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The Prospective Multicenter pOKRA Study: Diagnosing Allograft Rejection via Combined Novel biomarkers and Linking Donor-Derived Cell-Free DNA to Interstitial Fibrosis and Tubular Atrophy Severity in Pediatric Kidney Transplant Rejection

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Objectives : To enhance renal allograft injury detection beyond serum creatinine limitations, novel biomarkers like AlloMap™ (measuring gene expression) and AlloSure™ (assessing donor-derived cfDNA) have been developed. AlloMap quantifies 5 genes (DCAF12, MARCH8, FLT3, IL1R2, PDCD1) into a score (0-20). Donor-derived cfDNA, indicating allograft tissue damage, is expressed as a percentage of cell-free DNA. Combining AlloSure and AlloMap (KidneyCare™) we aim to improve acute rejection(AR)diagnosis in pediatric kidney transplant recipients.
Methods : The pOKRA study included 72 AlloSure and 69 AlloMap samples, drawn prospectively on the same morning before post-transplant biopsies, from 61 patients in 3 centers within the first year. CareDx labs conducted AlloMap and AlloSure assays. Samples were categorized into AR (including subclinical and borderline) or Quiescence cohorts. Area under the ROC assessed AlloSure and AlloMap performance in discriminating biopsy-proven AR from quiescence. Principal component analysis standardized and combined variables, used in logistic regression to evaluate the combined effectiveness. Interstitial fibrosis (ci) and tubular atrophy (ct; IFTA) scores followed Banff 2018 guidelines.
Results : In 18 biopsies with proven AR and 59 without, AlloSure median at AR was 1.7% (IQR 0.42%–3.9%) vs. quiescent 0.28% (IQR 0.18%–0.46%), AlloMap median at AR was 13 (IQR 12–14) vs. quiescent 9.9 (IQR 8.2–11). AUC for AlloSure alone was 0.83 (95% CI 0.72–0.95), AlloMap alone 0.82 (95% CI 0.71–0.93), and combined AUC improved to 0.94 (95% CI 0.88–0.99). At AlloSure 1% and AlloMap 11.5 threshold, PPV was 80.2% (95% CI 36.56%–96.60%), NPV 98.7% (95% CI 83.95%–99.23%), and accuracy 96.7% (95% CI 87.32%–99.71%). Combined tests, if normal, predicted and potentially avoided 40/41 biopsies. Elevations in both identified acute rejection in 8/9 biopsies. Donor-derived cfDNA levels correlated with IFTA severity, indicating worsening as interstitial fibrosis increased.
Conclusions : AlloSure and AlloMap together provide a precise evaluation of allograft integrity and immune status. Positive correlation observed between IFTA severity and dd-cfDNA indicates allograft injury.

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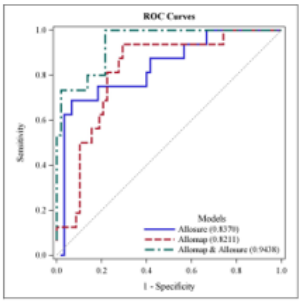
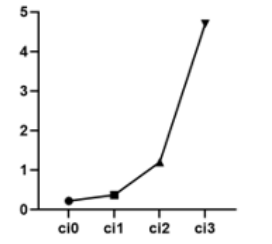
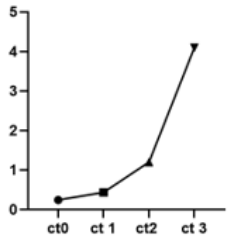
AlloMap	**Normal**	**Elevated**	**Elevated**	**Normal**
AlloSure	**Normal**	**Elevated**	**Normal**	**Elevated**
Interpretation	Rejection Unlikely	Rejection likely		
No of samples	41	9	11	5
Biopsy proven rejection	1	8	4	2
Biopsy proven quiescence	40	1	7	3





Interstitial fibrosis (ci) scores



Tubular Atrophy(ct)