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Association of Dual Noninvasive Biomarkers with 10-Year All Cause Graft Loss in A Multicenter Prospective Cohort

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Disclosure

At the time of analysis, I was a paid employee of Eurofins Transplant Genomics

Background

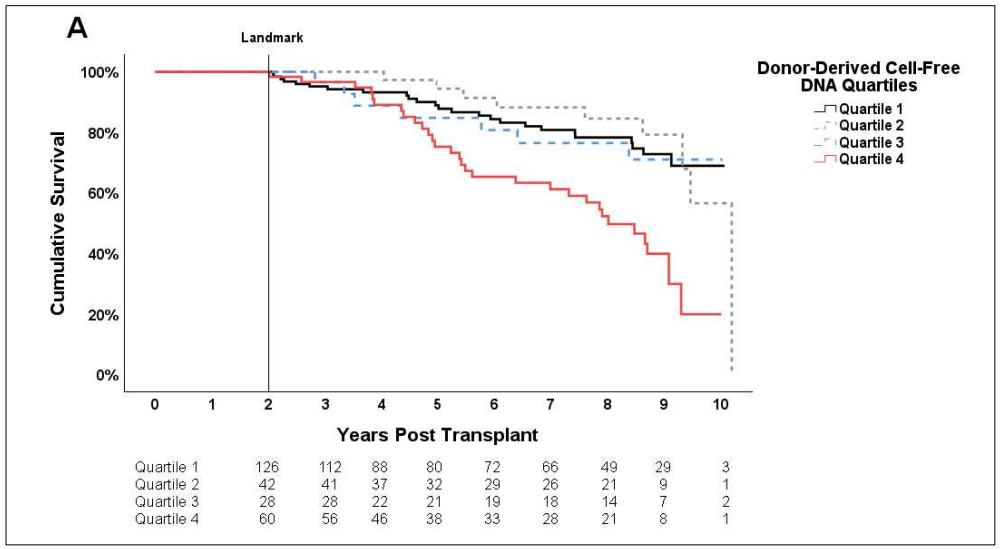
- Long-term kidney transplant outcomes remain suboptimal
- There is a need for dynamic markers of risk
- Positive peripheral blood GEP and dd-cfDNA have been associated with worse outcomes
- The association of the two complementary biomarkers on long-term outcomes has not been adequately studied

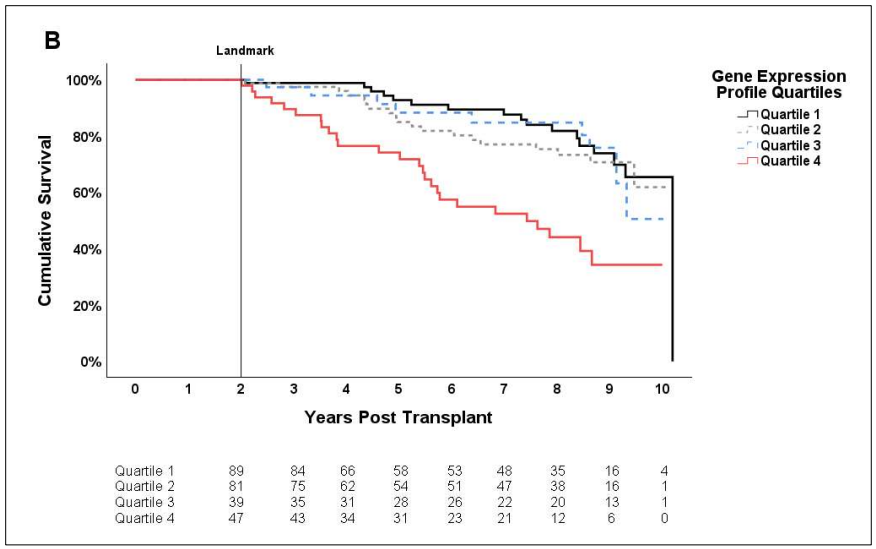
Methods

- CTOT-08 linked to the SRTR to assess 10-year outcomes
- Landmarked Time Dependent Cox Regression was used to determine the association between GEP and dd-cfDNA and ACGL
- Time Dependent Cox Regression with time-varying covariates used to test associations with ACGL with simultaneous and repeated biomarker results

	All (N=275)	Graft Loss (N=81)	No Graft Loss (N=194)
Recipient Age	52±14	56±15	50±13
Male	179 (65%)	53 (65%)	125 (64%)
Race			
Black/African American	54 (20%)	17 (21%)	36 (19%)
White	177 (64%)	55 (68%)	122 (63%)
Asian	11 (4%)	2 (2%)	9 (5%)
Native American/Alaskan	5 (2%)	3 (4%)	2 (1%)
Pacific Islander	3 (1%)	0 (0%)	3 (2%)
More than One Race	2 (1%)	0 (0%)	2 (1%)
Unknown/Not Reported	24 (9%)	4 (5%)	20 (10%)
Cause of ESKD			
Cystic	36 (13%)	9 (11%)	28 (14%)
Diabetes Mellitus	56 (20%)	24 (30%)	32 (16%)
Glomerulonephritis	75 (27%)	19 (23%)	56 (29%)
Hypertension	45 (16%)	12 (15%)	31 (16%)
Other	64 (23%)	17 (21%)	47 (24%)
Donor Age	41±14	43±15	40±14
cPRA	4 [0,60]	11 [0,69]	3 [0,55]
Living Donor	152 (55%)	35 (43%)	117 (60%)
Induction			
Anti-thymocyte globulin	71 (26%)	22 (27%)	49 (25%)
Alemtuzumab-1H	142 (51%)	36 (44%)	105 (54%)
Basiliximab	56 (20%)	22 (27%)	34 (18%)
Maintenance Immunosuppression			
Tacrolimus	275 (100%)	81 (100%)	193 (99%)
Mycophenolate	274 (99%)	80 (99%)	193 (99%)
Steroids	167 (61%)	55 (68%)	111 (57%)

Landmarked Kaplan Meier for dd-cfDNA and GEP





	Positivity Threshold	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Donor-Derived Cell-Free DNA	>0.69%	0 Positive Tests	1 Positive Test	2 Positive Tests	3+ Positive Tests
Gene Expression Profile	Not-TX (>50)	0 Positive Tests	1-2 Positive Tests	2-4 Positive Tests	5+ Positive Tests

Associations with ACGL with 2-year Landmark

Parameter	Reference	Classification	HR (95% CI)	P-value
Subclinical Acute Rejection	No Rejection	1 Subclinical Rejection	1.73 (1.04,2.88)	0.04
		2 or 3 Subclinical Rejections	2.17 (1.04,4.55)	0.04
Clinical Acute Rejection	No Rejection	1 Rejection	2.78 (1.42,5.47)	<0.01
		2 Rejections	14.34 (4.94,41.63)	<0.01
Living Donor Recipient	Deceased-Donor	Categorical	0.58 (0.37,0.92)	0.02
Diabetes	No Diabetes	Categorical	1.76 (1.06,2.92)	0.03
Recipient Age		Continuous	1.02 (1.01,1.04)	<0.01
Gene Expression Profile	No Positive Biomarker/Quartile 1	Quartile 2	1.32 (0.68,2.56)	0.42
		Quartile 3	1.19 (0.53,2.70)	0.68
		Quartile 4	3.75 (2.01,7.02)	<0.01
Donor-Derived Cell-Free DNA	No Positive Biomarker/Quartile 1	Quartile 2	0.81 (0.36,1.78)	0.59
		Quartile 3	1.03 (0.45,2.38)	0.95
		Quartile 4	2.77 (1.62,4.72)	<0.01
Depleting Induction Therapy	Non-Depleting Induction	Categorical	0.78 (0.47,1.30)	0.34
Black Race	Non-Black Race	Categorical	1.08 (0.62,1.92)	0.77
Steroid Maintenance	Steroid Withdrawal	Categorical	1.83 (1.12,2.98)	0.02

Multivariable Model

Parameter	Reference	Classification	aHR (95% CI)	P-value
Clinical Acute Rejection	No Rejection	1 Rejection	2.58 (1.30,5.13)	<0.01
		2 Rejections	3.41 (1.07,10.85)	0.04
Diabetes	No Diabetes	Categorical	1.71 (0.99,2.96)	0.05
Recipient Age		Continuous	1.02 (1.00,1.04)	0.02
Gene Expression Profile Quartile 4	Quartiles 1-3	Categorical	2.44 (1.45,4.10)	<0.01
Donor-Derived Cell-Free DNA Quartile 4	Quartiles 1-3	Categorical	2.91 (1.77,4.78)	<0.01

Association of Dual Biomarker Results with ACGL

			Univariate	Multivariable	
Parameter	**Reference**	**Classification**	**HR (95% CI)**	**aHR (95% CI)**	**P-value**
Subclinical Acute Rejection	No Rejection	Categorical	1.52 (0.92,2.50)		
Clinical Acute Rejection	No Rejection	Categorical	3.73 (1.41,9.84)	3.30 (1.41,7.71)	<0.01
Living Donor Recipient	Deceased-Donor	Categorical	0.43 (0.32,0.76)	0.60 (0.38,0.96)	0.03
Diabetes	No Diabetes	Categorical	1.63 (1.01,2.65)	1.56 (0.98,2.47)	0.06
Recipient Age		Continuous	1.02 (1.01,1.04)	1.02 (1.00,1.03)	0.14
Single Biomarker	No Positive Biomarker	Categorical	2.20 (1.37,3.55)	2.28 (1.40,3.69)	<0.01
Dual Biomarker	No Positive Biomarker	Categorical	4.46 (2.10,9.56)	4.29 (2.10,8.76)	<0.01
Depleting Induction Therapy	Non-Depleting Induction	Categorical	0.73 (0.45,1.18)		
Black Race	Non-Black Race	Categorical	1.30 (0.76,2.22)		
Steroid Maintenance	Steroid Withdrawal	Categorical	1.70 (1.08,2.68)		

Conclusions

- Results of a long-term, multicenter, prospectively collected cohort
- Demonstrate the independent association of two different noninvasive biomarkers with ACGL
- Time-varying analysis demonstrates that both biomarkers used together and repeatedly provides more informed risk stratification than either alone
- Future prospective interventional studies are needed to further clarify the utility of non-invasive biomarkers in clinical-decision making