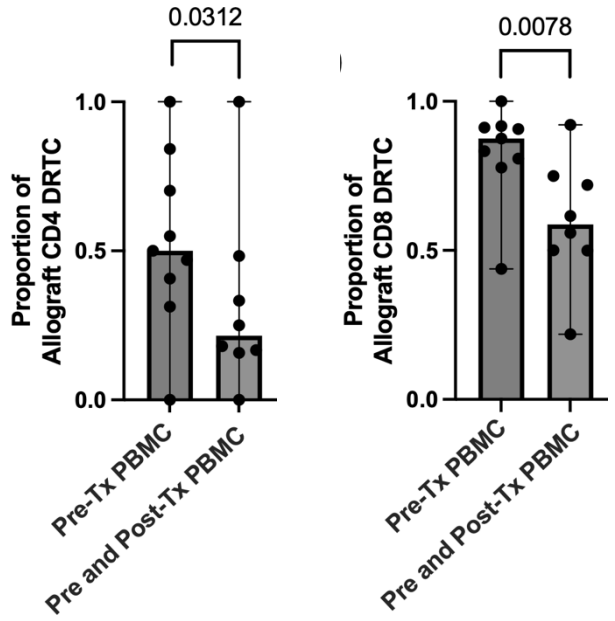
Number of Metrics = 30

Architectural Integrity Requires Data Foundation



CD4+ and CD8+ Mixed Lymphoid Reaction

Majority of Alloreactive T Cells are in the Blood Before Transplant

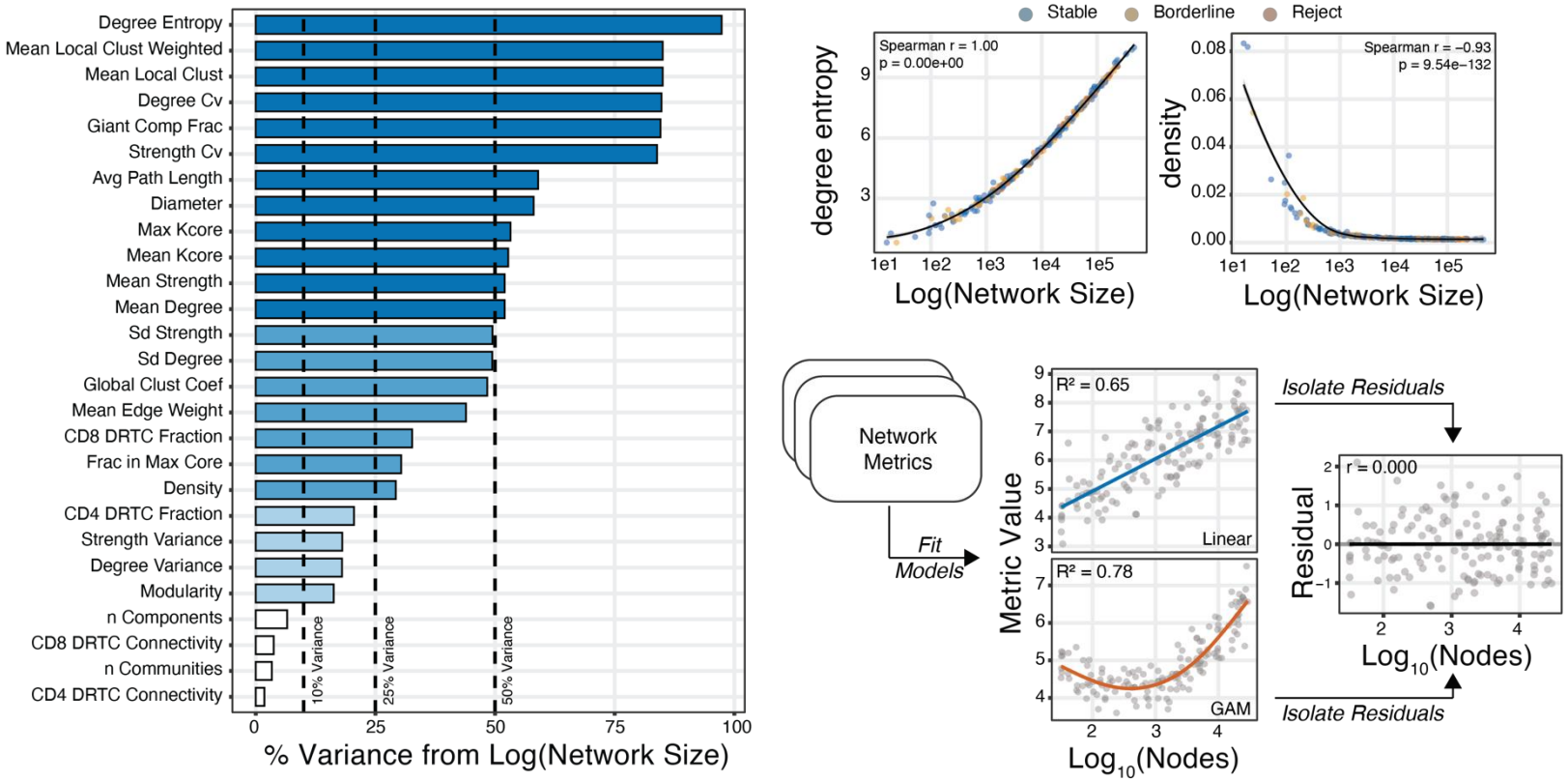


Do network topology metrics of the **pretransplant** immune repertoire significantly differentiate **stable versus unstable** graft outcomes?

Sanders et al 2025 PMID: 39981250

Network Size Confounds Network Metrics

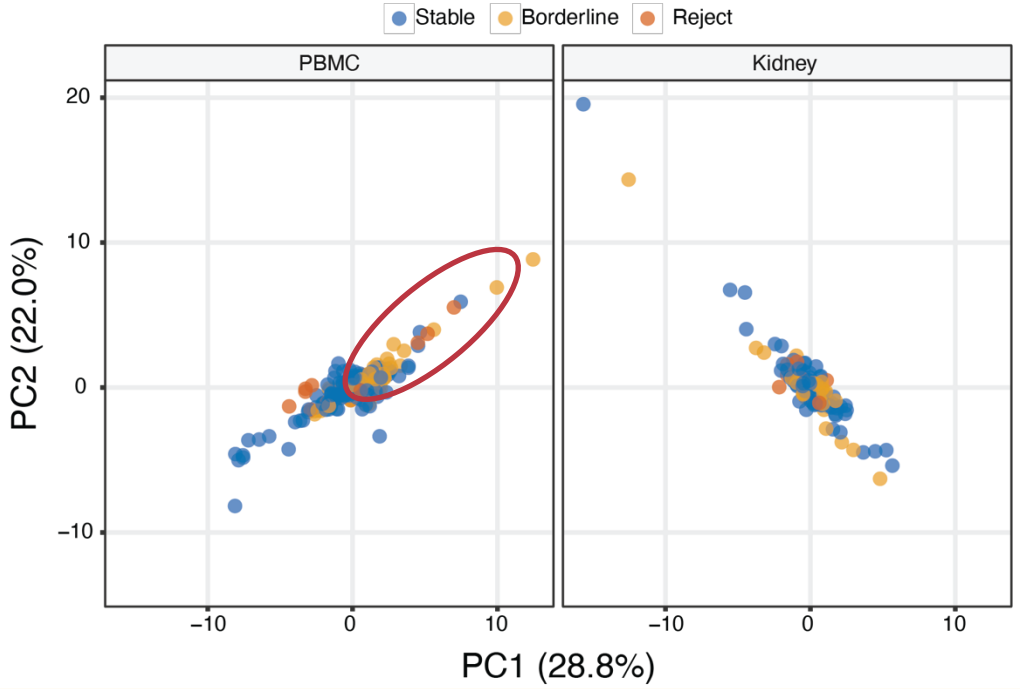
Residuals are size-adjust metrics, where networks are functioning above a baseline



Models built on uncorrected metrics will be **biased for the relative size of Non-stable patient**

Graft Outcomes Leave a Topological Fingerprint

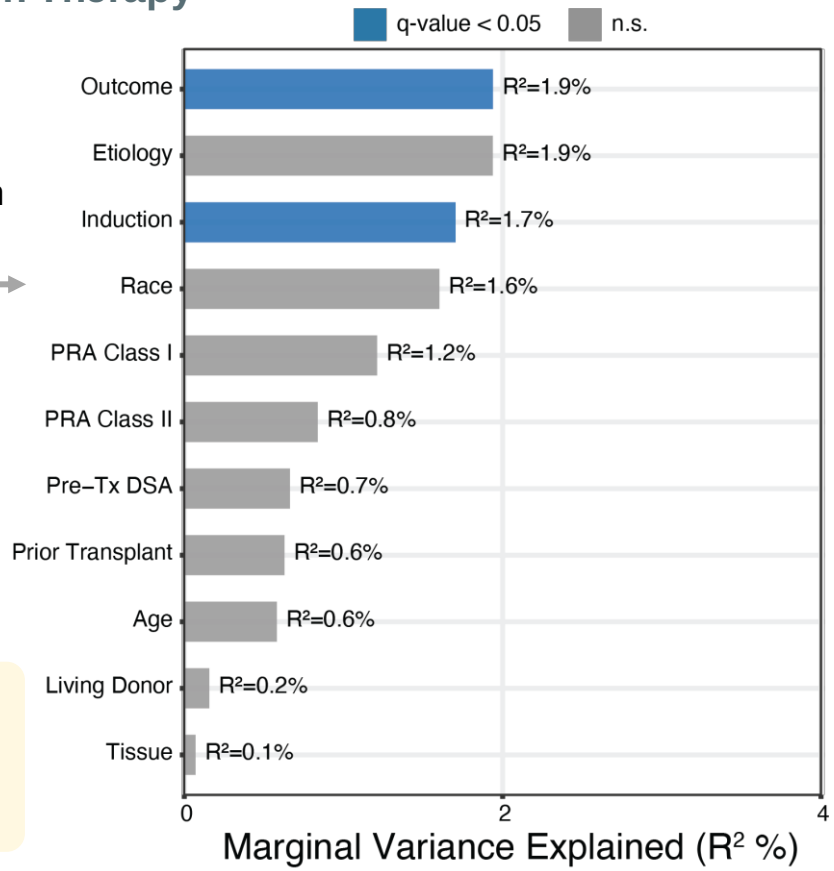
Pretransplant Samples



PCA Dimensions from Peripheral Blood

PERMANOVA

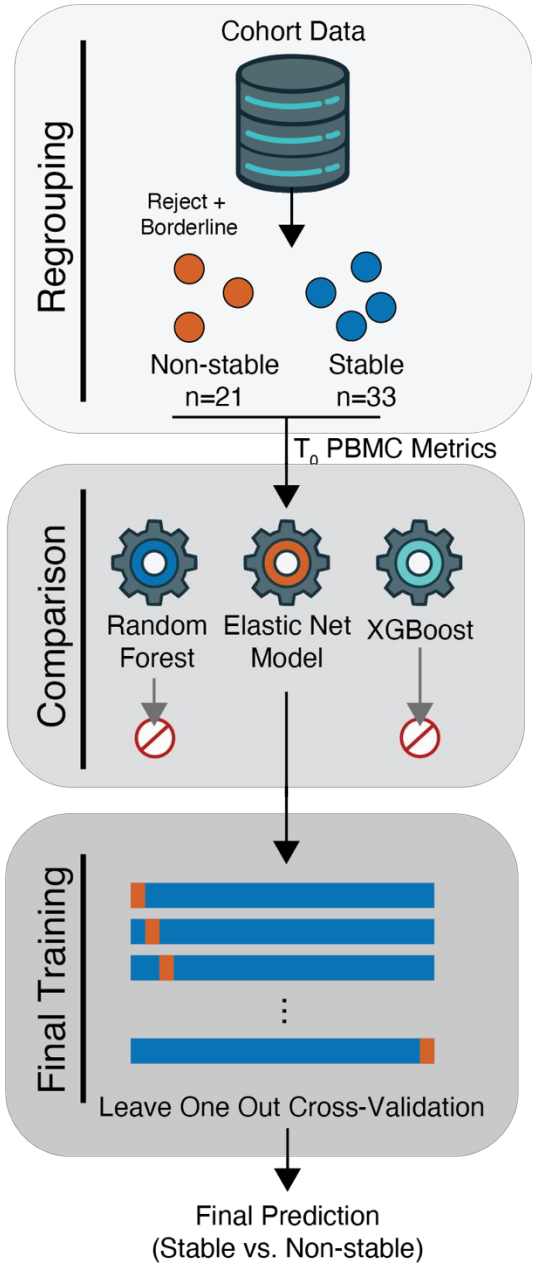
Network Topology of TCR associated with **Graft Outcome** and **Induction Therapy**

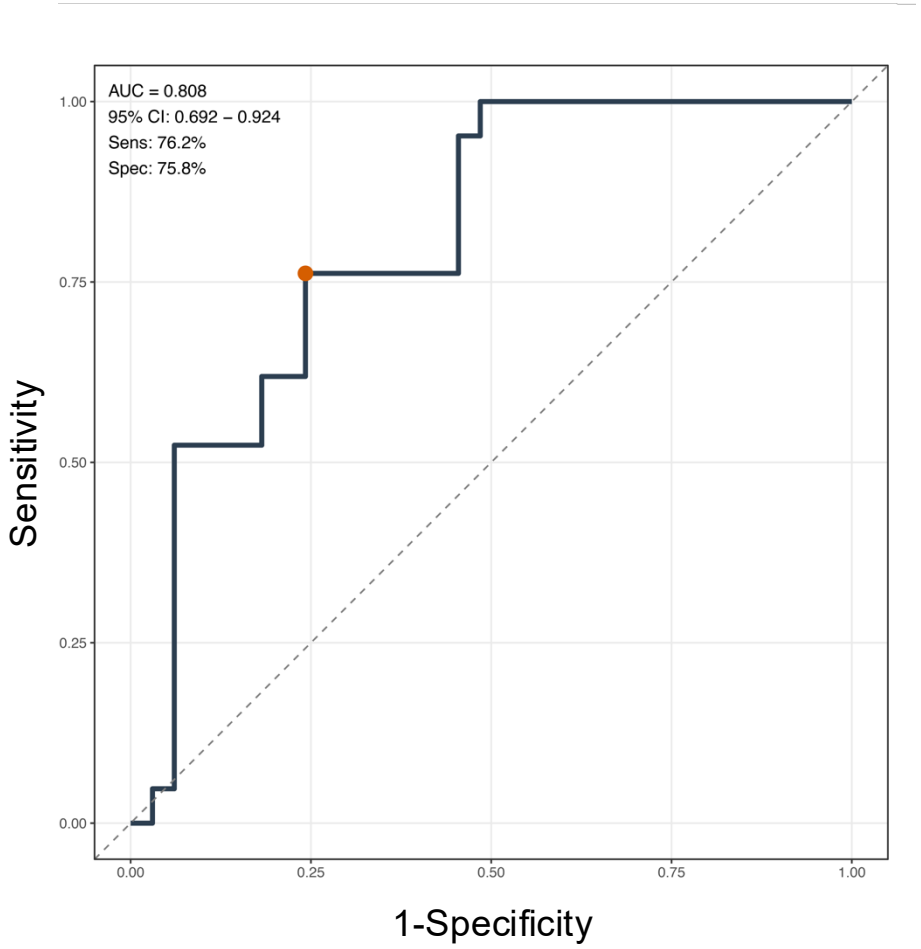


Non-stable patients have **higher PC1** = more fragmented, less connected networks

Signal Location: Found in PBMC (blood), not kidney tissue

Pretransplant Acute Rejection Prediction Model





0.81

PRE-TRANSPLANT AUC

Degree Entropy

Mean Degree

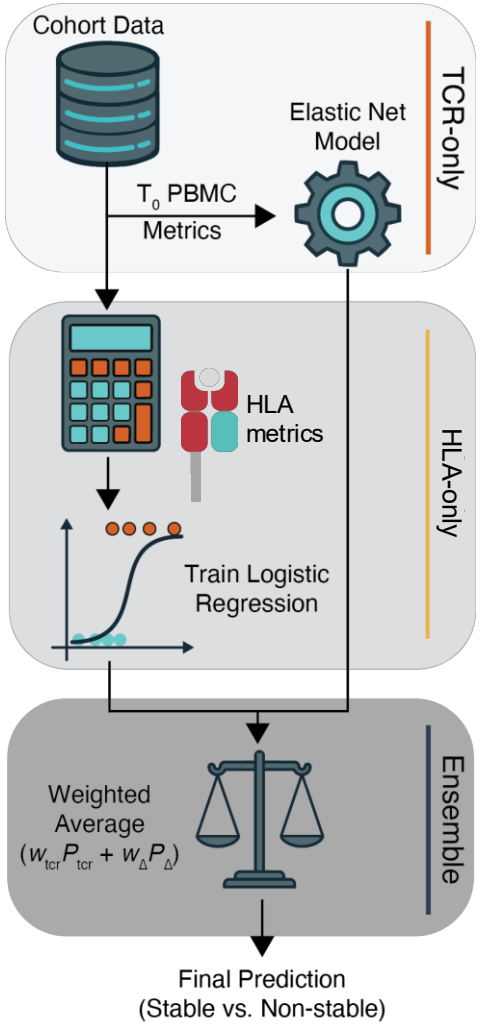
Mean K-Core

Mean Strength

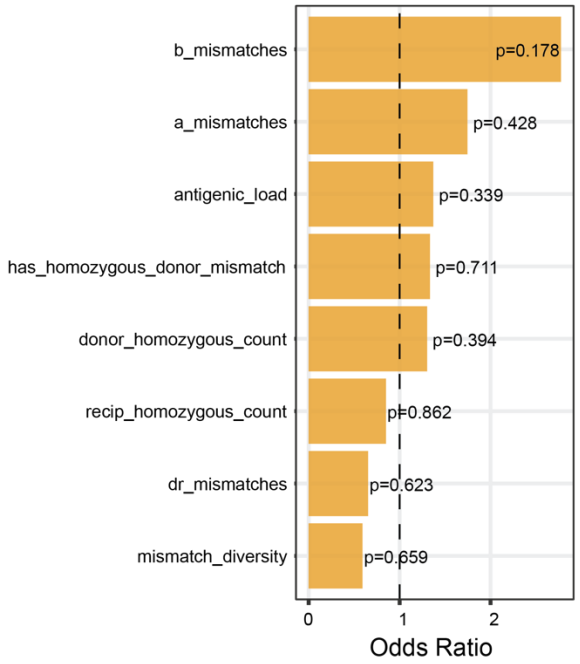
All Major Components of PC1

Events per variable (EPV) to limit overfitting

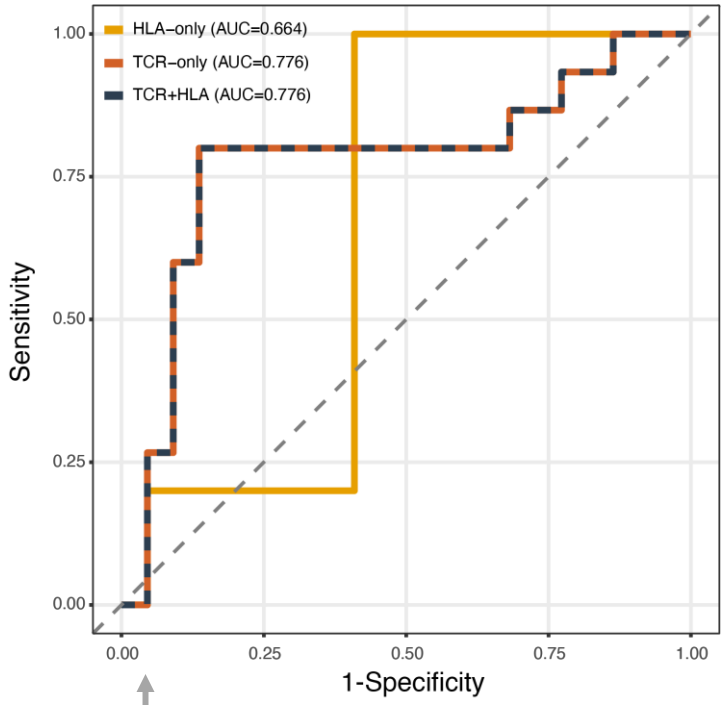
TCR Predictive Signal is Orthogonal to HLA Matching



No HLA Variable
Predicted Graft Outcome



Ensemble Model Set HLA-only
Model to W = 0



Major Caveat: HLA Typing information available for **37 of 54** patients

Three takeaways.

1

Network topology is a tractable, pre-operative readout.

A single blood draw, bulk TCRβ sequencing, no donor cells, no culture → AUC 0.81.

2

The signal is orthogonal to HLA.

It captures functional immune readiness, not donor–recipient genetic distance→ addresses a **clinical blind spot**.

3

Further Validation is needed

Single-center cohort, n = 54. External multi-center validation is the first required next step.

Cross-induction generalization is limited. Understand the biases associated with immunosuppression.

No phenotypic annotation per clone. Bulk TCRβ doesn't tell us if a network hub is memory, naive, regulatory, or effector.

Our Future Directions

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Questions?

Link for Preprint

Link for Code

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