

Noninvasive vs. Biopsy Surveillance of Rejection: The Heart Edition



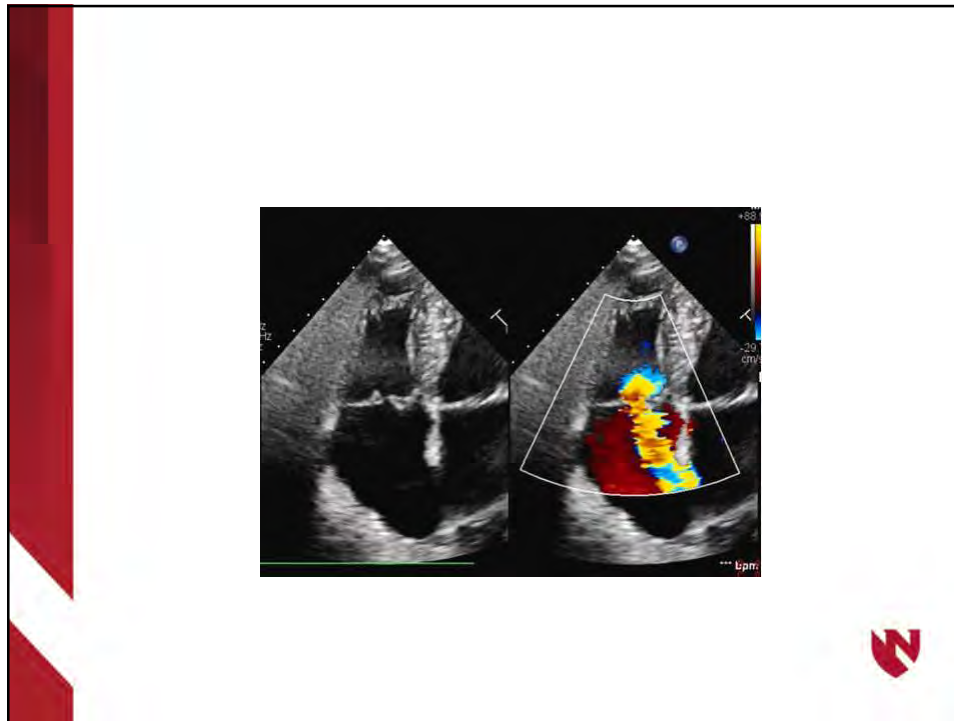
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Monitoring for Acute Rejection of Heart transplant

- **Historically monitoring was performed via frequent clinic visits with echocardiogram and routine scheduled endomyocardial biopsy. Biopsies were scheduled 11 times in the first year after heart transplantation.**
 - With recurrent biopsies rates of complications, particularly tricuspid regurgitation were increased
- **Tricuspid regurgitation occurs due to disruption of the tricuspid valve apparatus during biopsy.**
 - With increased number of biopsies performed, likelihood of obtaining sample of scar tissue is increased leading to more passes of the biopptome and higher risk of complication.



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Monitoring for Acute Rejection of Heart transplant

- **Gene expression profiling was developed which reduced scheduled biopsies. Biopsies were no longer scheduled after the first few months following transplant and were performed when testing was positive.**
 - High false positive rate, particularly when patient has acute viral infections
- **Donor derived cell free DNA testing allowed for further reduction in scheduled biopsies with significant reduction in false positive tests.**
 - Scheduled endomyocardial biopsies reduced to 5 total 9/1/2021 and recently further reduced to 3.

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Donor derived cell free DNA

- When allograft cells die they release short DNA fragments into the circulation
- These fragments can be identified, sequenced and a percentage of donor derived cell free DNA can be obtained.
- The percentage of donor derived cell free DNA highly correlates to acute rejection



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Table 2. %ddcfDNA for Primary and Secondary End Points From Day 28 Onward (Table view)

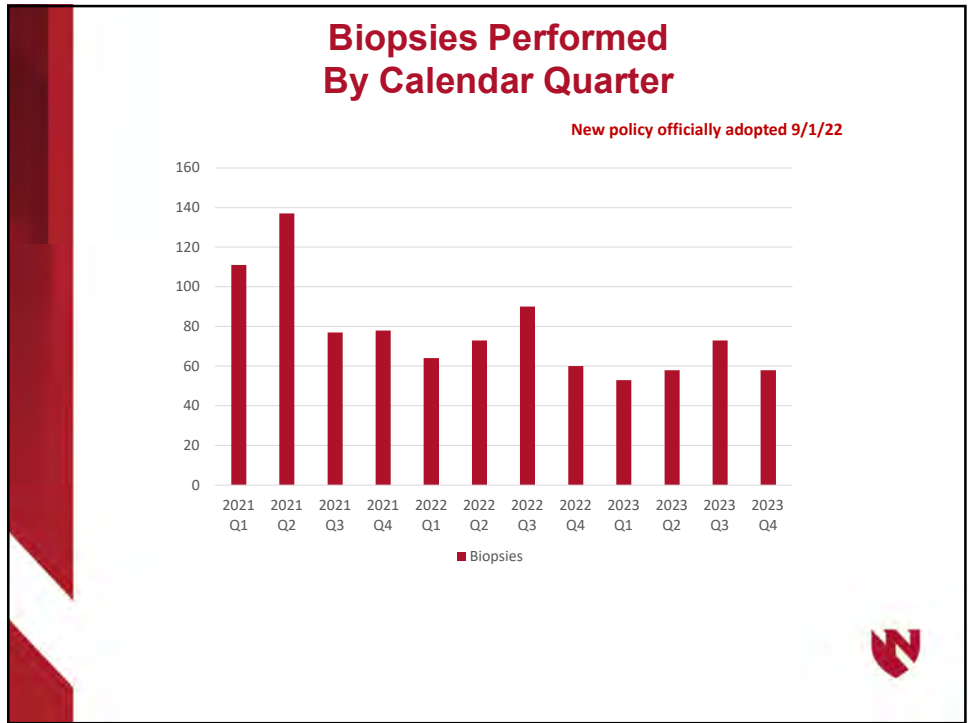
Clinical end point	Number of events	Subjects with events	Median %ddcfDNA	%ddcfDNA interquartile range (%)	P value
Controls (ACR 0, ACR 1, AMR 0)	1072	165	0.03	0.01–0.14	—
Acute rejection	49	31	0.38	0.31–0.83	<0.001*
ACR					
Grade 0	618	165	0.02	0.01–0.13	—
Grade 1	454	165	0.04	0.01–0.17	0.023†
Grade ≥2	28	21	0.34	0.28–0.72	<0.001‡
AMR					
Grade 0	1072	165	0.03	0.01–0.14	—
Grade 1	14	9	0.63	0.34–0.77	<0.001‡
Grade ≥2	11	9	1.68	0.49–2.79	<0.001‡
Allograft dysfunction					
None	866	165	0.02	0.01–0.12	—
Mild	168	83	0.06	0.01–0.27	0.068§
Moderate	62	49	0.19	0.01–0.60	0.018§
Severe	38	28	0.32	0.05–0.47	<0.001§

Sean Agbor-Enoh. Circulation. Cell-Free DNA to Detect Heart Allograft Acute Rejection, Volume: 143, Issue: 12, Pages: 1184-1197, DOI: (10.1161/CIRCULATIONAHA.120.049098)

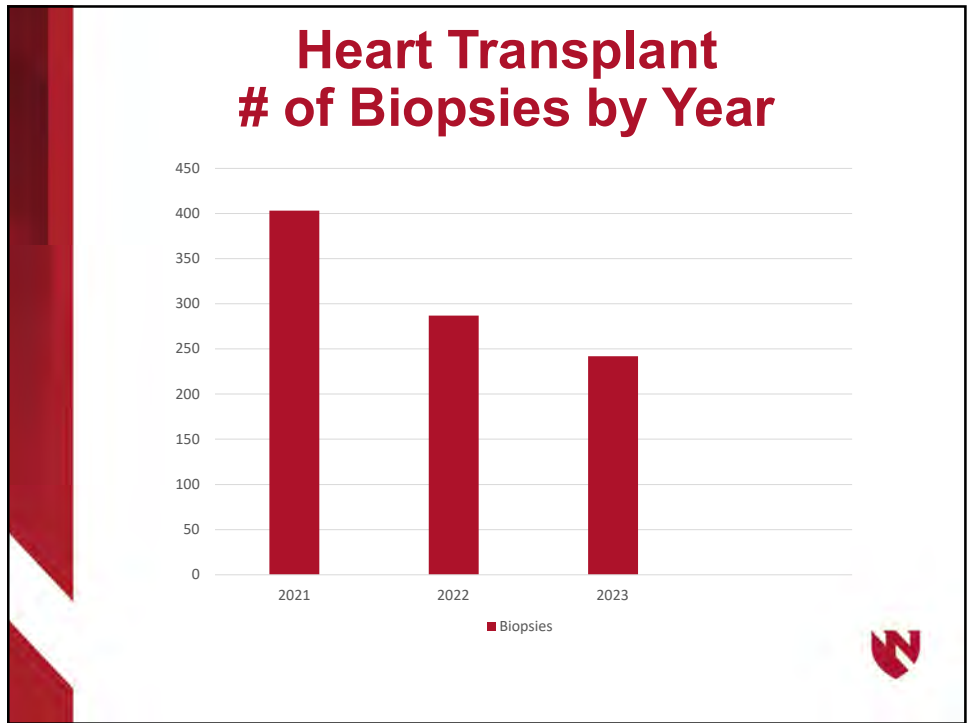
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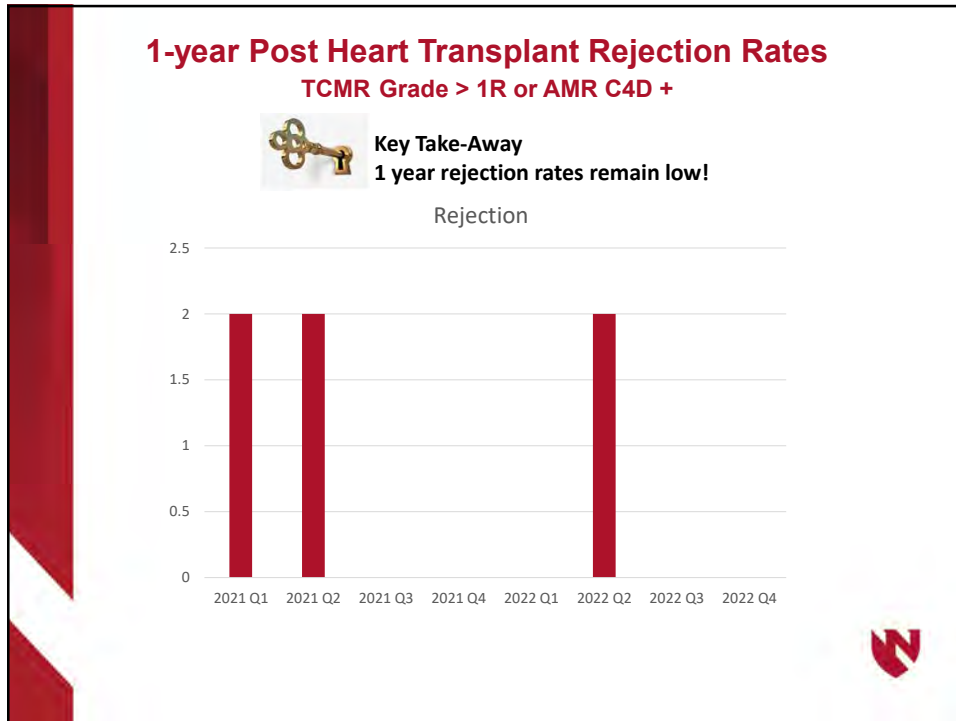
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MMDX

- **Molecular Microscope Diagnostic System uses gene expression profiling by measuring mRNA transcript levels in endomyocardial biopsy tissue.**
- **Endomyocardial biopsy performed per protocol and sent to pathology for histopathological evaluation. Additional samples obtained for MMDX and sent to outside lab.**



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Comparison	Rejection surveillance results			
		EMBx		
MMDx vs. EMBx		No Rejection	Rejection	Total
	No Rejection	167	3	172
	Rejection	32	24	56
	Total	199	27	226
MMDx vs. dd-cfDNA		dd-cfDNA		
		No Rejection	Rejection	Total
	No Rejection	80	36	128
	Rejection	12	26	38
Total	102	74	176	
dd-cfDNA vs. EMBx		EMBx		
		No Rejection	Rejection	Total
	No Rejection	101	52	153
	Rejection	1	22	23
Total	102	74	176	

Evolving the surveillance and workup of heart transplant rejection: A real-world analysis of the Molecular Microscope Diagnostic System Amit Alam, Johanna Van Zyl, Gregory Paul Milligan, Staci Michelle McKean, Raksha Patel, Shelley Anne Hall, *American Journal of Transplantation*, Volume 22 Issue 10 Pages 2443-2450 (October 2022)

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Nebraska Medicine Rejection Score

Rejection Score	
<u>When Allosure > 0.20%</u>	
LVEF < 50%	+1
Positive DSA's	+1
Positive histopathology	+2
MMDx Model 2 TCMR or ABMR > 0.4	+1
New onset arrhythmias	+1



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